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。

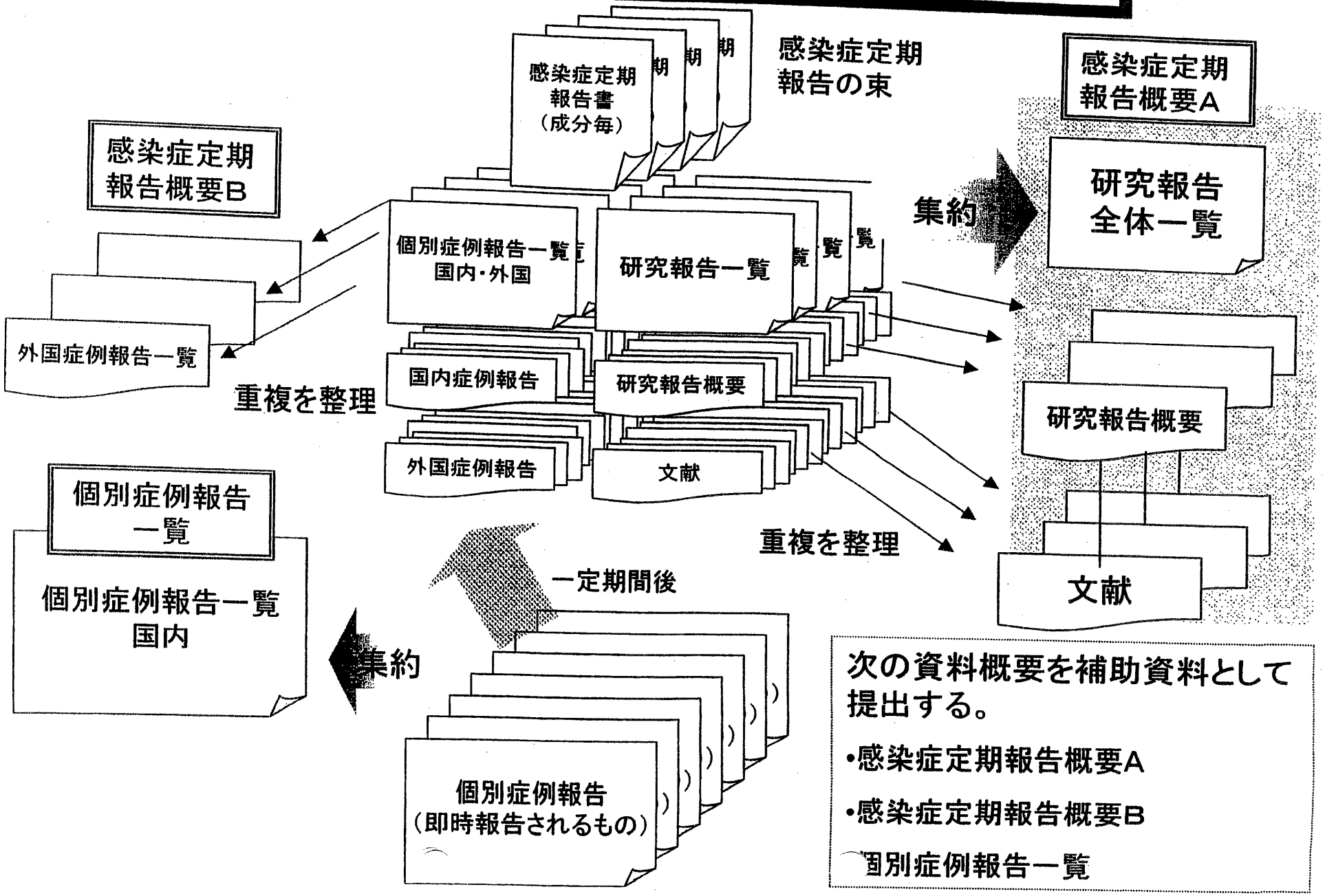
② 感染症発生症例報告のうち、発現国が「外国」の血漿分画製剤の使用による症例は、同一製品毎に報告期間を代表する感染症発生症例一覧（別紙様式第4）をまとめた**「資料概要B」**を事務局が作成し、送付する。

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・感染症個別症例報告の取り扱い



次の資料概要を補助資料として提出する。

- 感染症定期報告概要A
- 感染症定期報告概要B
- 個別症例報告一覧

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/Ba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。	

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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	BuaNews 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。	

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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FerraraとBolognaの間に住む80歳代の女性、2例目はFerrara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、1996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26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。微生物感染はバベシア症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件をバ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。膿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

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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。	

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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の霊長類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名の遡及調査の結果、弧発性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

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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, 小板橋優, 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
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)			日本

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。

(一)

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[2], 小板橋優[4], 長瀬良彦[3], 高橋秀明[1], 奥瀬千晃[1], 安田清美[4], 鈴木通博[3], 伊東文生[1], 飯野四郎[4], 小池和彦[2]
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], 清川病院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,アミノ酸の疎水性・親水性および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

○菅野有紀子, 本間史子, 物江恭子, 坂本夏美, 齋藤広信, 阿部和道, 高橋敦史, 横川順子, 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日当血液内科を紹介された.血液検査でトランスアミナーゼ正常,WBC 4100/μl, Ly 6% (CD4 3.93/μl), HBs抗原陽性, HBs抗体陰性, HBc抗体陽性, HBe抗原陽性, 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,硫酸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 2.2 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 3.8 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】

肝機能障害の推移は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の薬剤変更に伴う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ー輸血用全血・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。

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	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。

(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

Contains Nonbinding Recommendations

Draft – Not for Implementation

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Contains Nonbinding Recommendations

Draft – Not for Implementation

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:

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.

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.*

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)).

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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	今後の対応
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。	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

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 noncase 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

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DOI: 10.3201/eid1504.081450

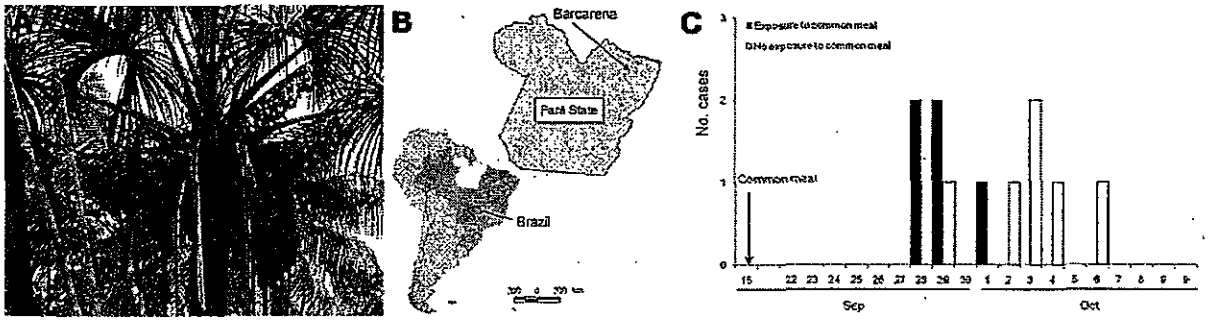

Figure 1. A) Açaí palm and açaí fruit. B) Location of Barcarena in Pará State, Brazil. C) Epidemic curve for 11 case-patients with acute Chagas disease, Barcarena, Brazil, September–October 2006.

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).

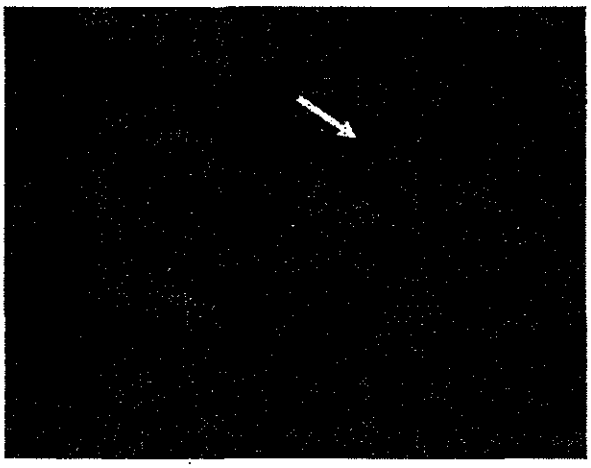

Figure 2. *Trypanosoma cruzi* (arrow) in a peripheral blood smear of a patient at a local health facility in a rural area of Pará State, Brazil (Giemsa stain, magnification ×100). Image provided by Adriana A. Oliveira, Brazilian Field Epidemiology Training Program, Brasília, Brazil.

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.

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
Açai 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.

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別紙様式第2-1

No. 10

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		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)		ProMED 20090406.1328, 2009 Apr 6. 情報源:El Universal, 2009 Apr 5.	ベネズエラ

研究報告の概要 38

○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。

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。

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

(4)

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
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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/qrccs_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 20090402.1279
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

or archived material. »

別紙様式第 2-1
番号 9

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 25 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	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るとする報告である。 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

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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.

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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/mm^3)	0	891	0–5
Neutrophils (%)		1	0
Lymphocytes (%)		93	70
Complete blood count			
White-cell count (cells/mm^3)	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

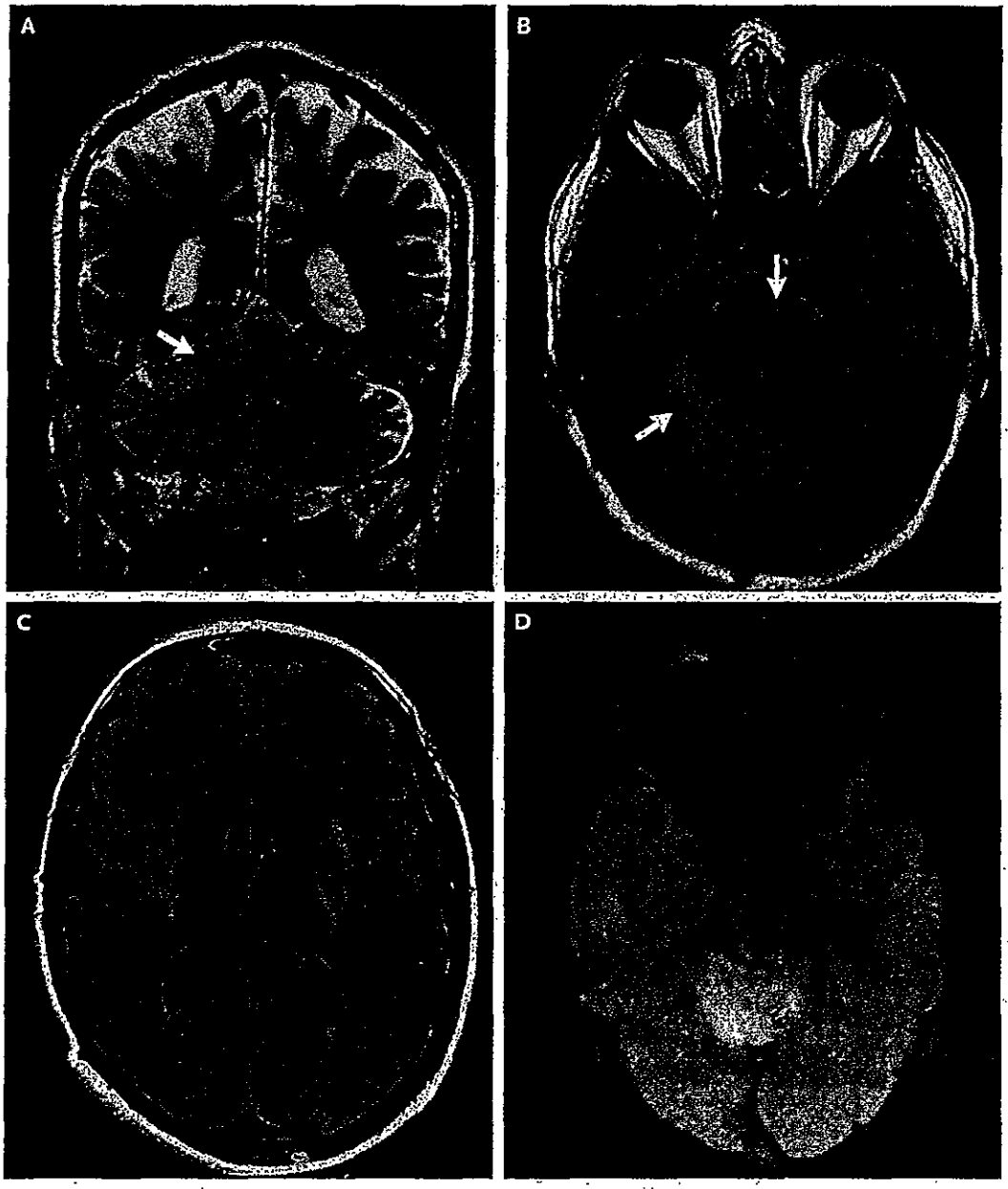

Figure 1. Magnetic Resonance Imaging (MRI) of the Brain on Hospital Admission.

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-

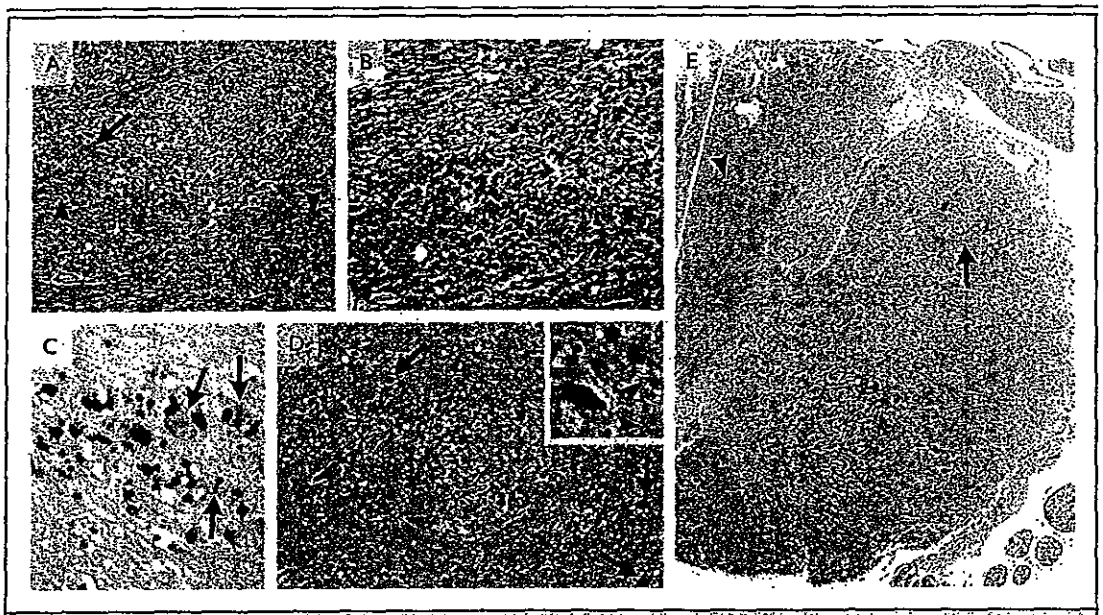

Figure 2. Histologic Findings at Autopsy.

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[3,4] (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 au-

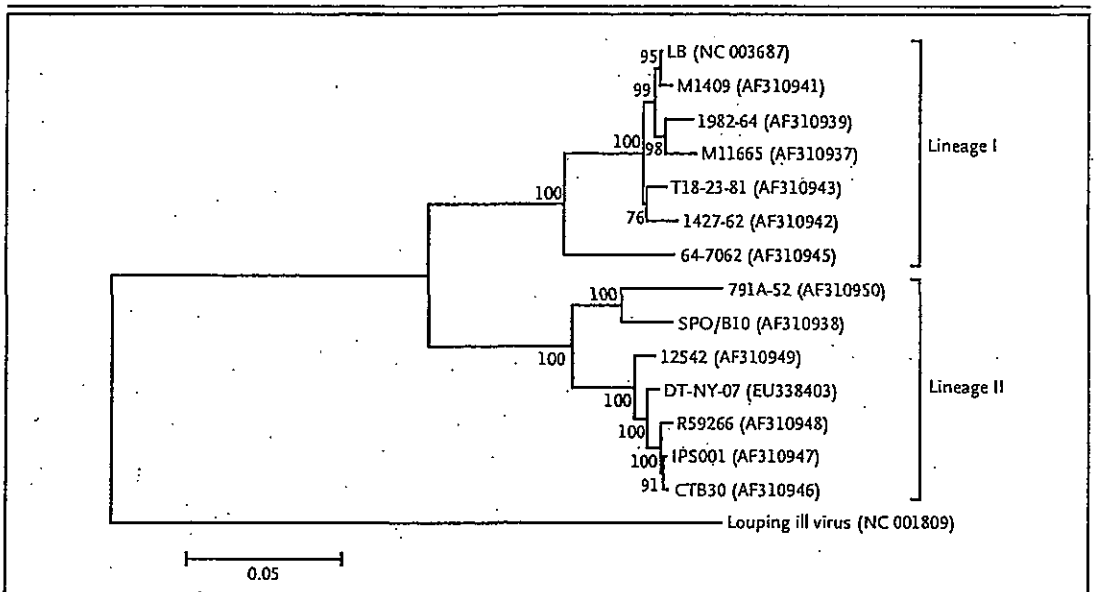

Figure 3. Phylogenetic Tree Showing the Relationship between the Virus (DT-NY-07) Detected in Tissue Sections from the Brain of the Patient and Other Powassan Viruses.

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 0.60849794 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]

topsy 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).

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-

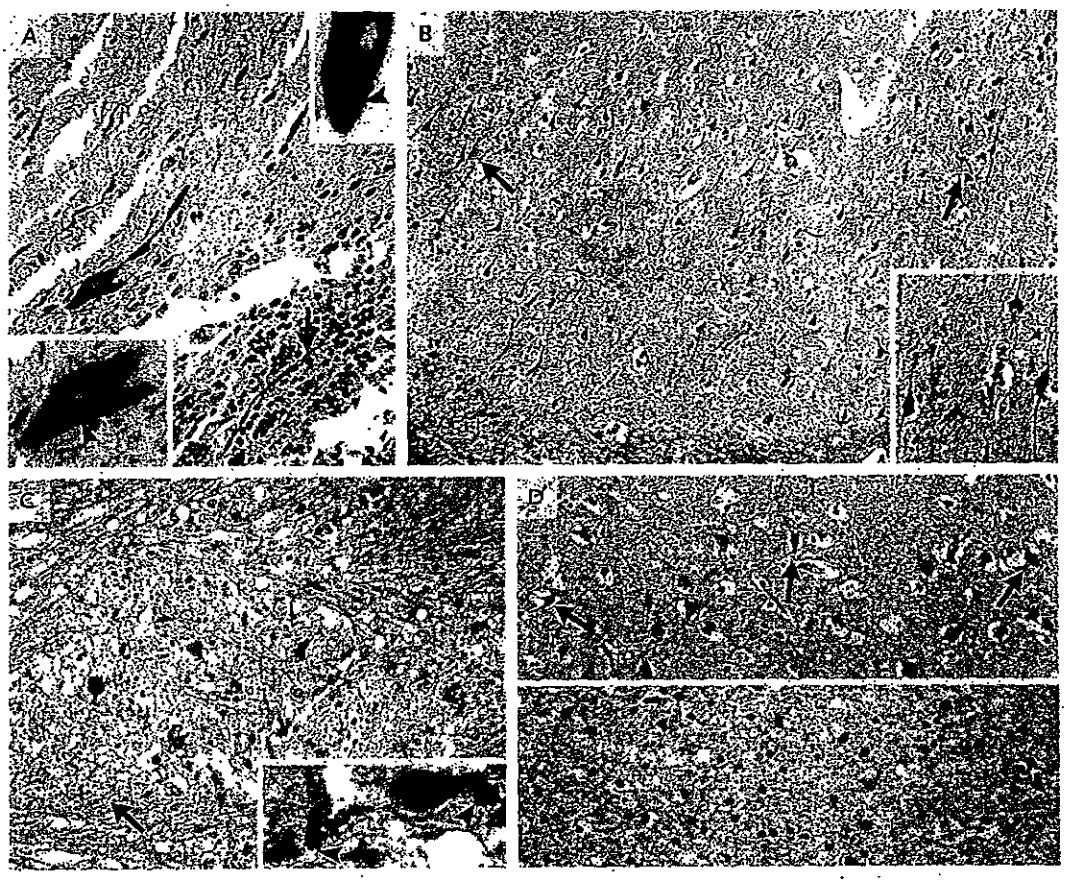

Figure 4. Immunohistochemical Analysis with Deer Tick Virus Antiserum Samples.

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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No potential conflict of interest relevant to this article was reported.

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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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 平成 21 年 6 月 8 日	新医薬品等の区分 該当なし	機構処理欄
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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）					

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
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、アウトブレークの犠牲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。	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。

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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 of 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 G1 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, genetically distinct, highly pathogenic arenavirus.

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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 termini. 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.

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

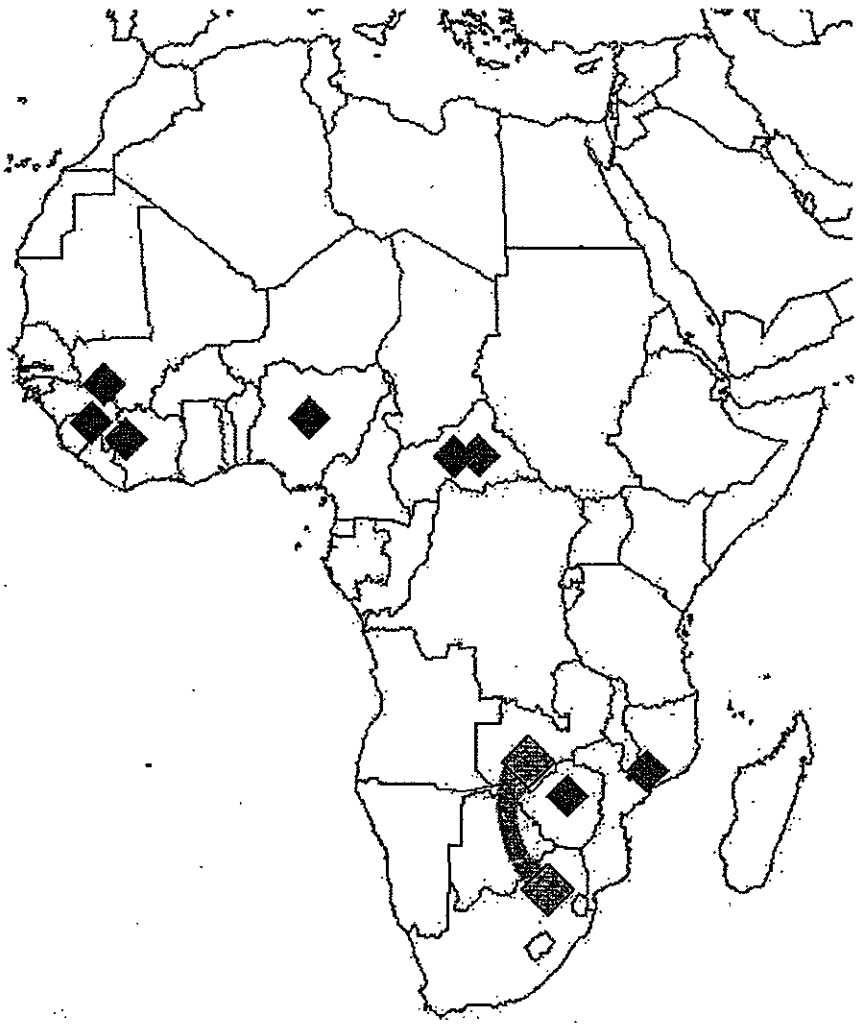

Figure 1. Geographic distribution of African arenaviruses. MOBV, MOPV, and IPPYV (blue) have not been implicated in human disease; LASV (red) can cause hemorrhagic fever. The origin of the LUJV index and secondary and tertiary cases linked in the 2008 outbreak are indicated in gold.
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arenaviruses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

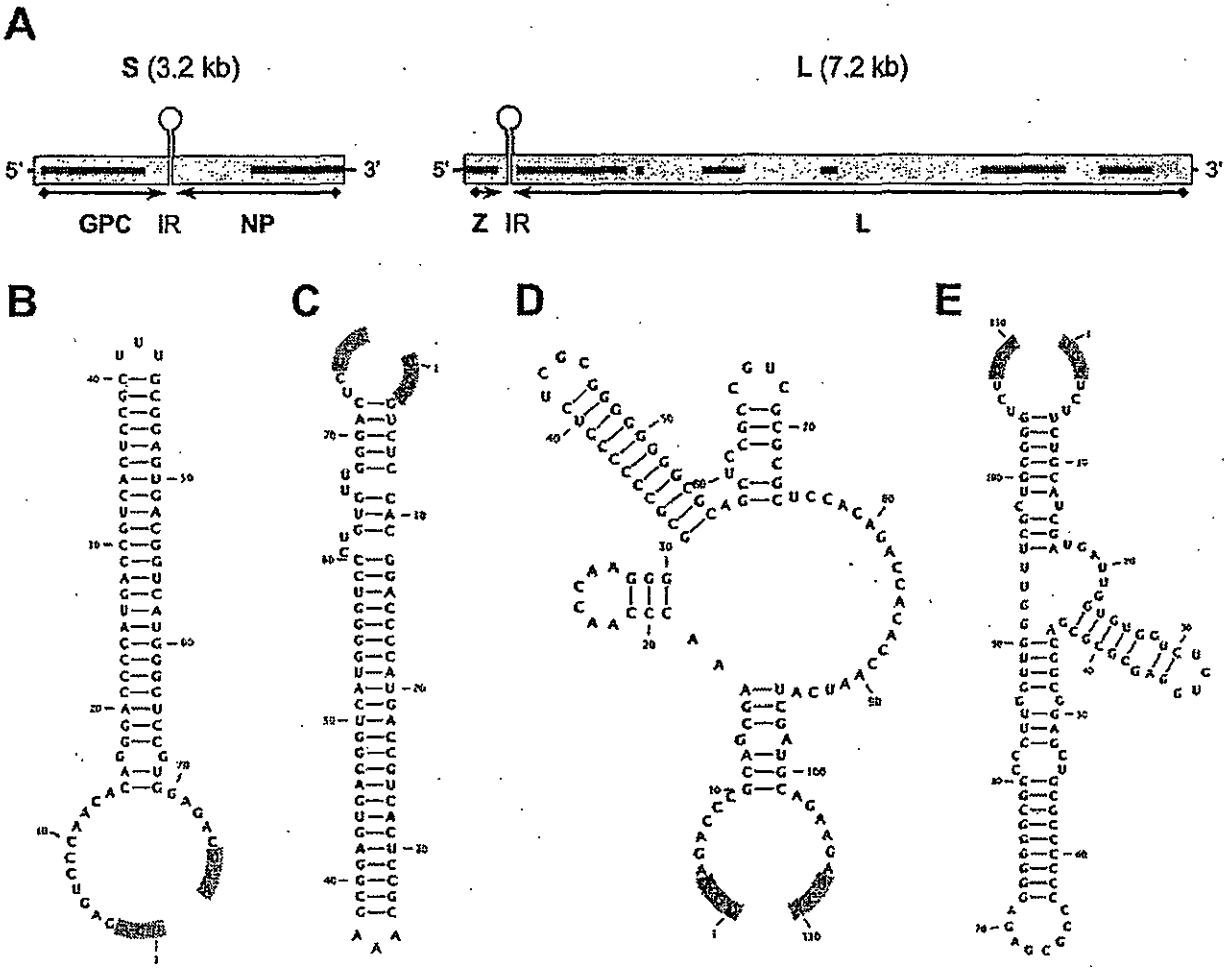

Figure 2. LUJV genome organization and potential secondary structure of intergenic regions. Open reading frames (ORF) for the glycoprotein precursor GPC, the nucleoprotein NP, the matrix protein analog Z, and the polymerase L, and their orientation are indicated (A); blue bars represent sequences obtained 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 (233 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_{352} (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).

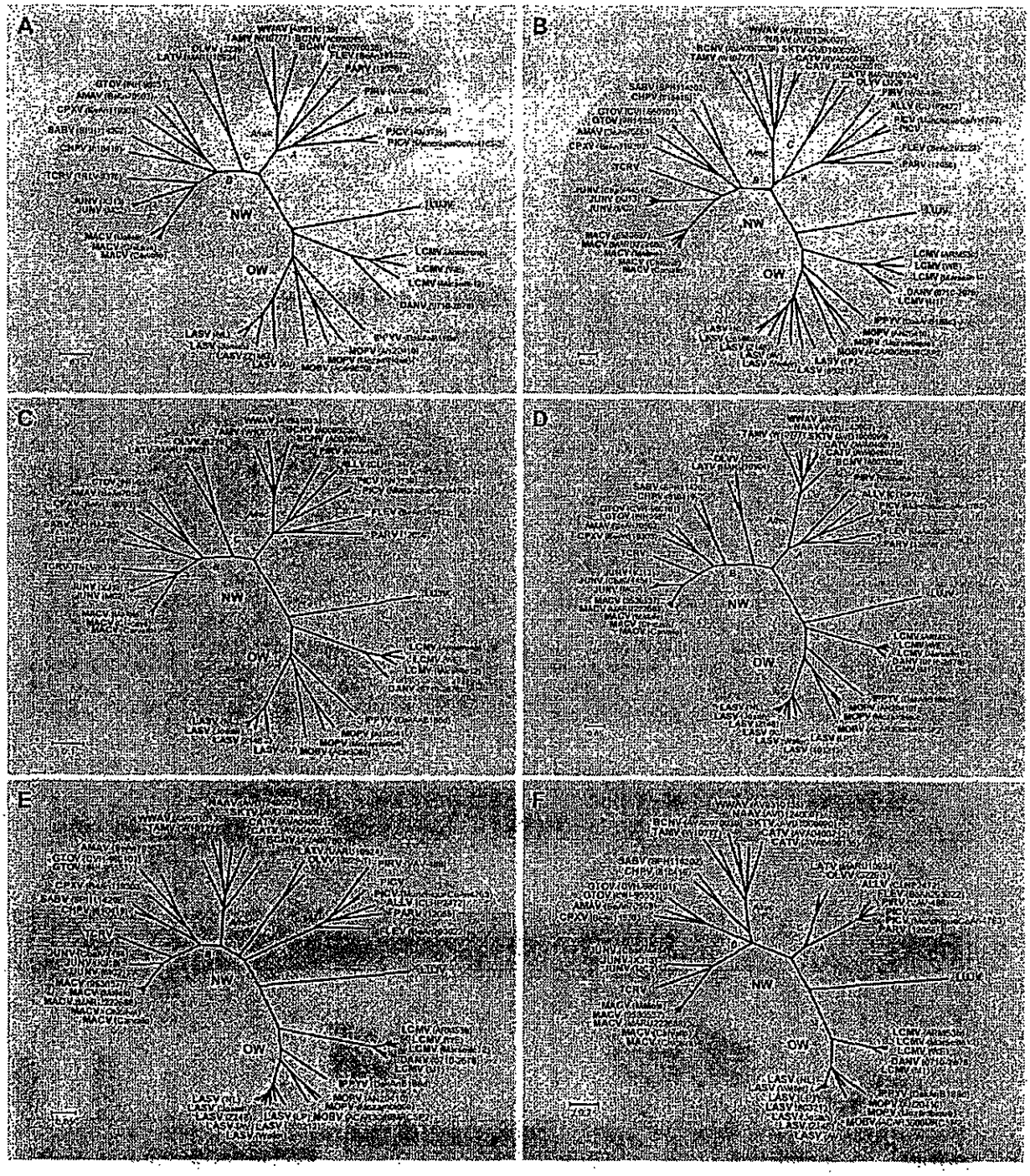

Figure 3. Phylogenetic analyses of LUJV. Phylogenetic relationships of LUJV were inferred based on full L (A) and S segment nucleotide sequence (B), as well as on deduced amino acid sequences of L (C), NP (D), Signal/G2 (E) and G1 (F) ORF's. Phylogenies were reconstructed by neighbor-joining analysis 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), CbaIV4454 (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).
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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,

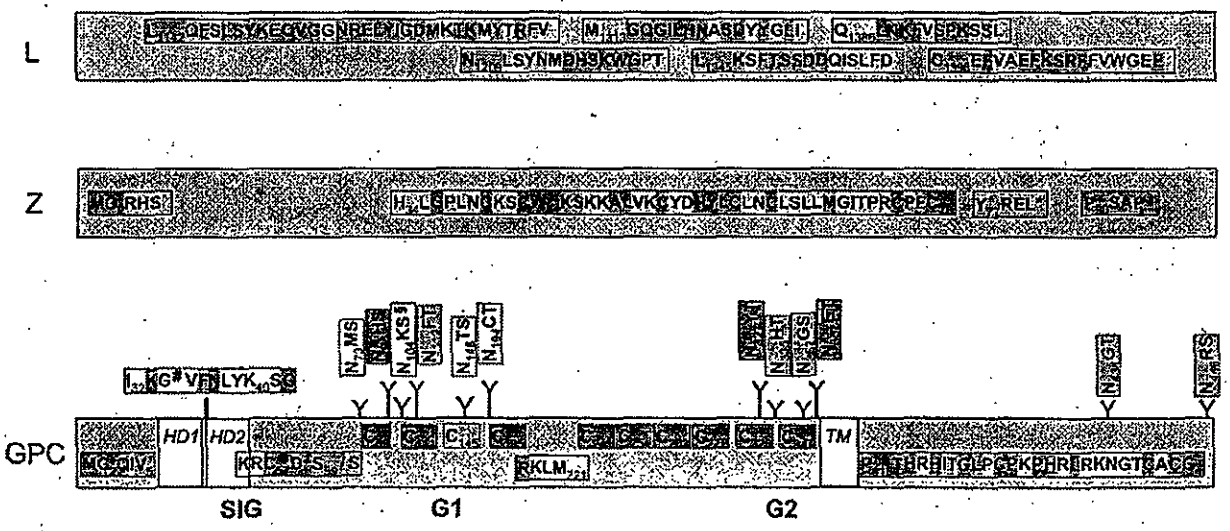

Figure 4. Schematic of conserved protein motifs. Conservation of LUJV amino acid motifs with respect to all other (green highlight), to OW (yellow highlight), or to NW (blue highlight) arenaviruses is indicated; grey highlight indicates features unique to LUJV. Polymerase motifs pre-A (L_{1142}), A (N_{1209}), 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.
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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 denaturation 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].

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.

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医薬品　研究報告　調査報告書

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販売名（企業名）	別紙のとおり				

研究報告の概要

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。

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。

使用上の注意記載状況・その他参考事項等

記載なし

MedDRA/J ver.11.1

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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－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P 1500 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
****

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: 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:

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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.
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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.
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intrauterine fetal deaths. Birth Defects Res A Clin Mol Teratol 2007 Jun;79(6):488-93.

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Bo Niklasson,
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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

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		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)		CDC. Available from: http://www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount08_detailed.htm.	米国

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。

報告企業の意見	今後の対応
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。	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。

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

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West Nile Virus Basics
- Fact Sheet
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- Guidelines for Surveillance, Prevention, & Control PDF (254 KB/77 pages)

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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	Fatalitie
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 encephali* or WN meningitis, such as acute flaccid paralysis. **Clinical/Unspecified** cases are those for whi sufficient clinical information was not provided.

See the **case definition** (2004) for Neuroinvasive and Non-Neuroinvasive Domestic Arbo[illegible]al Diseases. From the CDC Epidemiology Program Office.

Total Human Cases Reported to CDC: These numbers reflect both mild and severe human disease cases occurring between January 1, 2008 to December 31, 2008 as reported through Ap 10, 2009 to ArboNET by state and local health departments. ArboNET is the national, electroni 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 f further details regarding state case totals.

Note: The high proportion of neuroinvasive disease cases among reported cases of West Nile vi disease reflects surveillance reporting bias. Serious cases are more likely to be reported than m cases. Also, the surveillance system is not designed to detect asymptomatic infections. Data fro population-based surveys indicate that among all people who become infected with West Nile vi (including people with asymptomatic infections) less than 1% will develop severe neuroinvasiv *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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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		公表国
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)		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	米国

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 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[i]. 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[ii]. 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

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

Annie Fine, MD

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

[i] 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.
[ii] 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 2-1
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	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(S)：214	公表国 日本
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

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(R1/R2)、R. japonica を標的としたプライマー (Rj5/Ri10) 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. heilomgiangensis 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. heilomgiangensis に対して高い抗体価を示し、3 個体の Haemaphysalis conncina 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. heilomgiangensis) 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. conncina 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. conncina の分布をより明確にするとともに、R. heilomgiangensis 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。

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. heilomgiangensis 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 Heilomgiangensis 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。

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，溝部孝則，原富由香，和田正文，
糸永浩太郎，脇田富雄，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海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]，
大原綜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]，黒澤昌啓[2]，坂田明子[1]，藤田博己[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（Rj5/Rj10）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.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.heilomgiangensis*に対して高い抗体価を示し，3個体の*Haemaphysalis conncina*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.conncina*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.conncina*の分布をより明確にするとともに，*R.heilomgiangensis*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．

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）	－					
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．					使用上の注意記載状況等・その他参考事項等
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

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

船橋市立医療センター　検査科[1]，国立感染症研究所　細菌第二部[2]

長野則之[1,2]，○外山雅美[1]，長野由紀子[2]，荒川宜親[2]

【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差をもって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提案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．

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		公表国
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)		FDA, CBER. Available from: http://www.fda.gov/Cber/blood/fatal08.pdf.	米国

研究報告の概要

○FDAに報告された供血後及び輸血後の死亡例 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。

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。

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

(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
B. Transfusion Related Acute Lung Injury (TRALI)
C. Hemolytic Transfusion Reactions (HTR)
D. Microbial Infection
E. Transfusion Not Ruled Out as Cause of Fatality
F. Not Transfusion Related
G. Post-Donation Fatalities

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).

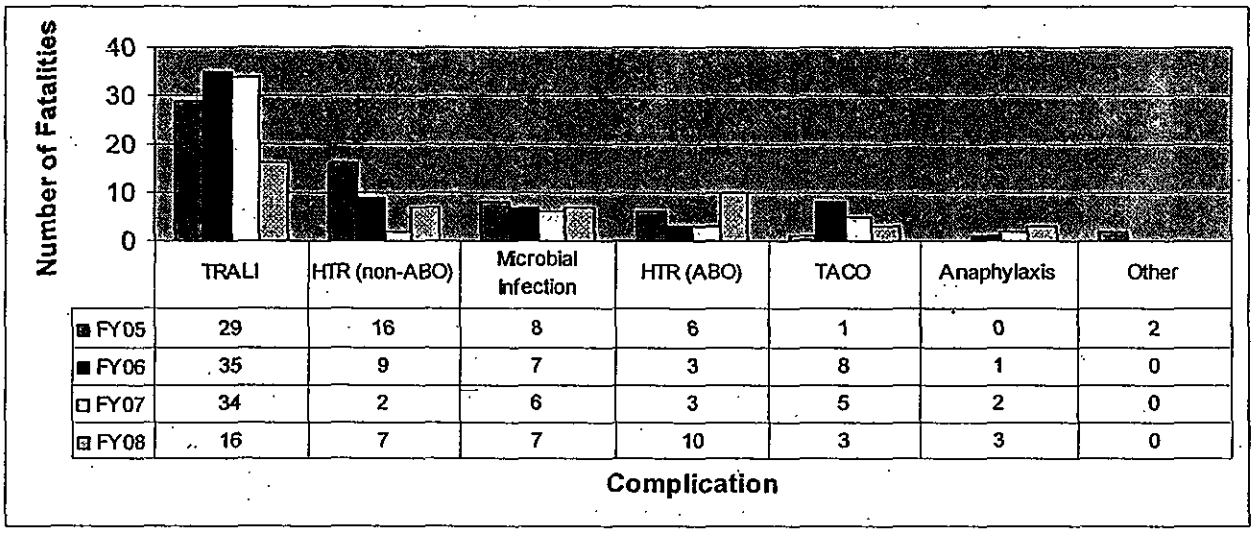
Table 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2008

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

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

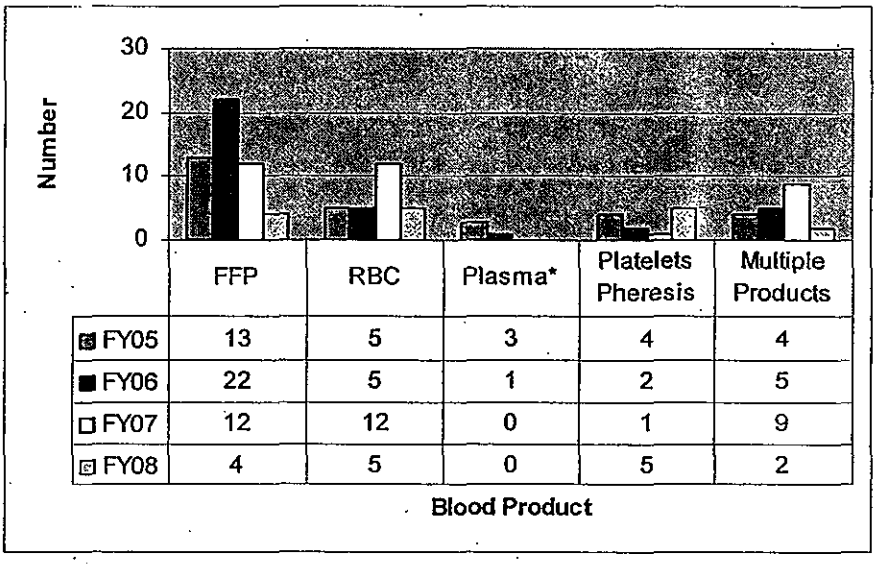
[6] Curtis, BR, Mcfarland JG. Mechanisms of transfusion-related acute lung injury (TRALI): anti-leukocyte antibodies. Crit Care Med 2006;34(5 Suppl):S118-S123.

[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

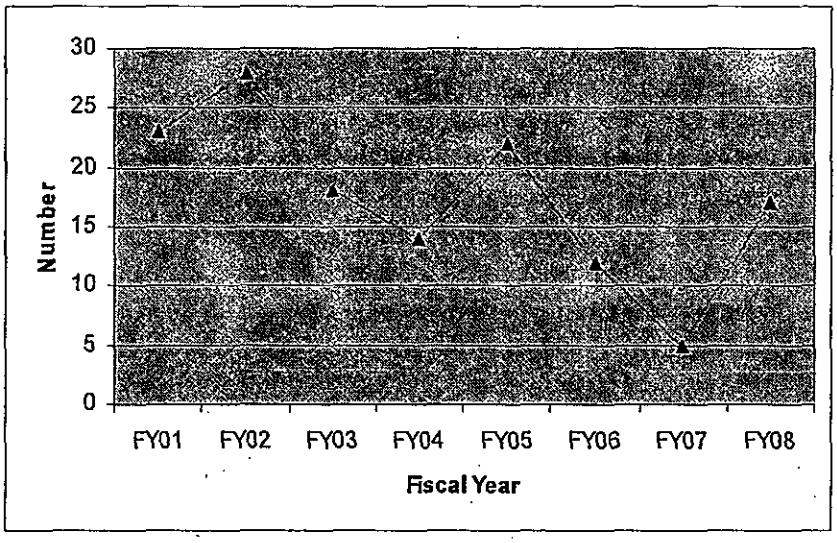
In FY2008, hemolytic transfusion reactions were the leading cause of transfusion related fatalities reported to CBER, representing 37% of confirmed transfusion related fatalities. The number of reported fatal hemolytic transfusion reactions increased to 17 in FY2008, as compared to 5 in FY2007, and 12 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

	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	Total	Total
Antibody	No.	%	No.	%	No.	%	No.	%	No.	%
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).

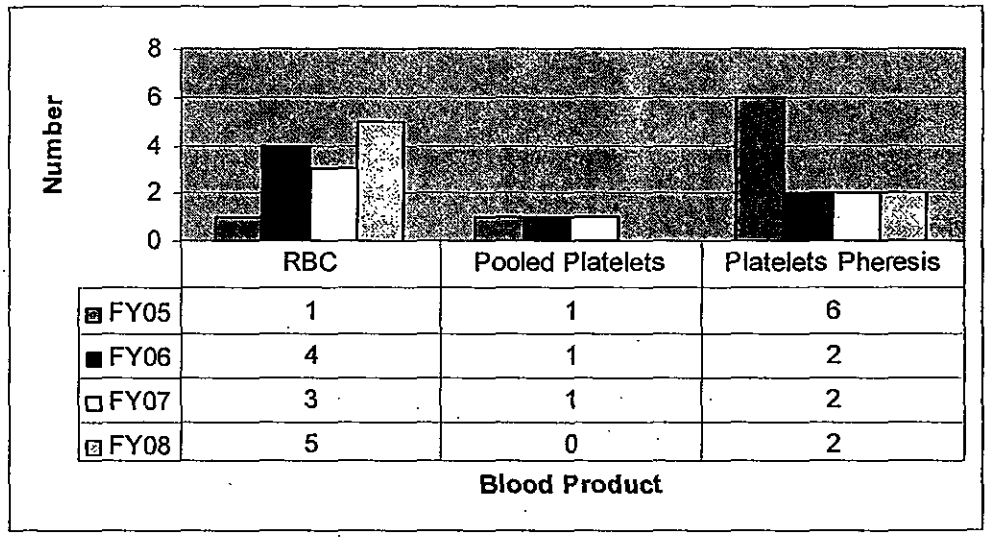
Table 4: Microbial Infection by Implicated Organism, FY2005 through FY2008

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

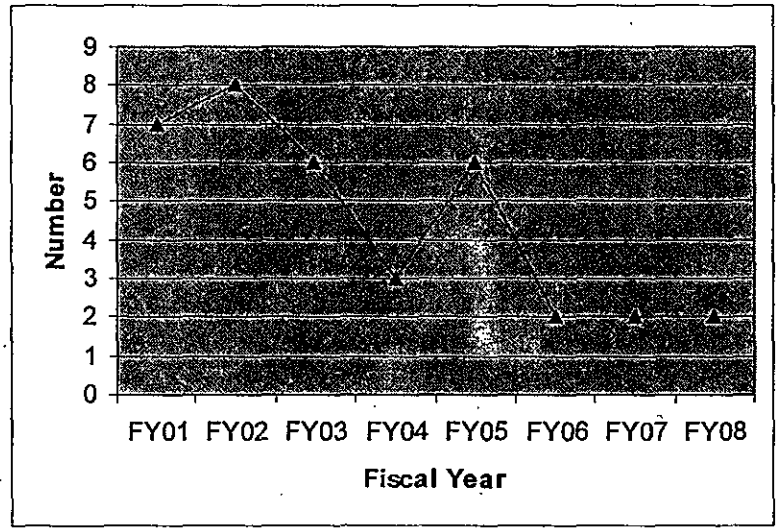
[13] Gubernot DM, Lucey CT, Lee KC et al. *Babesia* Infection through Blood Transfusions: Reports Received by the US Food and Drug Administration, 1997-2007. Clin Infect Dis 2009;48:000-000, electronically published, 26 November 2008.

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.

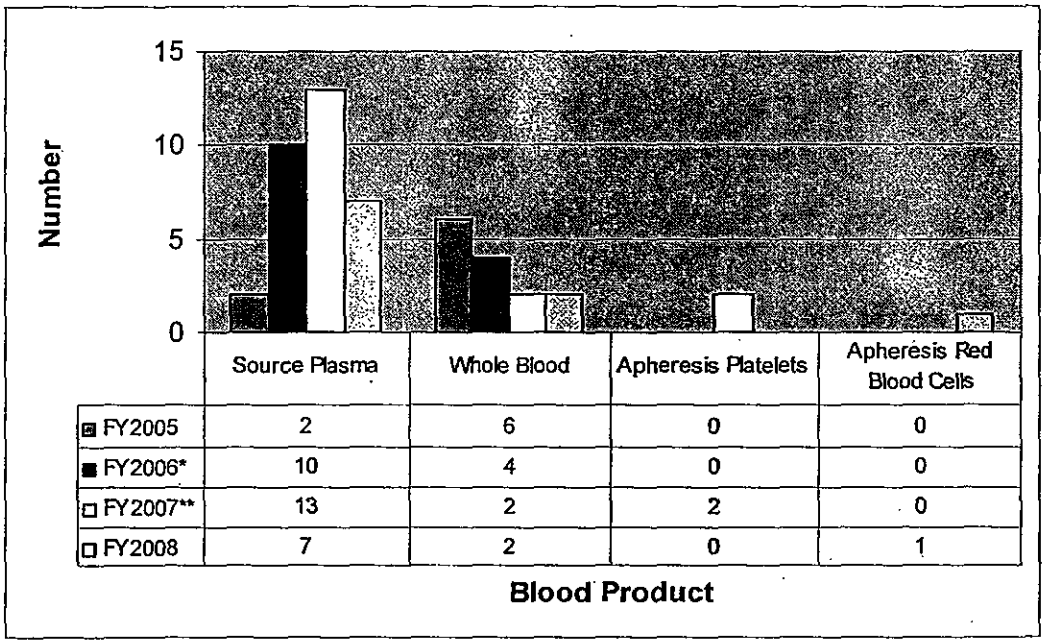
In FY2008, we received reports of two fatalities following Whole Blood donation collected by manual methods. In both cases, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor.

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 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

○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」
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

undefined

* 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(i)
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(i)
Switzerland	0	2	8	15	29	64	68	45	38	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)

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		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 - World Organisation for Animal Health. Available from: http://www.oie.int/eng/info/en_esbru.htm.	OIE

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。

報告企業の意見	今後の対応
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。	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」
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

undefined

* 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 cases of bovine spongiform encephalopathy (BSE) reported in the United Kingdom (1)

	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 93

○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。

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。

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」
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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

15

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^{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

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	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).

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.[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.[5,8] 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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別紙様式第2

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医薬品　研究報告　調査報告書

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一般的名称	乾燥濃縮人アンチトロンビンIII	研究報告の公表状況	Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study Transfusion 49 (5): p977-984 MAY 2009	公表国 米国	
販売名（企業名）	アンスロビンP-ベーリング（CSLベーリング株式会社）				

研究報告の概要

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%）が弧発性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。

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使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
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。

(17)

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^{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

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.[6,13,14] 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	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).

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.[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.[5,8] 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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研究報告の概要

Health Protection Agency による扁桃腺組織の大規模な研究結果によれば、vCJD の無症候の人数の最新の推定値は非常に低いままである（2009 年 5 月 22 日）。
63,000 のサンプルのいずれにも vCJD と関連している異常プリオン・タンパク質の証拠は見つからなかった。
2004 年、Health Protection Agency は抽出された扁桃腺から vCJD と関連しているプリオンタンパク質をさがすことによって、無症候性 vCJD の保有率を確定するために National Anonymous Tissue Archive（NATA）を開始した。
扁桃腺は一度感染すると vCJD プリオンが蓄積する部位の一つである（その他の部位は、脾臓、虫垂、リンパ節、脊椎及び脳）。
集団での vCJD 保有率を認識することは、集団に対するリスクのレベルを決定する、感染の影響を限定する、あるいは疾患を発病する可能性がある人々のために健康管理介入を計画するために重要である。
調査はすでに 63,000 の扁桃腺組織の収集と解析を行っており、合計 100,000 まで検体を収集し続ける予定である。
当初 100,000 のサンプルのうちの最高 50 検体が異常プリオン・タンパク質を含むことが推定されたが、現在までのところ陽性サンプルは一つもなかった。調査結果は集団中の無症候性の vCJD は予想より少ない可能性があることを示唆する。

報告企業の意見	今後の対応
2004 年に HPA は、摘出された扁桃腺における vCJD 関連プリオン蛋白質を検出することにより、無症候性 vCJD 有病率を確定するために NATA を開始したが、無症候性 vCJD 症例は当初予想されていたよりも少ない可能性があることを示唆する報告である。 血漿分画製剤は理論的な vCJD 伝播リスクを完全には排除できないため、投与の際には患者への説明が必要である旨を 2003 年 5 月から添付文書に記載している。2009 年 2 月 17 日、英国健康保護庁(HPA)は vCJD に感染した供血者の血漿が含まれる原料から製造された第Ⅷ因子製剤の投与経験のある血友病患者一名から、vCJD 異常プリオン蛋白が検出されたと発表したが、弊社の原料血漿採取国である日本及び米国では、欧州滞在歴のある献（供）血希望者を一定の基準で除外し、また国内での BSE の発生数も少数であるため、原料血漿中に異常型プリオン蛋白が混入するリスクは 1999 年以前の英国に比べて極めて低いと考える。また、製造工程においてプリオンが低減される可能性を検討するための実験を継続して進めているところである。	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) 略
1) 略
2) 現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、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。

Protecting people
Preventing harm
Preparing for threats

Latest research into prevalence of vCJD consistent with findings of existing studies

22 May 2009

Latest estimates of the number of people asymptomatic for variant Creutzfeldt-Jakob disease (vCJD) in the population remain very low, according to results from a large scale study of tonsil tissue by the Health Protection Agency, published in today's BMJ (Friday 22nd May 2009).

No evidence of the abnormal prion protein associated with vCJD was found in any of the 63,000 samples analysed.

In 2004, the Health Protection Agency launched the National Anonymous Tissue Archive (NATA) to determine prevalence of asymptomatic vCJD in the population, by looking for the prion protein associated with vCJD in extracted tonsils. The tonsils are one of the sites in the body where, once infected, vCJD prions can accumulate (other sites include the spleen, appendix, lymph nodes, spinal cord and brain).

Awareness of the prevalence of vCJD in the population is important to determine the level of risk to the population and to limit the impact of infection or plan healthcare interventions for people who may develop the disease.

The survey has already involved collection and analysis of 63,000 discarded tonsils, and will continue on until a total of 100,000 samples of leftover tonsil tissue have been examined.

When the archive was established it was estimated that up to 50 of the 100,000 samples could contain the abnormal prion protein, however so far none of the samples are positive.

The findings suggest there may be fewer undetected asymptomatic cases of vCJD in the population than were previously expected. However, only by testing a larger number of tonsils and continuing and expanding on the current survey, will scientists be confident that the prevalence is lower than earlier estimates.

Dr Jonathan Clewley, an expert on vCJD at the Health Protection Agency, said: "It may be that we have seen the worst of vCJD already, although we need to keep vigilant and implement appropriate public health measures to prevent any possible secondary spread of disease.

"Estimating the prevalence of people who are carrying vCJD unknowingly is important in guiding our public health response to this disease and ensuring all necessary precautions are taken to reduce this risk of further transmission of the agent through surgical operations and other healthcare settings.

"Further studies are planned to strengthen prevalence estimates, these will involve large scale anonymous tissue surveys, and continuation with the testing of tonsil specimens especially in the older age groups."

Ends

Notes to editors

1. The National Anonymous Tissue Archive (NATA) is managed by the CJD Team at the Health Protection Agency and the Transmissible Spongiform Encephalopathies Unit for the Department of Health.

2. The findings are published in the BMJ paper; *Prevalence of disease related prion protein in anonymous tonsil specimens in Britain: a cross-sectional opportunistic survey,* J Clewley *et al. BMJ* 2009; 338: b1442.

3. 63,007 samples were taken, of which 12,763 were from the birth cohort where most cases had arisen (1961-1985), 19,908 were in the 1985-1995 cohort who would have also been exposed to BSE from infected meat or meat products. None of the samples that were investigated by immunohistochemistry or immunoblotting were positive for the presence of PrP^{CJD}.

4. The archive is completely anonymous; after tonsils are removed, they are separated from any identifiable patient

information before going into the archive. Therefore if abnormal prion proteins are found in a tonsil sample, the results cannot be passed back to the patient.

This anonymous procedure is used because the significance for an otherwise well person of finding abnormal prion protein in their tonsil tissue is unknown at present. The Research Ethics Committee that reviewed the study supported the view that the tonsils should be tested anonymously.

5. Since 1995 there have been 168 definite or probable cases of vCJD in Britain, resulting in 115 deaths from vCJD and 49 deaths thought likely to be due to vCJD. Back calculation based on these cases would suggest between 10 and 190 further clinical cases over the next ten years.

6. The NATA study is able to detect presence of the prion protein regardless of the genotype of the prion protein gene.

7. For further information on this press release please contact the Health Protection Agency's Centre for Infections press office on:

Kate Swan 020 8327 7097
Georgina Fletcher 020 8327 6690
Louise Brown 020 8327 7080
Alex Baker 020 8327 7098
David Daley 020 8327 664

Last reviewed: 21 May 2009

別紙様式第2-1

No. 23

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		公表国
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)		Ferguson-Smith MA, Richt JA. Nature. 2009 Feb 26;457(7233):1079.	英国

研究報告の概要

○稀なBSE突然変異により公衆衛生リスクが懸念される
最近、非定型(H-型、L-型)のウシ海綿状脳症(BSE)が、日本、カナダ、米国に加え、複数のヨーロッパ諸国で発生した。これにより、ヒトの変異型クロイツフェルトヤコブ病(vCJD)が増加するというありがたくない可能性が浮上している。これまで検査された非定型BSE症例のうち、プリオンタンパク遺伝子(PRNP)の突然変異が検出されたのは1例(アラバマ州のBSE牛)のみで、このウシの健常な仔ウシにも突然変異が存在した。これは当該疾患が遺伝性である可能性を示す。実際、2000年のUK BSE Inquiryの報告では、英国のBSE流行はこうした変異による可能性が高いことが示され、スクレイピー関連とする仮説に反対の見解を示した。
非定型BSEを発症させる可能性のある稀なPRNP変異は、オーストラリアとニュージーランドのようなBSEが発生していないと考えられている国々でも起こる可能性がある。このため、ウシに対する厳しいBSE調査を継続し、反すう動物の厳密な飼料規制を行うことが重要である(現在でも多くの国がブタに反すう動物性タンパク質を与えている)。食肉処理時にウシの特定危険部位(脳や脊髄など)を除去することで、感染部位がヒトの食物連鎖に入り込むことを回避できる。
現在利用可能なウシのPRNP突然変異を調べるルーチン遺伝子スクリーニング検査により、公衆リスクについてさらなるデータが得られるだろう。アラバマのウシに同定された点突然変異は、ヒトで最も一般的な型の家族性(遺伝的)CJDの原因と同一であるため、これによって生じる感染性プリオンタンパク質は、より容易にウシ-ヒト関門を通過する可能性が考えられる。vCJD患者の特定は今後も続くだろう。発症頻度が減少しているからといって、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。

報告企業の意見	今後の対応
非定型ウシ海綿状脳症(BSE)が、日本、カナダ、米国に加え、複数のヨーロッパ諸国で発生し、オーストラリアとニュージーランドのようなBSEが発生していないと考えられている国々でも起こる可能性があるとの報告である。	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。

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」
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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

(18)

CORRESPONDENCE

Human dignity must be basis for debate on primate research

SIR — Bill Crum emphasizes a fundamental keynote of biomedical-research ethics in his Correspondence 'It should be possible to replace animals in research' (*Nature* **457**, 657; 2009) by stating that "good medical science" is not necessarily "morally justifiable or morally acceptable". On the other hand, many states and societies claim 'freedom of research' — meaning research being free from the need for justification — as a basic right. On the face of it, this looks like a discrepancy.

However, we have to recognize the fact that this freedom, like every other kind of freedom, has its ethical limits. Research can only be a right as long as it is not acting against our fundamental moral value: respect for human dignity. This is the basic point that we should agree on, regardless of our different opinions on what might constitute a breach of that principle.

With human dignity in mind, the ethical discussion about research on non-human primates has to focus on answering two questions. First, would prohibiting studies on primates constitute a threat to the human dignity of future generations, by reducing their chances of what we could consider a good life, as Roberto Caminiti states in his Correspondence 'Replacement of animals in research will never be possible' (*Nature* **457**, 147; 2009)? Second, is performing "invasive medical experiments" on creatures that "provide excellent experimental models of human cognition", as Crum states, a threat to our own dignity and our vision of how a good life should be led?

Only by using human dignity as the normative correlate for ethical decisions can we ensure that these decisions will be made on a basis that is equally important to all parties in this debate.

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Readers are welcome to comment at http://tinyurl.com/c62pgf

Rare BSE mutation raises concerns over risks to public health

SIR — Atypical forms (known as H- and L-type) of bovine spongiform encephalopathy (BSE) have recently appeared in several European countries as well as in Japan, Canada and the United States. This raises the unwelcome possibility that variant Creutzfeldt–Jakob disease (vCJD) could increase in the human population.

Of the atypical BSE cases tested so far, a mutation in the prion protein gene (*PRNP*) has been detected in just one, a cow in Alabama with BSE; her healthy calf also carried the mutation (J. A. Richt and S. M. Hall *PLoS Pathog.* **4**, e1000156; 2008). This raises the possibility that the disease could occasionally be genetic in origin. Indeed, the report of the UK BSE Inquiry in 2000 suggested that the UK epidemic had most likely originated from such a mutation and argued against the scrapie-related assumption.

Such rare potential pathogenic *PRNP* mutations could occur in countries at present considered to be free of BSE, such as Australia and New Zealand. So it is important to maintain strict surveillance for BSE in cattle, with rigorous enforcement of the ruminant feed ban (many countries still feed ruminant proteins to pigs). Removal of specified risk material, such as brain and spinal cord, from cattle at slaughter prevents infected material from entering the human food chain.

Routine genetic screening of cattle for *PRNP* mutations, which is now available, could provide additional data on the risk to the public. Because the point mutation identified in the Alabama animals is identical to that responsible for the commonest type of familial (genetic) CJD in humans, it is possible that the resulting infective prion protein might cross the bovine–human species barrier more easily. Patients with vCJD continue to be identified. The fact that this is happening less often should not lead to relaxation of the controls necessary to prevent future outbreaks.

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Scientific links with Cuba flourished despite US embargo

SIR — In your Editorial 'Cuba's biotech boom' (*Nature* **457**, 130; 2009), you state that "despite many constraints on interaction between Cuban and US scientists, biotech has prospered". In fact, US biotechnologists contributed in no small way to its development.

At the start, during the early 1980s, Cuban biotechnology was confined to a small house in a Havana suburb. An American group organized by Harlyn Halvorson, then director of Brandeis University's Rosenstiel Center and an inspirational leader, stepped in to help the venture. We were received warmly in Cuba whenever we visited.

The biotechnology effort soon transferred to a larger house across the street and from 1986 was housed in the majestic Center for Genetic Engineering and Biotechnology. The Cuban scientists set up symposia where one or more of us would speak.

The US government allowed us to travel to Cuba on the condition that we spent no American dollars there. We therefore continued to advise this fledgling group until the Soviet Union ceased to support Cuba financially and they could no longer pay for our visits.

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Idea of a love drug was no mystery to Shakespeare

SIR — In his Essay 'Love: neuroscience reveals all' (*Nature* **457**, 148; 2009), Larry Young claims that the biochemical understanding of love is not poetry. But at least one poet, namely William Shakespeare, foretold the application of drugs to manipulate the brain systems associated with pair bonding.

In *A Midsummer Night's Dream*, Oberon maintains that topical applications of the juice of the wild pansy (*Viola tricolor*, called 'love-in-idleness' in the play) "Will make or man or woman madly dote Upon the next live creature that it sees" (Act 2, Scene 1). The potion proves highly effective, supplying much of the humour in the play as Titania falls in love with the donkey-headed Bottom. Shakespeare also suggests that other substances from "Dian's bud" — variously identified as a species of wormwood (*Artemisia* spp.) or chaste tree (*Vitex agnus-castus*, a species not native to England but long known for its anti-libidinal properties) — could reverse the neurobiological results of the pansy. Perhaps poets have something to teach us about neurobiology and love after all.

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別紙様式第2-1

No. 25

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		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)		ProMED 20090108.0076, 2009 Jan 8. 情報源:UK: National CJD Surveillance Unit – monthly statistics as of 5 Jan 2009, 2009 Jan 5.	英国

研究報告の概要

○プリオン病最新情報 英国:国立CJDサーベイランスユニット、月次vCJD・CJD統計、2009年1月5日時点
英国のCJDサーベイランスユニットから公表されたvCJDを始めとするプリオン病の患者数に関する最新情報である。2008年は、12月31日時点で140名の照会があった。内訳は、孤発性CJDによる死亡患者:73名、医原性CJDによる死亡患者:5名、GSS:3名、家族性CJD:2名、vCJD:1名。vCJD確定例または可能性例総数は前月から変化なく167名のままである。このデータは英国におけるvCJD流行は減少しつつあるとする見解に一致する。死亡患者数のピークは2000年の28名であり、その後2001年に20名、2002年に17名、2003年に18名、2004年に9名、2005年に5名、2006年に5名、2007年に5名、2008年に1名と減少している。

報告企業の意見	今後の対応
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日の時点で、vCJD死亡患者総数には前月から変化なく167名のままであり、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。

使用上の注意記載状況・その他参考事項等

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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

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Archive Number 20090108.0076
Published Date 08-JAN-2009
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PRION DISEASE UPDATE 2009 (01)
****
A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

[With the continuing decline in the number of cases in the human population of variant Creutzfeldt-Jakob disease -- abbreviated previously as vCJD or CJD (new var.) in ProMED-mail -- it has been decided to broaden the scope of the occasional ProMED-mail updates to include other prion-related diseases. Data on vCJD cases and other forms of CJD: sporadic, iatrogenic, familial, and GSS (Gerstmann-Straussler-Scheinker disease) are included also when they have some relevance to the incidence and etiology of vCJD. - Mod.CP

In this update:
[1] UK: National CJD Surveillance Unit - monthly statistics as of 5 Jan 2009
[2] France: Institut de Veille Sanitaire - as of 30 Dec 2008
[3] US National Prion Disease Pathology Surveillance Center - as of 30 Nov 20
[4] and [5] Prion protein function
[6] CJD Update

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[1] UK: National CJD Surveillance Unit - monthly statistics as of 5 Jan 2009
Date: Mon 5 Jan 2009
Source: UK National CJD Surveillance Unit, monthly statistics [edited]
<http://www.cjd.ed.ac.uk/figures.htm>

The number of suspect cases of vCJD referred to the CJD surveillance unit in Edinburgh and the number of deaths of definite and probable variant Creutzfeldt-Jakob disease [abbreviated in ProMED-mail as CJD (new var.) or vCJD], the form of the disease thought to be linked to BSE (bovine spongiform encephalopathy), remain unchanged since the previous monthly report; that is, the number of definite or probable vCJD cases (dead and alive) remains 16

This situation is consistent with the view that the vCJD outbreak in the UK is in decline. The 1st cases were observed in 1995, and the peak number of deaths was 28 in the year 2000, followed by 20 in 2001, 17 in 2002, 18 in 2003, 9 in 2004, 5 in 2005, 5 in 2006, 5 in 2007, and only one so far (up to the end of 2008).

Totals for all types of CJD cases in the year 2008

As of 31 Dec 2008 in the UK, so far there have been 140 referrals, 73 deaths from sporadic CJD, 5 deaths from iatrogenic CJD, 3 from GSS, 2 from familial CJD, and one from vCJD.

--
Communicated by:

ProMED-mail
<promed@promedmail.org>

******
[2] France: Institut de Veille Sanitaire - as of 30 Dec 2008
Date: 30 Dec 2008
Source: IVS - Maladie de Creutzfeldt-Jakob et
maladies apparentees [French, trans. & summ. Mod.CP, edited]
<http://www.invs.sante.fr/display/?doc=publications/mcj/donnees_mcj.html>

During the period 1992 to 2008, there were 23
cases of vCJD, all now deceased. They occurred
between 1996 and 2007: one case in 1996, one in
2000, one in 2001, 3 in 2002, none in 2003, 2 in
2004, 6 in 2005, 6 in 2006, 3 in 2007, and none
so far in 2008. There were 12 male and 11 female patients.

Their ages at time of death ranged from 19 to 58
years (mean 39); 6 of the patients resided in the
Ile-de-France [Paris area] and 17 in the
provinces. All the cases were met-met homozygotes
for codon 129 of the prion protein gene. No
special risk factors were evident, which
distinguished these patients from those with
other forms of CJD (sporadic, genetic,
iatrogenic). However, one patient had visited the UK at regular intervals.

Totals for all types of CJD cases in the year 2008

As of 30 Dec 2008 in France, during the course of
2008 there have been 1438 referrals, 76 deaths
from sporadic CJD, 3 deaths from iatrogenic CJD,
8 from familial CJD, none from GSS, and none from vCJD.

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Communicated by:
ProMED-mail
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******
[3] US National Prion Disease Pathology Surveillance Center - as of 30 Nov 20(
Date: 30 Nov 2008
Source: US National Prion Disease Pathology Surveillance Center [edited]
<http://www.cjdsurveillance.com/resources-casereport.html>

Cases examined - as of 30 Nov 2008

During the period 1997 to 30 Nov 2008, 2 cases of
vCJD were reported, both contracted overseas. The
1st case was recorded in 2004, disease contracted
in the UK, and the 2nd in 2006, disease contracted in Saudi Arabia.

Totals for all types of CJD cases in the year 2008 as of 30 Nov 2008

So far in 2008 there have been 332 referrals, 199
cases of prion disease, including 151 cases of
sporadic CJD, 21 cases of familial CJD, no cases
of atrogenic CJD and no indigenous cases of vCJD.

Overall during the period 1997 to 2008, there
have been 3018 referrals, 1745 cases of prion
disease, 1456 cases of sporadic CJD, 252 cases of
familial CJD, 4 cases of iatrogenic CJD and no indigenous cases of vCJD.

[During 2008 so far the USA with approximately
2.5x the combine populations of the UK and France
have reported a similar number of cases of
sporadic CJD (149 versus 151). Whether this is
due ot a difference in surveillance procedure or
actual disease incidence is unclear at the present time. - Mod.CP]

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Communicated by:

ProMED-mail
<promed@promedmail.org>

******
[4] Prion protein function
Date: Sun 21 Dec 2008
Source: BBC News online [edited]
<http://news.bbc.co.uk/1/hi/health/7788444.stm>

Scientists sniff out prion secret

The brain protein which has a hand, when defective, in the lethal disease CJD may also be involved in aiding our sense of smell. Mice bred to lack the prion protein could not find buried food or choose between smells. Columbia University scientists said some symptoms of prion disease might be due to the loss of the protein's original role. The study was published in the journal Nature Neuroscience [see below].

The prion protein has historically received something of a bad press, being blamed in its misshapen form for degenerative brain diseases in humans and other animals. However, many scientists have been trying to uncover what it actually does when it is behaving correctly. Dr Stuart Firestein's team believe that one of these roles is to help us smell. While his prion-protein free mice were still able to detect scents, they had lost some higher functions which required that smell information to be analysed and processed by the brain. The scientists found changes in the communication between neurons in the nerve cells of the olfactory bulb, part of the forebrain which deals with odours. When the protein was restored to this part of the brain, the ability to discriminate between odours came back.

The scientists said that while the discovery had no direct link to the diseases caused by faulty prion proteins, it might help account for some of the symptoms experienced by patients, which might be due to the failure of the proteins to do their normal job properly, rather than the damage caused by accumulation of defective prions.

This is not the 1st suggested role for the prion protein -- in 2007, Leeds University scientist Professor Nigel Hooper said that it might help reduce the formation of "plaques" linked to the onset of Alzheimer Disease. He said of the newly-reported research: "It's likely that these proteins have a number of roles in various different body systems, including the olfactory system, as suggested here. "I don't think you can say that it is so mysterious any more, or that we do not understand what it does."

[Reference: Nature Neuroscience, Published online: 21 December 2008 doi:10.1038/nn.2238
<http://www.nature.com/neuro/journal/v12/n1/abs/nn.2238.html>

Title: Olfactory behavior and physiology are disrupted in prion protein knockout mice
Authors: Claire E Le Pichon1, Matthew T Valley1, Magdalini Polymenidou2,3, Alexander T Chesler1, Botir T Sagdullaev1,3, Adriano Aguzzi2 & Stuart Firestein1

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Abstract: The prion protein PrPC is infamous for its role in disease, but its normal physiological function remains unknown. Here we found a previously unknown behavioral phenotype of Prnp-/- mice in an odor-guided task. This phenotype was manifest in three Prnp knockout lines on different genetic backgrounds, which provides strong evidence that the phenotype is caused by a lack of PrPC rather than by other genetic factors. Prnp-/- mice also showed altered behavior in a 2nd olfactory task, suggesting that the phenotype is olfactory specific. Furthermore, PrPC deficiency affected oscillatory activity in the deep layers of the main olfactory bulb, as well as dendrodendritic synaptic transmission between olfactory bulb granule and mitral cells. Notably, both the behavioral and electrophysiological alterations found in Prnp-/- mice were rescued by transgenic neuronal-specific expression of PrPC. These data suggest that PrPC is important in the normal processing of sensory information by the olfactory system.]

[And from the same issue of Nature Neuroscience. See below - Mod.CP]

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[5] Prion protein function
Date: Sun 21 Dec 2008
Source: Nature Neuroscience 12, 7 - 8 (2009) [edited]
<http://www.nature.com/neuro/journal/v12/n1/full/nn0109-7.htm>

Title: Sniffing out a function for prion proteins

Abstract

When prion proteins go wrong, they can do serious damage, but little is known about their normal function, despite their ubiquitous expression in the brain. A new report in this issue [see above] suggests a critical role for prions in olfactory discrimination.

Introduction

Although the word prion was coined by Stanley Prusiner to describe the "proteinaceous infectious particle" that causes a family of fatal neurodegenerative diseases known as transmissible spongiform encephalopathies more than 20 years ago, little is known about the normal function of prion proteins. Most of what is known about them comes from studies of their involvement in these devastating diseases, which include Creutzfeld-Jakob disease, bovine spongiform encephalopathy ('mad-cow disease') and chronic wasting disease in elk and deer. These diseases are distinguished by rapidly progressive neurological deterioration and a pattern of neurodegeneration that is characterized by prominent vacuolization of neuronal cytoplasm, which gives the brain a sponge-like histological appearance. The key pathogenic event in these diseases is the conversion of an endogenous cell-surface glycoprotein, the prion protein (PrPc), to a pathological isoform (PrPsc) that has an abnormal conformation and an unusual resistance to proteolytic degradation. PrPsc accumulates in cells and plaque-like extracellular deposits, converting more PrPc into the pathogenic form and triggering neurodegeneration by mechanisms that are still not fully understood. Conversion of PrPc can be a result of inherited mutations, infection of the

host with a prion-infected tissue or rare sporadic events. Although the formation of PrPsc is believed to result in a gain of toxic function, a loss of function of PrPc has not been excluded as being involved in prion disease PrPc is most abundantly expressed in the brain and it would be expected that the loss of this protein would result in substantial neurobehavioral modifications. However, the specific role of PrPc in neural function and behavior is far from clear. In fact, previous work suggests that the most robust phenotype of PrPc loss in transgenic mice is protection from prion diseases. Although changes in PrPc expression influence a variety of critical cellular processes in neurons, including cell survival, synaptic maintenance and plasticity, and axonal maintenance, data on these issues have occasionally been contradictory. Thus, 'elusive' remains one of the descriptors most commonly attached to this protein in papers and reviews on PrPc. Fortunately, a clue to the elusive prion function may lie right under, in, our noses. Le Pichon and colleagues have begun this investigation in this issue [see proceeding report].

There are several major hurdles to learning about the function of a particular protein. One of these is knowing where the protein resides in cells. This localization can help narrow down the potential functions of the protein. Earlier this year [2008], it was demonstrated, using new highly specific antibodies, that PrPc in the olfactory system is localized to the axons of both peripheral olfactory sensory receptor neurons and central neurons such as the mitral cells of the olfactory bulb. Glia or support cells in the olfactory bulb or olfactory epithelium were not detectably labeled. In addition to axons, PrPc was also observed in the dendritic spines of axonless olfactory bulb granule cells. These spines are both pre- and postsynaptic to mitral cells, forming reciprocal synapses. Combined with the axon staining, this suggests a potential role for PrPc in presynaptic function. However, given how widely expressed PrPc is throughout the brain, simply showing its presence in the olfactory system was only circumstantial; further tests were required to determine whether it has a functional role in olfaction.

The observation that PrPc is expressed in olfactory sensory neurons, mitral cells and granule cells raises the possibility that it is important for the local circuit function of the olfactory bulb. Olfactory sensory neurons in the nose send axons directly into the brain, terminating on mitral cells, which send their axons directly to olfactory cortex. In the olfactory bulb, local circuits, which include granule cells, refine spatiotemporal patterns of sensory neuron input, and this local circuit function can be monitored electrophysiologically through oscillations in local field potentials. Previous work in a variety of laboratories has demonstrated that manipulation of local circuit function in the olfactory bulb can modulate various aspects of odor perception, 7). Thus, the stage was set to ask whether loss of PrPc affects normal olfaction. Le Pichon and colleagues provide a convincing affirmative answer and with it a clue to PrPc function. Specifically, the loss of PrPc in neurons of the olfactory system of transgenic mice impairs odor-guided behaviors such as finding buried food and simple odor discrimination. The deficit was expressed

regardless of the genetic background of the mice and was not a simple anosmia but was rather an apparent impairment in odor discrimination per se. Although PrPc is found in olfactory sensory neurons, the behavioral deficits were not associated with detectable changes in receptor function. In fact, the sense of smell could be rescued by selectively replacing PrPc in olfactory bulb neurons alone, suggesting a central brain site of action.

Given that PrPc deletion disrupted odor-guided behavior, the final question is raised of whether or not there are neural correlates of this behavioral change in the olfactory bulb. Using electrophysiological recordings, Le Pichon et al. demonstrated specific changes in local circuit function in the olfactory bulb in the PrPc knockouts. For example, using in vivo electrical stimulation to assay local circuit interneuron function, the authors found a decrease in inhibition of mitral cells by granule cell interneurons. This mitral cellgranule cell reciprocal interaction has been hypothesized to be important for everything from lateral inhibition to odor memory to state-dependent modulation of olfactory bulb function. Physiologically, activity in this local feedback circuit underlies high-frequency oscillations in olfactory bulb activity in response to odor stimulation. These olfactory bulb local field potential oscillations may facilitate temporal coding and/or binding of disparate odor features by target neurons in the olfactory cortex. Le Pichon et al. found that these odor-evoked high-frequency oscillations were abnormal in PrPc knockout mice.

The results suggest that PrPc may be important in local circuit function in the olfactory system and may in turn influence odor perception. There has been some debate over whether neural damage done by prion diseases is solely caused by the buildup of PrPsc or whether the concomitant loss of PrPc may also be involved. By demonstrating a systems-level effect of PrPc loss, Le Pichon et al. suggest that both may be important.

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

[The references cited in the text can be found by accessing the original text of tis report in Naute Neuroscinece using the URL at the beginining of the report. - Mod.CP]

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[6] CJD Update
Date 12 Dec 2008
Source: Health Protection Agency Report, Emerging Infections/CJD [abbreviated and edited]

<http://www.hpa.org.uk/hpr/infections/ei_cjd>.htm>

Creutzfeldt-Jakob disease (CJD) update report

This 6-monthly report provides an update on reports of incidents of potential iatrogenic (healthcare-acquired) exposure to CJD via surgery, and on the National Anonymous Tonsil Archive. Data are correct as of 5 Dec 2008. For numbers of CJD case reports, readers should consult data provided by the national CJD Surveillance Unit (NCJDSU), Edinburgh [1], and the ProMED-mail monthly Prion Disease Updates]. The latest yearly analysis of vCJD reports (onsets and deaths) is also available from the NCJDSU Web site [2], and the ProMED-mail monthly Prion Disease Update.

Reports of incidents of potential iatrogenic exposure to CJD via surgery: 1 Jan 2000 to 30 Jun 2008

There were a total of 350 incidents reported during this period (tabulated in the original text). 12 surgical incidents were reported between 1 Jan and 30 Jun 2008. A surgical incident occurs when a patient undergoes surgery but is only identified as having CJD or being at risk of CJD at a later date. (This means that the ACDP TSE Working Group infection control guidelines would not have been followed). The surgery carried out on an index patient with, or at risk of CJD, may result in contamination of the instruments with abnormal prion protein. (A table in the original text gives the number of CJD surgical incidents reported to the CJD Incidents Panel from January 2000 to June 2008 by the diagnosis of the index patient.)

Investigation of surgical incidents may result in advice to remove surgical instruments from clinical use (to quarantine, destroy, or donate for research). Such advice is generally only given for instruments considered to be potentially contaminated with the CJD agent that have not undergone a certain number of cycles of use and decontamination since their use on an index patient. Hospitals are asked to consider sending any instruments to be permanently removed from use to the Surgical Instrument Store (held by the Health Protection Agency, Porton Down) for research. In the 2nd half of 2007, there were no incidents in which instruments were permanently removed from use.

The Panel may advise contacting and informing some patients of their possible exposure to CJD in a surgical incident. Such advice is generally only given for patients who have definitely been exposed to potentially contaminated instruments which have been used on risk tissues in certain index patients. The Panel may advise that some of these patients should be considered "at-risk of CJD for public health purposes" and asked to take certain precautions (i.e., not to donate blood or other tissues and to inform their medical and dental carers prior to any invasive procedures) in order to reduce the risk of transmitting the CJD agent further. Since 2000, 20 incidents have given rise to such advice (tabulated in the original text). One of these incidents was reported in the 1st half of 2008. The Panel has so far categorised 64 patients as "at-risk"; 13 of whom died before notification. 3 patients have not been notified due to local, clinical decisions. (One index patient undergoing a cataract operation was also a blood component

recipient with evidence of vCJD infection.)

National anonymous tonsil archive for studies of detectable abnormal prion protein

The National Anonymous Tonsil Archive (NATA) continues to receive approximately 400 tonsil pairs per week. The archive had received a total of 67 696 tonsil pairs up to the end of October 2008 from hospitals in England and Scotland. A further 3000 tonsil pairs have been received from the Medical Research Council Prion Unit. Therefore the total number of tonsil pairs in the archive was 70 696.

Testing of homogenates of the tonsil tissue from the archive began at the end of January 2007. 2 enzyme immunoassays (EIAs) are being used for the initial screening of the homogenates for the presence of abnormal prion protein. These EIAs allow the identification of any tonsils that need to be investigated further by the more specific tests of Western blotting (WB) and immunohistochemistry (IHC) [4].

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別紙様式第2

別紙(2)-4

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日 2009年5月7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	乾燥濃縮人アンチトロンビンⅢ		研究報告の公表状況	Information about Newly Emerging 2009 H1N1 Influenza Virus and Blood Safety http://www.fda.gov/cber/flu/h1n1bldsafety.htm	公表国 米国	
販売名（企業名）	アンスロビンP-ベーリング（CSLベーリング株式会社）					

研究報告の概要

問題点（2009 年の新興の H1N1 型インフルエンザウイルス感染と血液の安全性）

米国で 2009 年に新興の H1N1 型インフルエンザウイルス感染が発生していて、このウイルスが輸血により感染するか疑問視されている。

米国や他の国において輸血による季節性インフルエンザが伝播した症例は報告がなく、現在まで輸血による H1N1 型インフルエンザウイルスの伝播の報告はない。FDA は継続して CDC と共同作業しており、またこのインフルエンザの発生と血液の安全性及び有用性に対するインパクトを監視するため、AABB のパンデミックインフルエンザ及び血液供給に関する組織間作業委員会と密接に連絡を取っている。今のところ、臨床上必要な場合、輸血のベネフィットが血液や血液製剤による H1N1 型インフルエンザウイルス伝播の理論的な危険性を含むリスクを上回ることを忘れないのが重要である。FDA の規制（FDA regulations at 21 CFR 640.3）において、健康でない人は献血には適していないし、血液事業者はこれらの潜在的な供血者の供血を保留しなければならない。

現在、血液事業者が実施している供血者スクリーニングにより、H1N1 型インフルエンザウイルスの症状を有する患者を同定すべきである。H1N1 型インフルエンザウイルスの人での症状は、通常のヒトインフルエンザと似ていて発熱、咳や喉の痛み、体の痛み、頭痛、寒気や疲労である。H1N1 型インフルエンザウイルスに関連した下痢や嘔吐の報告もある。メキシコや米国において重症化や死亡例が報告されている。現在実施している供血者スクリーニングは、特にヒトに H1N1 型インフルエンザが発生している地域での H1N1 型インフルエンザ伝播のリスクを減少する上で重要な手段である。さらに、良い衛生状態を維持する際に血液事業者が実施している標準的な手法や感染制御の手法は、血液事業における H1N1 型インフルエンザの起こりうる拡大を最小限にするのに役立つであろう。

2006 年 10 月の FDA ガイダンス" Biologic Product Deviation Reporting for Blood and Plasma Establishments"に従い、血液事業者は、供血者のインフルエンザ様疾患の供血後報告（a post donation report）が、既に収集された製品の適切性またはその供血者の将来の供血の適格性を評価すべきかを示していないか検討すべきである。さらに H1N1 型インフルエンザが同定された症例の国及び現地当局への通常の報告に加えて、インフルンザの輸血による伝播に関する懸念を引き起こす症例がある血液事業者は、州及び現地健康部門と同様に適切に"Therapeutics and Blood Safety Branch of the CBER Office of Biostatistics and Epidemiology"に電話する。

新興の 2009 年の H1N1 型インフルエンザウイルスはエンベロープを有する大きなウイルスである。製造販売業者が実施したバリデーションテストでは、現在の血液製剤の製造工程により類似ウイルスが不活化・除去されることが示されている。

報告企業の意見	今後の対応
本剤によるインフルエンザウイルス伝播の報告はない。 鳥インフルエンザウイルスが 60℃10 時間の液状加熱で不活化される報告があるため、本剤の製造工程でインフルエンザウイルスが不活化されると考えられる。	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

1.27

ABJ2009204

2009 H1N1 Flu Virus

Information about Newly Emerging 2009 H1N1 Influenza Virus and Blood Safety

I. Background

The ongoing outbreak of new emerging 2009 H1N1 Influenza Virus (H1N1 flu) infections in the United States has raised questions about whether this virus can be transmitted through blood transfusion. No case of transfusion transmitted seasonal influenza has ever been reported in the United States or elsewhere, and, to date, no cases of transfusion transmitted H1N1 flu have been reported. FDA is continuing to work with the Centers for Disease Control and Prevention (CDC) and is in close contact with the AABB Interorganizational Task Force on Pandemic Influenza and the Blood Supply to monitor this outbreak and its impact on blood safety and availability.

At this time, it is important to remember that, when clinically indicated, the benefits of a transfusion far outweigh the risks, including any theoretical risk of H1N1 flu transmission through blood or blood products.

II. Blood Safety Provisions

Donor Deferral

Under FDA regulations, individuals who are not in good health are not suitable to donate blood and blood establishments must defer these potential donors. (See FDA regulations at 21 CFR 640.3.) Blood donor screening procedures currently in place at blood establishments should identify persons with symptoms of H1N1 flu infection. The symptoms of H1N1 flu in people are similar to the symptoms of regular human influenza and include fever, cough, sore throat, body aches, headache, chills and fatigue. Some people have reported diarrhea and vomiting associated with H1N1 flu. Severe illness and deaths have been reported among infected individuals in Mexico and in the U.S.

The donor screening procedures in place today are important measures in reducing the theoretical risk of transfusion transmitted H1N1 flu, particularly in areas where human cases are occurring. In addition, the continued standard practice of blood establishments in maintaining good hygiene and infection control practices will help to minimize possible spread of H1N1 flu in blood establishments. Staff member hand washing between contacts with different donors is especially important.

Additional information on illness with H1N1 flu and general control strategies can be obtained at the Centers for Disease Control and Prevention (CDC) website at http://www.cdc.gov/swineflu/index.htm.

Potential Component Quarantine and Retrieval

Consistent with FDA's October 2006 Guidance on Biologic Product Deviation Reporting for Blood and Plasma Establishments (see http://www.fda.gov/cber/gdlns/devbld.htm) Medical Directors of blood establishments should consider whether a post donation report of a flu-like illness in a donor indicates that the previously collected products are unsuitable and that the donor's suitability for future donations should be assessed (e.g. deferral until well.) In addition to routine reporting of identified cases of H1N1 flu to state and local health departments, medical directors with any case

raising concerns regarding potential transfusion transmission of influenza, may contact us at the Therapeutics and Blood Safety Branch of the CBER Office of Biostatistics and Epidemiology at 301-827-3974, as well as the CDC via state and local health departments, as appropriate.

Safety of Plasma Derivatives

The newly emerging 2009 H1N1 Influenza Virus is a large lipid-enveloped virus. Validation studies performed by the product manufacturers have shown that viruses with similar characteristics to this agent are effectively inactivated and/or removed by the manufacturing processes in place for these products.

Return to 2009 H1N1 Flu Virus Main Page

Updated: April 30, 2009

別紙様式第2-1
番号5

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4月22日	新医薬品等の区分 該当なし	厚生労働省処理欄

一般的名称	①ポリエチレングリコール処理抗破傷風人免疫グロブリン ②乾燥抗破傷風人免疫グロブリン	研究報告の公表状況	CDC／MMWR 2009; 58(DISPATCH): 1-3	公表国 アメリカ
販売名 (企業名)	①テタノブリンーIH（ベネシス） ②テタノブリン（ベネシス）			

研究報告の概要

米カリフォルニア南部におけるブタインフルエンザA（H1N1）ウイルス感染症例2例および感染源特定などのため現在実施中の調査に関する報告である。

2009年4月17日，米CDCは，カリフォルニア南部の隣接する地区に居住する小児2例の熱性呼吸器疾患はブタインフルエンザA（H1N1）ウイルス感染が原因であると特定した。2例からのウイルスはアマンダジンとリマンダジンに抵抗性があり，米国およびその他の国でのブタインフルエンザ又はヒトインフルエンザウイルスにおいてこれまで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。両症例ともブタに接触していなかった。感染源は不明である。感染源を同定するために、他にブタインフルエンザウイルスで感染している人がいないか調査を現在進めている。

この報告は、この2症例と現在進行中の調査を簡潔に述べる。

ヒトにおけるインフルエンザAの新しいサブタイプではないが、ブタ・インフルエンザA(H1N1)の新しい株は、ヒト・インフルエンザA(H1N1)ウイルスとかなり相異する。かなりの人口が感染し、季節性インフルエンザワクチンH1N1株で予防できないかもしれない。

2症例ともブタに接触していないことは、この新しいインフルエンザウイルスのヒトーヒト感染が起こった可能性を大きくしている。

臨床医は、発熱性の呼吸疾患にかかっている以下に該当する患者の鑑別診断として、季節的なインフルエンザウイルス感染と同様に動物インフルエンザについても考慮すべきである。1）サンディエゴ郡およびインペリアル郡に居住する、2）これらの郡に旅行するかまたはこれらの疾患発症の7日前にこれらの郡から来た発症者と接触があった、3）ブタに最近接触した。

患者がブタインフルエンザに感染していることを推測する臨床医は、呼吸器検体を採取し、州の公共衛生研究所での検査を容易にするために国又は地方の衛生当局に連絡すべきである。

報告企業の意見	今後の対応
米カルフォルニア南部の小児2例の熱性呼吸器疾患はブタインフルエンザA（H1N1）ウイルスによるものであり、当該ウイルスにはブタ及びヒトインフルエンザウイルスでこれまで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とするCDCからの報告である。 インフルエンザA(H1N1)はオルソミクソウイルス科に属し、ビリオンは球形で、直径80～120nmの脂質エンベロープを有するRNAウイルスである。万一、インフルエンザA(H1N1)が原料血漿に混入したとしてもBVDをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程にて十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

代表としてテタノブリンーIHの記載を示す。

2. 重要な基本的注意

(1) 本剤の原材料となる血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体陰性で、かつALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の破傷風抗毒素を含有する血漿を原料として、Cohnの低温エタノール分画で得た画分からポリエチレングリコール4000処理、DEAEセファデックス処理等により抗破傷風人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びろ過膜処理（ナノフィルトレーション）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。

MMWR

Dispatch

April 21, 2009 / 58 (Dispatch);1-3

Swine Influenza A (H1N1) Infection in Two Children --- Southern California, March--April 2009

On April 17, 2009, CDC determined that two cases of febrile respiratory illness occurring in children who resided in adjacent counties in southern California were caused by infection with a swine influenza A (H1N1) virus. The viruses from the two cases are closely related genetically, resistant to amantadine and rimantadine, and contain a unique combination of gene segments that previously has not been reported among swine or human influenza viruses in the United States or elsewhere. Neither child had contact with pigs; the source of the infection is unknown. Investigations to identify the source of infection and to determine whether additional persons have been ill from infection with similar swine influenza viruses are ongoing. This report briefly describes the two cases and the investigations currently under way. Although this is not a new subtype of influenza A in humans, concern exists that this new strain of swine influenza A (H1N1) is substantially different from human influenza A (H1N1) viruses, that a large proportion of the population might be susceptible to infection, and that the seasonal influenza vaccine H1N1 strain might not provide protection. The lack of known exposure to pigs in the two cases increases the possibility that human-to-human transmission of this new influenza virus has occurred. Clinicians should consider animal as well as seasonal influenza virus infections in their differential diagnosis of patients who have febrile respiratory illness and who 1) live in San Diego and Imperial counties or 2) traveled to these counties or were in contact with ill persons from these counties in the 7 days preceding their illness onset, or 3) had recent exposure to pigs. Clinicians who suspect swine influenza virus infections in a patient should obtain a respiratory specimen and contact their state or local health department to facilitate testing at a state public health laboratory.

Case Reports

Patient A. On April 13, 2009, CDC was notified of a case of respiratory illness in a boy aged 10 years who lives in San Diego County, California. The patient had onset of fever, cough, and vomiting on March 30, 2009. He was taken to an outpatient clinic, and a nasopharyngeal swab was collected for testing as part of a clinical study. The boy received symptomatic treatment, and all his symptoms resolved uneventfully within approximately 1 week. The child had not received influenza vaccine during this influenza season. Initial testing at the clinic using an investigational diagnostic device identified an influenza A virus, but the test was negative for human influenza subtypes H1N1, H3N2, and H5N1. The San Diego County Health Department was notified, and per protocol, the specimen was sent for further confirmatory testing to reference laboratories, where the sample was verified to be an unsubtypable influenza A strain. On April 14, 2009, CDC received clinical specimens and determined that the virus was swine influenza A (H1N1). The boy and his family reported that the child had had no exposure to pigs. Investigation of potential animal exposures among the boy's contacts is continuing. The patient's mother had respiratory symptoms without fever in the first few days of April 2009, and a brother aged 8 years had a respiratory illness 2 weeks before illness onset in the patient and had a second illness with cough, fever, and rhinorrhea on April 11, 2009. However, no respiratory specimens were collected from either the mother or brother during their acute illnesses. Public health officials are conducting case and contact investigations to determine whether illness has occurred among other relatives and contacts in California, and during the family's travel to Texas on April 3, 2009.

Patient B. CDC received an influenza specimen on April 17, 2009, that had been forwarded as an unsubtypable influenza A virus from the Naval Health Research Center in San Diego, California. CDC identified this specimen as a swine influenza A (H1N1) virus on April 17, 2009, and notified the California Department of Public Health. The source of the specimen, patient B, is a girl aged 9 years who resides in Imperial County, California, adjacent to San Diego County. On March 28, 2009, she had onset of cough and fever (104.3°F [40.2°C]). She was taken to an outpatient facility that was participating in an influenza surveillance project, treated with amoxicillin/clavulanate

potassium and an antihistamine, and has since recovered uneventfully. The child had not received influenza vaccine during this influenza season. The patient and her parents reported no exposure to pigs, although the girl did attend an agricultural fair where pigs were exhibited approximately 4 weeks before illness onset. She reported that she did not see pigs at the fair and went only to the amusement section of the fair. The Imperial County Public Health Department and the California Department of Public Health are now conducting an investigation to determine possible sources of infection and to identify any additional human cases. The patient's brother aged 13 years had influenza-like symptoms on April 1, 2009, and a male cousin aged 13 years living in the home had influenza-like symptoms on March 25, 2009, 3 days before onset of the patient's symptoms. The brother and cousin were not tested for influenza at the time of their illnesses.

Epidemiologic and Laboratory Investigations

As of April 21, 2009, no epidemiologic link between patients A and B had been identified, and no additional cases of infection with the identified strain of swine influenza A (H1N1) had been identified. Surveillance data from Imperial and San Diego counties, and from California overall, showed declining influenza activity at the time of the two patients' illnesses. Case and contact investigations by the county and state departments of health in California and Texas are ongoing. Enhanced surveillance for possible additional cases is being implemented in the area.

Preliminary genetic characterization of the influenza viruses has identified them as swine influenza A (H1N1) viruses. The viruses are similar to each other, and the majority of their genes, including the hemagglutinin (HA) gene, are similar to those of swine influenza viruses that have circulated among U.S. pigs since approximately 1999; however, two genes coding for the neuraminidase (NA) and matrix (M) proteins are similar to corresponding genes of swine influenza viruses of the Eurasian lineage (*1*). This particular genetic combination of swine influenza virus segments has not been recognized previously among swine or human isolates in the United States, or elsewhere based on analyses of influenza genomic sequences available on GenBank.* Viruses with this combination of genes are not known to be circulating among swine in the United States; however, no formal national surveillance system exists to determine what viruses are prevalent in the U.S. swine population. Recent collaboration between the U.S. Department of Agriculture and CDC has led to development of a pilot swine influenza virus surveillance program to better understand the epidemiology and ecology of swine influenza virus infections in swine and humans.

The viruses in these two patients demonstrate antiviral resistance to amantadine and rimantadine, and testing to determine susceptibility to the neuraminidase inhibitor drugs oseltamivir and zanamivir is under way. Because these viruses carry a unique combination of genes, no information currently is available regarding the efficiency of transmission in swine or in humans. Investigations to understand transmission of this virus are ongoing.

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Editorial Note:

In the past, CDC has received reports of approximately one human swine influenza virus infection every 1--2 years in the United States (*2,3*). However, during December 2005--January 2009, 12 cases of human infection with swine influenza were reported; five of these 12 cases occurred in patients who had direct exposure to pigs, six in patients reported being near pigs, and the exposure in one case was unknown (*1,4,5*). In the United States, novel influenza A virus infections in humans, including swine influenza infections, have been nationally notifiable conditions since 2007. The recent increased reporting might be, in part, a result of increased influenza testing capabilities in public health laboratories, but genetic changes in swine influenza viruses and other factors also might be a factor (*1,4,5*). Although the vast majority of human infections with animal influenza viruses do not result in human-to-human

transmission (*2,3*), each case should be fully investigated to be certain that such viruses are not spreading among humans and to limit further exposure of humans to infected animals, if infected animals are identified. Such investigations should include close collaboration between state and local public health officials with animal health officials.

The lack of known exposure to pigs in the two cases described in this report increases the possibility that human-to-human transmission of this new influenza virus has occurred. Clinicians should consider animal as well as seasonal influenza virus infections in the differential diagnosis of patients with febrile respiratory illness who live in San Diego and Imperial counties or have traveled to these areas or been in contact with ill persons from these areas in the 7 days before their illness onset. In addition, clinicians should consider animal influenza infections among persons with febrile respiratory illness who have been near pigs, such as attending fairs or other places where pigs might be displayed. Clinicians who suspect swine influenza virus infections in humans should obtain a nasopharyngeal swab from the patient, place the swab in a viral transport medium, and contact their state or local health department to facilitate transport and timely diagnosis at a state public health laboratory. CDC requests that state public health laboratories send all influenza A specimens that cannot be subtyped to the CDC, Influenza Division, Virus Surveillance and Diagnostics Branch Laboratory.

Interim guidance on infection control, treatment, and chemoprophylaxis for swine influenza is available at http://www.cdc.gov/flu/swine/recommendations.htm. Additional information about swine influenza is available at http://www.cdc.gov/flu/swine/index.htm.

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研究報告の概要

○中国においてブタがヒト様H1N1インフルエンザウイルスに感染しているさらなるエビデンス
典型的ブタおよびトリ様H1N1インフルエンザウイルスは世界中のブタから数多く報告されているが、ヒト様H1N1ブタ・ウイルスの報告は少ない。2006年にヒト様H1N1ブタ・ウイルス(A/swine/Guangdong/96/06)が広東省のブタから分離されたが、これは中国で初めての報告であった。ブタにおけるヒト様H1N1インフルエンザウイルス感染の更なる証拠を得るため、中国で分離された3つのヒト様ブタH1N1ウイルス(A/swine/Guangdong/96/06、A/swine/Tianjin/01/04、A/swine/Henan/01/06)の8つの遺伝子セグメントを分析した。3ウイルスにおける8つの遺伝子セグメントは、いずれも、最近(2000年頃)および早期(1980年代)のヒトH1N1インフルエンザウイルスと高い相同性を示した。系統発生解析では、A/Swine/Guangdong/96/06は、2000年頃のヒトH1N1インフルエンザウイルスに直接由来し、他のウイルス2種は、1980年代に循環したヒトH1N1ウイルスに由来すると考えられることが判明した。我々の分離株(A/swine/Guangdong/96/06)の血清陽性率から、中国のブタにヒト様H1N1ウイルスが存在することが確認された。これらインフルエンザウイルス(特に過去のウイルスであるA/swine/Tianjin/01/04とA/swine/Henan/01/06)の存在は、ヒト様H1N1インフルエンザウイルスがブタにおいて長期間不変でいることを示しており、ブタがヒト・パンデミックを引き起こす古いインフルエンザウイルスの保有宿主である証拠を示している。

報告企業の意見	今後の対応
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・パンデミックを引き起こす古いインフルエンザウイルスの保有宿主である証拠が示されたとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、問診で発熱などの体調不良者を献血不適としている。更に、平成21年5月18日付薬食血発第0518001号「新型インフルエンザの国内発生に係る血液製剤の安全性確保について」に基づき、新型インフルエンザの患者又は罹患の疑いのある患者と7日以内に濃厚な接触があった人の献血を制限するほか、献血後に新型インフルエンザと診断された場合には当該製剤の回収と医療機関への情報提供を行うこととしている。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

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Further evidence for infection of pigs with human-like H1N1 influenza viruses in China

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ABSTRACT

Classical swine and avian-like H1N1 influenza viruses were reported widely in swine population worldwide, but human-like H1N1 swine viruses were reported occasionally. In 2006, a human-like H1N1 swine virus (A/swine/Guangdong/96/06) was isolated from pigs in Guangdong province, which was reported in China for the first time. To get further evidence for infection of pigs with human-like H1N1 influenza viruses, we analyzed eight gene segments of three human-like swine H1N1 viruses (A/swine/Guangdong/96/06, A/swine/Tianjin/01/04 and A/swine/Henan/01/06) isolated in China. All the eight genes of the three viruses are highly homologous to recent (about 2000) and early (1980s) human H1N1 influenza viruses, respectively. Phylogenetic analyses revealed that A/Swine/Guangdong/96/06 was directly derived from about 2000 human H1N1 influenza viruses, while A/swine/Tianjin/01/04 and A/swine/Henan/01/06 seemed to be descendants of human H1N1 viruses circulating in 1980s. Seroprevalence of our isolate (A/swine/Guangdong/96/06) confirmed the presence of human-like H1N1 virus in pigs in China. Existence of these influenza viruses, especially older viruses (A/swine/Tianjin/01/04 and A/swine/Henan/01/06), indicates that human-like H1N1 influenza viruses may remain invariant for long periods in pigs and provides the evidence that pigs serve as reservoirs of older influenza viruses for human pandemics.

1. Introduction

Swine influenza is an acute respiratory disease caused by influenza A virus within the Orthomyxoviridae family. The primary clinical manifestations of viral infection are fever and acute respiratory distress. Currently, three main subtypes of influenza viruses are circulating in the swine population throughout the world: subtypes H1N1, H3N2 and H1N2 (Brown, 2000). These include classical swine H1N1, avian-like H1N1, human-like or avian-like H3N2, reassortant H3N2 and various genotype H1N2 viruses (Brown, 2000; Qi and Lu, 2006; Webby et al., 2000). These viruses have remained largely endemic in pig populations worldwide and have been responsible for one of most prevalent respiratory diseases in pigs.

China, especially southern China, is regarded as an epicenter of pandemic influenza viruses throughout history (Shortridge and Stuart-Harris, 1982). The tracheal epithelium in pigs expresses receptors for both human and avian influenza viruses, and this provides a biological basis for the susceptibility of pigs to both avian and human influenza viruses (Ito et al., 1998; Peiris et al., 2001). Pi can therefore function as intermediate hosts or "mixing vessels" in establishing new influenza virus lineages by supporting coinfection, replication, and reassortment among human, avian, and swine influenza viruses (Brown, 2000; Landolt et al., 2003). In the past, a number of influenza viruses have been isolated from pigs in China. These mainly include classical swine H1N1 viruses, avian-like H1N1 viruses, human-like H3N2 viruses, double-reassortant H3N2 viruses containing genes from the human and avian influenza viruses, triple-reassortant H3N2 viruses containing genes from the human, classical swine and avian viruses, avian-like H9N2 viruses, and double-reassortant H1N2 virus containing genes similar to those of human and swine viruses (Guan et al., 1996; Peiris et al., 2001; Shortridge and Webster, 1979; Xu et al., 2004; Yu et al., 2008a,b).

Human H1N1 viruses can infect pigs and pig-to-pig transmission has been demonstrated under experimental conditions (Brown, 2000). Serological surveillance studies worldwide suggest that the prevailing human H1N1 strains are readily transmitted to pigs and

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have resulted occasionally in the isolation of virus (Katsuda et al., 1995; Nerome et al., 1982; Yu et al., 2007). In 2006, a human-like H1N1 swine virus (A/swine/Guangdong/96/06) was isolated from pigs in Guangdong province, which was reported by us in China for the first time (Yu et al., 2007). To get further evidence for infection of pigs with human-like H1N1 influenza viruses, we made full use of our isolate and another two human-like H1N1 swine influenza viruses isolated and sequenced by scientists of Huazhong Agricultural University of China, and we analyzed their genetic evolution. In this study, we summarize and report, for the fist time, the coexistence of recent (about 2000) human-like and early (1980s) human-like swine H1N1 influenza viruses in pigs in China.

2. Materials and methods

2.1. Viruses

A/swine/Guangdong/96/06(H1N1) was isolated from pigs in a farm of Guangdong province of southern China, by inoculation into and subsequent passage in the allantoic cavity of 10-day-old SPF embryonated chicken eggs (Yu et al., 2007). Viral gene sequencing was carried out as follows. In brief, viral RNA was directly extracted from infected allantoic fluids using RNeasy Mini Kit (Qiagen, Chatsworth, CA) and reverse transcription (RT) were carried out under standard conditions using Uni12 (AGCAAAAGCAGG) primer. PCR was performed using specific primers for eight genes (primer sequences are available on request). PCR products were purified with the QIA quick PCR purification Kit (Qiagen, Inc.) and cloned into pMD18-T vector (TaKaRa, Dalian), then sequenced using synthetic oligonucleotides by Invitrogen Company.

In addition, A/swine/Tianjin/01/04(H1N1) and A/swine/Henan/01/06(H1N1) were isolated and sequenced by scientists of Huazhong Agricultural University of China. The nucleotide sequences were made available in GenBank under accession numbers: EU004440-EU004455.

2.2. Serum samples of pigs

From 2006 to 2007, we carried out swine influenza virus surveillance in China, a total of a total of 717 serum samples were randomly collected from apparently healthy pigs from nine provinces (Heilongjiang, Henan, Shandong, Zhejiang, Anhui, Jiangxi, Guangdong, Guangxi and Beijing).

2.3. Sequence analysis

All eight-gene segments of these three H1N1 swine influenza viruses were characterized and phylogenetically together with the representative sequence data available in GenBank. Sequence data were compiled and edited by using the Lasergene sequence analysis software package (DNASTAR Inc., Madison, WI). Multiple sequence alignment was carried out by using CLUSTAL W, and the unrooted phylogenetic trees were generated by the distance-based neighbor-joining method using MEGA 3.1. Bootstrap values were calculated on 1000 replicates of the alignment.

2.4. Serology tests

All sera were pretreated with the "Trypsin-Heat-Periodate" method to abolish interference by nonspecific serum inhibitors and used for hemagglutination inhibition (HAI) tests using chicken erythrocytes (World Health Organization, 2002). Neutralization tests were carried out by mixing 100 50% tissue culture infective doses of the virus with serial dilutions of serum and incubating for 2 h followed by inoculation onto MDCK cells grown in 96-well microtiter plates. After adsorption of the virus–serum mixture for 2 h, the inoculum was removed and fresh serum-free tissue culture medium containing trypsin (2 μg/ml) was added. Complete neutralization of cytopathic effect (read under an inverted microscope) was considered evidence of neutralizing antibody (Peiris et al., 2001; World Health Organization, 2002).

3. Results

3.1. Homology analysis of nucleotide sequences

Analysis of the homology of nucleotide sequences of eight genes of our isolate (A/swine/Guangdong/96/06) and another two isolates (A/swine/Tianjin/01/04 and A/swine/Henan/01/06) was performed by comparison with sequences available in GenBank (Table 1). All eight-gene segments of A/swine/Guangdong/96/06 were similar to H1N1 influenza viruses circulating in human in 2000 or 2001, with homologies ranging from 98.8 to 99.6%. But interestingly, A/swine/Tianjin/01/04 and A/swine/Henan/01/06 were closely related to human H1N1 viruses isolated in 1980s, with homologies ranging from 98.2 to 100%.

3.2. Phylogenetic relationship of H1N1 swine influenza viruses from China

In the swine influenza virus surveillance in eight provinces (Heilongjiang, Henan, Shandong, Guangdong, Zhejiang, Anhui, Jiangxi, and Beijing) during 2005–2006, one human-like H1N1 influenza virus (A/swine/Guangdong/96/06) was isolated from pigs, which was reported in China for the first time (Yu et al., 2007). Recently, the sequences of two human-like H1N1 swine viruses (A/swine/Tianjin/01/04 and A/swine/Henan/01/06) were published in GenBank. To characterize the gene segments of the three human-like H1N1 influenza viruses from pigs more precisely, we constructed the phylogenetic trees using the nucleotide sequences of the HA, NA, PB1, PB2, PA, NP, M and NS genes available in GenBank and the information from the trees was analyzed.

Phylogenetic analysis of the HA gene reveals that all of the H1N1 swine viruses isolated in China can be separated into three lineages, including human strains, classical swine strains and avian strains (Fig. 1). Previously most of the H1N1 swine influenza viruses, isolated in China, belong to classical swine or avian lineage. Classical swine lineage mainly includes A/swine/Guangdong/711/01, A/swine/Hong Kong/273/94, A/swine/Beiing/47/91, A/swine/Hong Kong/172/93 and so on. A/swine/Hong Kong/168/93 and A/swine/Hong Kong/176/93, had emerged in China, belong to avian lineage. A/swine/Guangdong/96/06, A/swine/Tianjin/01/04 and A/swine/Henan/01/06 are incorporated into the human lineage. Our isolate (A/swine/Guangdong/96/06) was closely related to A/Dunedin/2/00, while A/swine/Tianjin/01/04 and A/swine/Henan/01/06 were derived from A/Memphis/12/86.

Phylogenetic analyses of NA, PB1, PB2, PA (Fig. 2), NP, M and NS (data not shown) genes showed a clear division of each of these genes into different lineages including classical swine lineage, human lineage and avian lineage, similar to the HA gene. A/swine/Guangdong/96/06, A/swine/Tianjin/01/04 and A/swine/Henan/01/06 belong to human lineage in the seven phylogenetic trees. Because of the lack of sequence data of swine H1N1 influenza viruses isolated in China, these genes of classical swine lineage and avian lineage of China were not analyzed.

Based on the phylogenetic trees and homology of the nucleotide sequence of gene segments of the three viruses, A/Swine/Guangdong/96/06 was directly derived from about 2000 human H1N1 influenza viruses. But A/swine/Tianjin/01/04 and A/swine/Henan/01/06 seemed to be descendants of human H1N1 viruses circulating in 1980s.

Table 1
Genetic homology of the human-like swine influenza viruses isolated in China with related sequences available in GenBank.

Viruses	Gene	Virus with the highest identity	Identity (%)	GenBank accession no.
A/swine/Guangdong/96/06	HA	A/Dunedin/2/00(H1N1)	99.6	CY011584
	NA	A/Canterbury/43/00(H1N1)	99.4	CY010094
	PB1	A/New York/233/00(H1N1)	99.2	CY002646
	PB2	A/New York/443/01(H1N1)	99.4	CY003479
	PA	A/New York/443/01(H1N1)	99.1	CY003477
	NP	A/New York/234/00(H1N1)	99.3	CY002651
	M	A/New York/443/01(H1N1)	98.8	CY003473
	NS	A/New York/443/01(H1N1)	99.0	CY003476
A/swine/Tianjin/01/04	HA	A/Suita/1/89(H1N1)	99.0	D13573
	NA	A/Yamagata/120/86(H1N1)	99.1	D31948
	PB1	A/Singapore/6/86(H1N1)	99.8	CY020483
	PB2	A/New York/2924-1/86(H1N1)	99.6	CY021740
	PA	A/Fiji/15899/83(H1N1)	100.0	AJ605762
	NP	A/New York/2924-1/86(H1N1)	99.2	CY021736
	M	A/Singapore/6/86(H1N1)	98.4	CY020478
	NS	A/Chile/1/83/(H1N1)	98.2	X15282
A/swine/Henan/01/06	HA	A/Suita/1/89(H1N1)	98.9	D13573
	NA	A/Singapore/6/86(H1N1)	99.6	CY020479
	PB1	A/Singapore/6/86(H1N1)	99.9	CY020483
	PB2	A/New York/2924-1/86(H1N1)	99.3	CY021740
	PA	A/New York/2924-1/86(H1N1)	99.5	CY021738
	NP	A/New York/2924-1/86(H1N1)	99.2	CY021736
	M	A/Singapore/6/86(H1N1)	99.8	CY020478
	NS	A/Chile/1/83/(H1N1)	98.3	X15282

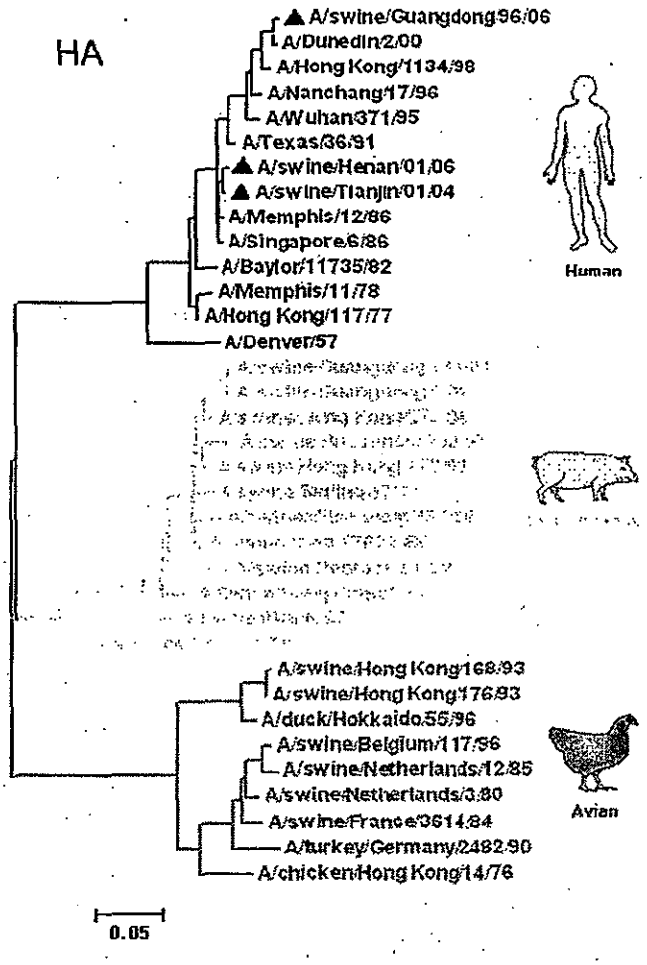

Fig. 1. Phylogenetic tree of the HA (positions 84–1061) gene of the H1N1 influenza viruses. The unrooted phylogenetic tree was generated by the distance-based neighbor-joining method using MEGA 3.1. Reliability of the tree was assessed by bootstrap analysis with 1000 replications, only bootstraps values >90% were shown. Different lineages are marked with different colors.

3.3. Molecular analysis

To try to identify possible determinants of interspecies transmission of H1N1 influenza viruses from human to pigs, the deduced amino acid sequences of HA1 region were aligned. The proposed antigenic sites (Caton et al., 1982; Lubeck and Gerhard, 1981; Olsen et al., 1993), receptor-binding sites (Nobusawa et al., 1991) and potential glycosylation sites were analyzed (Fig. 3).

Antigenic sites are regions of molecules involved in antibody binding and four sites (Sa, Sb, Ca and Cb) of H1N1 influenza virus have been defined (Caton et al., 1982; Wiley et al., 1981). A/swine/Guangdong/96/06 and A/Dunedin/2/00 have the same amino acids in antigenic sites, while A/swine/Tianjin/01/04, A/swine/Henan/01/06 and A/Memphis/12/86 also have the same amino acids in antigenic sites, which indicate these three viruses may have the similar antigenicity to rece (about 2000) and early (1980s) human H1N1 influenza virus respectively.

The host range of influenza A viruses is associated with differences in specificity of HA for attachment to sialic acid-containing receptors on susceptible cells. So the receptor-binding property of the HA protein of influenza virus is an important molecular determent of host-range restrictions (Matrosovich et al., 2000; Weis et al., 1988). The amino acids at positions 91, 131–135, 150, 180, 187, 191, 192, and 221–226 (98, 134–138, 153, 183, 190, 194, 195, and 224–229 according to H3 number) are components of receptor-binding sites of the HA of H1N1 influenza viruses (Nobusawa et al., 1991). The three human-like H1N1 swine influenza viruses and the two reference human viruses (A/Dunedin/2/00 and A/Memphis/12/86) had the same amino acids at Y^{91}, G^{131}, V^{132}, A^{134}, S^{135}, W^{150}, T^{152}, H^{180}, Y^{192}, R^{221}, Q^{223}, E^{224}, G^{225}, and R^{226} (receptor-binding sites). At position 133, the three swine influenza viruses and A/Dunedin/2/00 had the same amino acids (S). At position187, A/swine/Tianjin/01/04 and A/swine/Henan/01/06 had the unique amino acid (E). The two amino acids of the three human-like swine influenza viruses at positions 191 and 222 were identical to A/Dunedin/2/00 and A/Memphis/12/86, respectively.

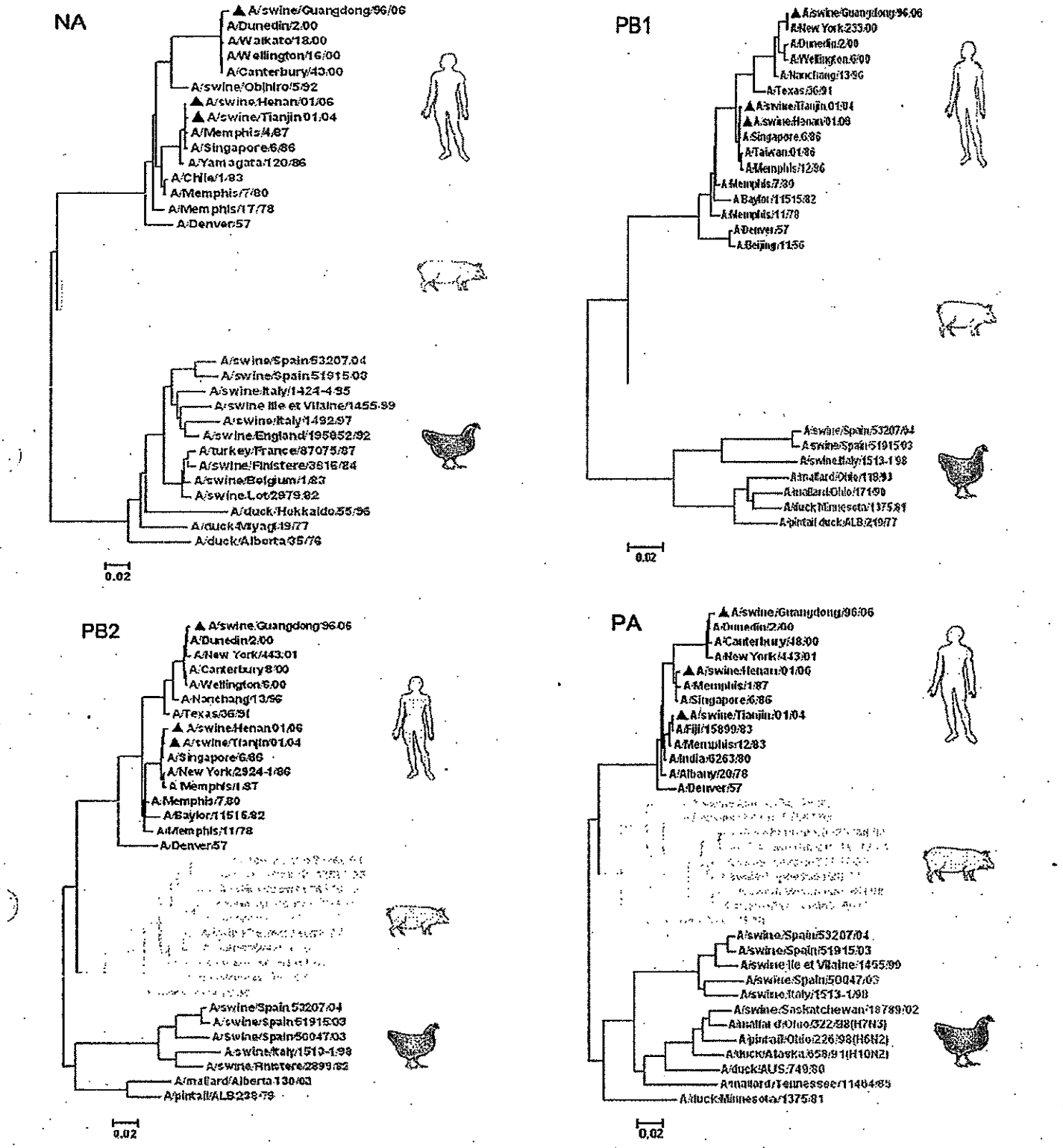

Fig. 2. Phylogenetic trees of the NA (positions 93–1415), PB1 (positions 14–2286), PB2 (positions 52–2295) and PA (positions 40–2175) genes of the H1N1 influenza viruses. The method used is as given in the legend of Fig. 1. Different lineages are marked with different colors.

Some glycosylation sites have a significant effect on receptor-binding property of the influenza virus HA protein, and glycosylation is therefore an important process in the generation of new virus (Schulze, 1997). Eight potential glycosylation sites (N-X-S/T) were conserved at positions 10, 11, 23, 54, 87, 125, 160, and 287 in the HA1 protein of the three human-like H1N1 swine influenza viruses and the two reference human viruses.

3.4. Seroprevalence of the human-like H1N1 influenza viruses in swine populations of China

The isolation and genetic characterization of human-like H1N1 influenza viruses in pigs suggested that these viruses might form a stable lineage in swine populations in China. So we conducted a serological surveillance to get some useful information about

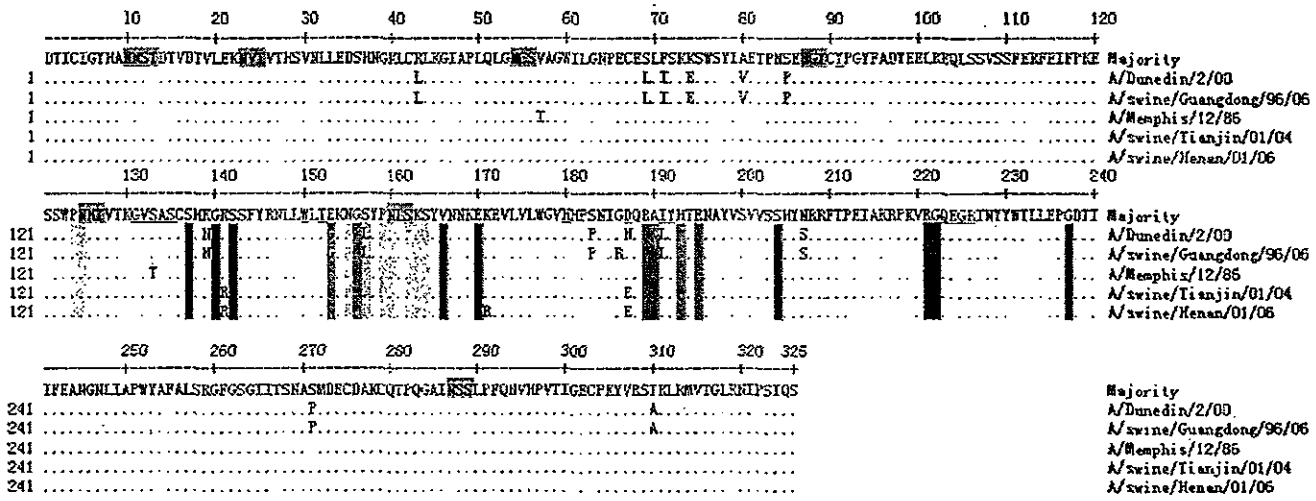

Fig. 3. Molecular analysis of HA1 amino acid sequences of the three H1N1 swine influenza viruses and reference strains. Potential glycosylation sites are marked with pink shade. Previously defined antigenic sites are indicated: site Sa (green shade), site Sb (red shade), site Ca (blue shade), site Cb (yellow shade). Underlined residues are receptor-binding sites. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 2
Seroprevalene of the human-like H1N1 influenza virus in swine populations of China.[a]

Province or city	Number of sera collected	HAI positive rate (%)	NT positive rate[b] (%)
Henan	68	17.6	11.8
Shandong	123	5.7	0
Heilongjiang	54	3.7	0
Zhejiang	92	7.6	6.5
Anhui	30	0	0
Jiangxi	44	4.5	2.3
Beijing	38	7.9	5.3
Guangxi	110	9.1	6.4
Guangdong	158	20.8	13.9

[a] HAI and neutralization positives were taken as titers of 1/80 or more.
[b] NT, neutralization test.

seroprevalence of the human-like H1N1 influenza viruses in swine populations of China. A collection of 717 pig serum samples from nine provinces in China was analyzed in HAI and neutralization tests for the presence of antibody to human-like H1N1 swine influenza virus (A/swine/Guangdong/96/06) (Table 2). Serological surveillance results indicated that the human-like H1N1 swine influenza virus might sporadically infect pigs in China. In the HAI test antibody to A/swine/Guangdong/96/06 was detected with prevalence ranging from 0 to 20.8%, while in the neutralizing test antibody to the H1N1 virus was relatively low with prevalence ranging from 0 to 13.9%.

4. Discussion

Influenza virus infection is an important cause of respiratory disease among pigs throughout the swine producing regions of the world (Karasin et al., 2000). Swine influenza was first observed in 1918 at the time of the human pandemic and the virus was isolated and identified in 1930 by shope (Brown, 2000; Shope, 1931). This virus was the prototype strain of a group of viruses now known as classical swine influenza viruses. Virologic and serological surveillance has shown that classical swine H1N1 is prevalent throughout the major pig population of the world (Brown, 2000; Chambers et al., 1991; Guan et al., 1996; Hinshaw et al., 1978). Since 1979, classical swine influenza viruses have been replaced by avian-like H1N1 viruses that are antigenically distinguishable from classical swine H1N1 viruses in Europe. Human H1N1 viruses can infect pigs and pig-to-pig transmission has been demonstrated under experimental conditions. Serological surveillance studies worldwide suggest that the prevailing human H1N1 strains are readily transmitted to pigs (Brown, 2000), but there are a few reports about isolation of the human-like swine H1N1 viruses. In China, classical swine H1N1 viruses were the predominant influenza virus infecting pigs and circulated in pigs in China in northern, central (Henan and Jiangxi), and southern (Guizhou and Guangdong) provinces (Guo et al., 1992). Since 1993, avian-like swine influenza viruses had been isolated from pigs and circulated with classical H1N1 viruses (Guan et al., 1996). In 2006, human-like swine H1N1 influenza viruses were reported by us for the first time. In this study, we summarized and reported coexistence of recent (about 2000) and early (1980s) human-like swine H1N1 influenza viruses, which provides further evidence for infection of pigs with human-like H1N1 influenza viruses in China.

Serological surveillance had indicated that classical swine H1 and human-like H3 subtype influenza infections widely existed in the pig populations in China, and avian H4, H5 and H9 influenza viruses had been transmitted to pig populations in southeastern China (Li et al., 2004; Ninomiya et al., 2002). No type of swine influenza vaccine has been used in pigs in China, and therefore the serological surveillance of human-like H1N1 swine influenza viruses conducted in this study could reflected the real situation of swine influenza infection. In this study, a total of 717 pig serum samples from nine provinces in China were detected in HAI and neutralization tests for the presence of antibody to human-like H1N1 swine influenza virus (A/swine/Guangdong/96/06). In the HAI test antibody to A/swine/Guangdong/96/06 was detected with prevalence ranging from 0 to 20.8%, while in the neutralizing test antibody to the H1N1 virus as relatively low with prevalence ranging from 0 to 13.9%. All these indicated that the human-like H1N1 swine influenza virus might sporadically infect pigs in China.

Influenza virus genomes are well known to undergo antigenic drift or antigenic shift that enable escape from preexisting immunity and cause new outbreaks of influenza in animals and even humans (Chi et al., 2005; Potter, 2001; Subbarai and Joseph, 2007), so influenza viruses exhibit the greatest genetic diversity and change every year. In this study, we analyzed eight gene segments of three human-like swine H1N1 viruses (A/swine/Guangdong/96/06, A/swine/Tianjin/01/04 and A/swine/Henan/01/06) isolated in China. Why were all the eight genes of the three viruses closely related to recent (about 2000) or early (1980s) human H1N1 influenza viruses? A possible explanation may be that these influenza viruses were introduced into

pigs at the time they circulated in humans and have persisted in pigs without antigenic drift. In China, Pigs have a short lifespan (approximately 6 months) and are not inoculated any type of swine influenza vaccine. Once the influenza viruses were introduced into pigs, these viruses might appear to have been under less immune selection pressure and all genes evolved more slowly than in humans and poultry. We describe here genetic relatedness of these swine isolates with recent (about 2000) or early (1980s) human H1N1 influenza viruses and provide evidence of long term conservation of human H1N1 influenza viruses in pigs.

Of the four pandemic strains of human influenza A virus occurred in the 20th century, the 1977 pandemic strain was very similar in all eight genes to a 1950 human H1N1 strain (Kilbourne, 2006). Therefore, pandemic strains of influenza A virus could arise by re-emergence of these older viruses that may have caused an epidemic many years earlier. In this study, we phylogenetically analyzed eight gene segments of three human-like H1N1 influenza viruses isolated from pigs in China. A/Swine/Guangdong/96/06 was directly derived from about 2000 human H1N1 influenza viruses. But A/swine/Tianjin/01/04 and A/swine/Henan/01/06 seemed to be descendants of human H1N1 viruses circulating in 1980s, which owed the possibility that pigs serve as reservoirs for older influenza viruses.

China, especially Southern China, is thought to be the epicenter for the human influenza pandemics throughout history (Shortridge and Stuart-Harris, 1982). The special environment and lifestyle in southern China provide more chances for wild aquatic birds, domestic poultry, pigs and humans to contact closely, and create the opportunity for interspecies transmission and generation of new reassortment influenza viruses. Although, it is virtually impossible to prevent new outbreaks of influenza in human and animals, it is now well recognized that animal influenza virus surveillance can play a key role in the early recognition of outbreak threats. So it is of great significance to carry out swine influenza virus surveillance. Existence of these influenza viruses, especially older viruses (A/swine/Tianjin/01/04 and A/swine/Henan/01/06), in pigs provides the evidence that pigs serve as reservoirs of older influenza viruses for human pandemics and emphasizes the importance of reinforcing swine influenza virus surveillance in China.

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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 2009年７月22日	第一報入手日 2009年4月25日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	ヘパリンナトリウム	研究報告の公表状況	http://www.who.int/csr/don/2009_04_24/en/index.html http://www.who.int/csr/don/2009_04_27/en/index.html http://www.who.int/mediacentre/news/statements/2009/h1n1_20090427/en/index.html	公表国 米国		
販売名（企業名）	ヘパリンナトリウム注1万単位/10mL「味の素」 ヘパリンナトリウム注5万単位/50mL「味の素」 ヘパリンナトリウム注10万単位/100mL「味の素」 ヘパリンナトリウム注N5千単位/5mL「味の素」 ヘパリンナトリウム注N1万単位/10mL「味の素」					

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研究報告の概要

米国、メキシコにおけるインフルエンザ様疾患について（2009.4.24　WHO EPR サイト）

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人がカリフォルニア、2人がテキサス）と９人の疑いがある症例を報告した。確定症例７人は、１例のみ短期入院を要したが、いずれも軽度のインフルエンザ様疾患であり、死亡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た。メキシコ連邦区における調査で、3月18日からインフルエンザ様疾患の症例が挙がり始めた。4月中に症例数は確実に増え、4月23日までに854人以上の肺炎が首都圏で発生している。うち、59人は死亡している。メキシコ中部のSan Luis Potosiでは24人のインフルエンザ様疾患が発生し、3人が死亡と報告されている。また、米国国境近くのMexicaliからは、4人のインフルエンザ様疾患（死亡例はなし）が報告されている。メキシコの症例では、18例がカナダの研究機関で豚インフルエンザA/H1N1であることが確認されており、そのうち12症例はカリフォルニアの豚インフルエンザA/H1N1ウイルスと遺伝学的に一致している。

これらの症例は主に若年健常人に発生している。インフルエンザは、通常幼児か高齢者が罹患するが、メキシコではこの年齢層に大きな影響が出ていない。人の症例が動物インフルエンザウイルスに関連していること、地理的に離れた多地域で発生していること、さらに通常見られない年齢層が罹患していることにより、これらの事例は非常に危惧される。

今回流行した豚インフルエンザA/H1N1ウイルスはこれまでに豚やヒトから検出されていない。このウイルスは少なくともオセルタミビルには感受性を示すが、アマンタジンとリマンタジンには耐性を示している。

豚インフルエンザ　update３（2009.4.27　WHO EPRサイト）

最近の豚インフルエンザA(H1N1)の発生状況は刻々と変化している。2009.4.27現在、米国政府は、40症例（死亡例なし）で人への豚インフルエンザ（H1N1）感染を確認したと報告した。メキシコは、7症例の死亡を含む同ウイルスへの感染を26症例で確認したと報告した。スペインが1症例（死亡例なし）、カナダは、6症例（死亡例なし）を報告した。

豚インフルエンザ　（2009.4.27　WHO Media centre サイト）

国際保健規則（2005年）にのっとり設立した緊急委員会が2009年４月27日、２回目となる会合を開催した。

委員会は米国、メキシコ、カナダで確認された豚インフルエンザA/H1N1型の発生について入手可能なデータを検討した。また、ほかの国への感染拡大可能性の報告についても検討された。

委員会の助言を基に、WHOの事務局長は次のように決定した。

インフルエンザの大流行についてのパンデミックアラートを現行のフェーズ３からフェーズ４に引き上げる。引き上げは大流行の危険性が高まったことを示すが、大流行は不可避ではない。さらなる情報によっては、WHOはパンデミックアラートをフェーズ３に戻すか、より高度な水準へ引き上げることを決定するかもしれない。引き上げの決定は、第一に疫学的データが人から人への感染を示すこと、また地域レベルでの感染を引き起こすウイルスである可能性があることに基づいてなされた。

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	
豚由来のインフルエンザA/H1N1が人に感染し、感染拡大を示唆する報告、人において死亡する恐れがある報告、及びインフルエンザA/H1N1が人から人に感染することが示されたとの報告。既知の感染症であるが、発生頻度の増加、感染症の重大性、新たに人から人へ感染することが示された点から研究報告に該当すると判断する。 弊社ヘパリンナトリウム製剤は、ウイルス不活性能力が高いと考えられる工程を経て製造を行っている。 現時点で特別な安全対策を講じる必要はないと考える。	今後も情報収集に努める。	

Influenza-like illness in the United States and Mexico

24 April 2009 -- The United States Government has reported seven confirmed human cases of Swine Influenza A/H1N1 in the USA (five in California and two in Texas) and nine suspect cases. All seven confirmed cases had mild Influenza-Like Illness (ILI), with only one requiring brief hospitalization. No deaths have been reported.

The Government of Mexico has reported three separate events. In the Federal District of Mexico, surveillance began picking up cases of ILI starting 18 March. The number of cases has risen steadily through April and as of 23 April there are now more than 854 cases of pneumonia from the capital. Of those, 59 have died. In San Luis Potosi, in central Mexico, 24 cases of ILI, with three deaths, have been reported. And from Mexicali, near the border with the United States, four cases of ILI, with no deaths, have been reported.

Of the Mexican cases, 18 have been laboratory confirmed in Canada as Swine Influenza A/H1N1, while 12 of those are genetically identical to the Swine Influenza A/H1N1 viruses from California.

The majority of these cases have occurred in otherwise healthy young adults. Influenza normally affects the very young and the very old, but these age groups have not been heavily affected in Mexico.

Because there are human cases associated with an animal influenza virus, and because of the geographical spread of multiple community outbreaks, plus the somewhat unusual age groups affected, these events are of high concern.

The Swine Influenza A/H1N1 viruses characterized in this outbreak have not been previously detected

Alert & Response Operations

Diseases

Global Outbreak Alert & Response Network

Biorisk Reduction

confirmed cases and one mild influenza-like illness (ILI) with only one requiring brief hospitalization. No deaths have been reported.

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Because there are human cases associated with an animal influenza virus, and because of the geographical spread of multiple community outbreaks, plus the somewhat unusual age groups affected, these events are of high concern.

The Swine Influenza A/H1N1 viruses characterized in this outbreak have not been previously detected in pigs or humans. The viruses so far characterized have been sensitive to oseltamivir, but resistant to both amantadine and rimantadine.

The World Health Organization has been in constant contact with the health authorities in the United States, Mexico and Canada in order to better understand the risk which these ILI events pose. WHO (and PAHO) is sending missions of experts to Mexico to work with health authorities there. It is helping its Member States to increase field epidemiology activities, laboratory diagnosis and clinical management. Moreover, WHO's partners in the Global Alert and Response Network have been alerted and are ready to assist as requested by the Member States.

WHO acknowledges the United States and Mexico for their proactive reporting and their collaboration with WHO and will continue to work with Member States to further characterize the outbreak.

27 April 2009

Swine influenza - update 3

27 April 2009 -- The current situation regarding the outbreak of swine influenza A(H1N1) is evolving rapidly. As of 27 April 2009, the United States Government has reported 40 laboratory confirmed human cases of swine influenza A(H1N1), with no deaths. Mexico has reported 26 confirmed human cases of infection with the same virus, including seven deaths. Canada has reported six cases, with no deaths, while Spain has reported one case, with no deaths.

Further information on the situation will be available on the WHO website on a regular basis.

WHO advises no restriction of regular travel or closure of borders. It is considered prudent for people who are ill to delay international travel and for people developing symptoms following international travel to seek medical attention, in line with guidance from national authorities.

There is also no risk of infection from this virus from consumption of well-cooked pork and pork products. Individuals are advised to wash hands thoroughly with soap and water on a regular basis and should seek medical attention if they develop any symptoms of influenza-like illness.

Related links

Swine influenza web site
Daily updates will be posted on this site.

Statement by WHO Director-General, Dr Margaret Chan
27 April 2009

Swine influenza

The Emergency Committee, established in compliance with the International Health Regulations (2005), held its second meeting on 27 April 2009.

The Committee considered available data on confirmed outbreaks of A/H1N1 swine influenza in the United States of America, Mexico, and Canada. The Committee also considered reports of possible spread to additional countries.

On the advice of the Committee, the WHO Director-General decided on the following.

- The Director-General has raised the level of influenza pandemic alert from the current phase 3 to phase 4.

  The change to a higher phase of pandemic alert indicates that the likelihood of a pandemic has increased, but not that a pandemic is inevitable.

  As further information becomes available, WHO may decide to either revert to phase 3 or raise the level of alert to another phase.

  This decision was based primarily on epidemiological data demonstrating human-to-human transmission and the ability of the virus to cause community-level outbreaks.

- Given the widespread presence of the virus, the Director-General considered that containment of the outbreak is not feasible. The current focus should be on mitigation measures.

Related links

Swine influenza

Current WHO phase of pandemic alert

International Health Regulations (IHR)

(2005), held its second meeting on 27 April 2009.

News
Events
Fact sheets
Multimedia
Contacts

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Swine influenza

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  This decision was based primarily on epidemiological data demonstrating human-to-human transmission and the ability of the virus to cause community-level outbreaks.

- Given the widespread presence of the virus, the Director-General considered that containment of the outbreak is not feasible. The current focus should be on mitigation measures.

- The Director-General recommended not to close borders and not to restrict international travel. It was considered prudent for people who are ill to delay international travel and for people developing symptoms following international travel to seek medical attention.

- The Director-General considered that production of seasonal influenza vaccine should continue at this time, subject to re-evaluation as the situation evolves. WHO will facilitate the process needed to develop a vaccine effective against A(H1N1) virus.

- The Director-General stressed that all measures should conform with the purpose and scope of the International Health Regulations.

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5月7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	乾燥濃縮人アンチトロンビンⅢ		研究報告の公表状況	Information about Newly Emerging 2009 H1N1 Influenza Virus and Blood Safety http://www.fda.gov/cber/flu/h1n1bldsafety.htm	公表国 米国	
販売名（企業名）	アンスロビンP-ベーリング（CSLベーリング株式会社）					

研究報告の概要 148

問題点（2009 年の新興の H1N1 型インフルエンザウイルス感染と血液の安全性）

米国で 2009 年に新興の H1N1 型インフルエンザウイルス感染が発生していて、このウイルスが輸血により感染するか疑問視されている。

米国や他の国において輸血による季節性インフルエンザが伝播した症例は報告がなく、現在まで輸血による H1N1 型インフルエンザウイルスの伝播の報告はない。FDA は継続して CDC と共同作業しており、またこのインフルエンザの発生と血液の安全性及び有用性に対するインパクトを監視するため、AABB のパンデミックインフルエンザ及び血液供給に関する組織間作業委員会と密接に連絡を取っている。今のところ、臨床上必要な場合、輸血のベネフィットが血液や血液製剤による H1N1 型インフルエンザウイルス伝播の理論的な危険性を含むリスクを上回ることを忘れないのが重要である。FDA の規制（FDA regulations at 21 CFR 640.3）において、健康でない人は献血には適していないし、血液事業者はこれらの潜在的な供血者の供血を保留しなければならない。

現在、血液事業者が実施している供血者スクリーニングにより、H1N1 型インフルエンザウイルスの症状を有する患者を同定すべきである。H1N1 型インフルエンザウイルスの人での症状は、通常のヒトインフルエンザと似ていて発熱、咳や喉の痛み、体の痛み、頭痛、寒気や疲労である。H1N1 型インフルエンザウイルスに関連した下痢や嘔吐の報告もある。メキシコや米国において重症化や死亡例が報告されている。現在実施している供血者スクリーニングは、特にヒトに H1N1 型インフルエンザが発生している地域での H1N1 型インフルエンザ伝播のリスクを減少する上で重要な手段である。さらに、良い衛生状態を維持する際に血液事業者が実施している標準的な手法や感染制御の手法は、血液事業における H1N1 型インフルエンザの起こりうる拡大を最小限にするのに役立つであろう。

2006 年 10 月の FDA ガイダンス" Biologic Product Deviation Reporting for Blood and Plasma Establishments"に従い、血液事業者は、供血者のインフルエンザ様疾患の供血後報告（a post donation report）が、既に収集された製品の適切性またはその供血者の将来の供血の適格性を評価すべきかを示していないか検討すべきである。さらに H1N1 型インフルエンザが同定された症例の国及び現地当局への通常の報告に加えて、インフルンザの輸血による伝播に関する懸念を引き起こす症例がある血液事業者は、州及び現地健康部門と同様に適切に"Therapeutics and Blood Safety Branch of the CBER Office of Biostatistics and Epidemiology"に電話する。

新興の 2009 年の H1N1 型インフルエンザウイルスはエンベロープを有する大きなウイルスである。製造販売業者が実施したバリデーションテストでは、現在の血液製剤の製造工程により類似ウイルスが不活化・除去されることが示されている。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
本剤によるインフルエンザウイルス伝播の報告はない。 鳥インフルエンザウイルスが 60℃10 時間の液状加熱で不活化される報告があるため、本剤の製造工程でインフルエンザウイルスが不活化されると考えられる。	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。

ABJ20092704

2009 H1N1 Flu Virus

Information about Newly Emerging 2009 H1N1 Influenza Virus and Blood Safety

I. Background

The ongoing outbreak of new emerging 2009 H1N1 Influenza Virus (H1N1 flu) infections in the United States has raised questions about whether this virus can be transmitted through blood transfusion. No case of transfusion transmitted seasonal influenza has ever been reported in the United States or elsewhere, and, to date, no cases of transfusion transmitted H1N1 flu have been reported. FDA is continuing to work with the Centers for Disease Control and Prevention (CDC) and is in close contact with the AABB Interorganizational Task Force on Pandemic Influenza and the Blood Supply to monitor this outbreak and its impact on blood safety and availability.

At this time, it is important to remember that, when clinically indicated, the benefits of a transfusion far outweigh the risks, including any theoretical risk of H1N1 flu transmission through blood or blood products.

II. Blood Safety Provisions

Donor Deferral

Under FDA regulations, individuals who are not in good health are not suitable to donate blood and blood establishments must defer these potential donors. (See FDA regulations at 21 CFR 640.3.) Blood donor screening procedures currently in place at blood establishments should identify persons with symptoms of H1N1 flu infection. The symptoms of H1N1 flu in people are similar to the symptoms of regular human influenza and include fever, cough, sore throat, body aches, headache, chills and fatigue. Some people have reported diarrhea and vomiting associated with H1N1 flu. Severe illness and deaths have been reported among infected individuals in Mexico and in the U.S.

The donor screening procedures in place today are important measures in reducing the theoretical risk of transfusion transmitted H1N1 flu, particularly in areas where human cases are occurring. In addition, the continued standard practice of blood establishments in maintaining good hygiene and infection control practices will help to minimize possible spread of H1N1 flu in blood establishments. Staff member hand washing between contacts with different donors is especially important.

Additional information on illness with H1N1 flu and general control strategies can be obtained at the Centers for Disease Control and Prevention (CDC) website at http://www.cdc.gov/swineflu/index.htm.

Potential Component Quarantine and Retrieval

Consistent with FDA's October 2006 Guidance on Biologic Product Deviation Reporting for Blood and Plasma Establishments (see http://www.fda.gov/cber/gdlns/devbld.htm) Medical Directors of blood establishments should consider whether a post donation report of a flu-like illness in a donor indicates that the previously collected products are unsuitable and that the donor's suitability for future donations should be assessed (e.g. deferral until well.) In addition to routine reporting of identified cases of H1N1 flu to state and local health departments, medical directors with any case

raising concerns regarding potential transfusion transmission of influenza, may contact us at the Therapeutics and Blood Safety Branch of the CBER Office of Biostatistics and Epidemiology at 301-827-3974, as well as the CDC via state and local health departments, as appropriate.

Safety of Plasma Derivatives

The newly emerging 2009 H1N1 Influenza Virus is a large lipid-enveloped virus. Validation studies performed by the product manufacturers have shown that viruses with similar characteristics to this agent are effectively inactivated and/or removed by the manufacturing processes in place for these products.

Return to 2009 H1N1 Flu Virus Main Page

Updated: April 30, 2009

別紙様式第 2－1

NNPL2009-infl002

医薬品 研究報告 調査報告書

識別番号・報告回数	非該当	非該当	報告日 非該当	第一報入手日 非該当	新医薬品等の区分 非該当	総合機構処理欄
一般的名称	エプタコグアルファ(活性型)(遺伝子組換え)		研究報告の公表状況	CIDRAP News, 2009 年 4 月 24 日	公表国 米国	
販売名(企業名)	注射用ノボセブン 1.2mg 注射用ノボセブン 4.8mg					

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
研究報告の題名： インフルエンザ A ウイルス(H1N1)-ブタ・ヒト 器官別大分類： 感染症および寄生虫症／基本語： インフルエンザ 2009 年 4 月 24 日、CDC は、メキシコでの致死的な呼吸器疾患発生例から得た検体は、米国の患者からのブタインフルエンザ株と一致したと発表した。	【使用上の注意の記載状況】 感染症発現については、記載なし。 感染症に対する安全対策については、冒頭に記載あり。 【その他参考事項】 ブタ皮由来ゼラチンについては今回の調査期間後の一部変更承認によって、新たに感染症定期報告対象の成分となっており、次回より感染症定期報告を行なう。

報告企業の意見	今後の対応
本剤は製造工程においてブタ膵臓由来トリプシンおよびブタ皮由来ゼラチンを使用しているが、本剤の製造工程においてはウイルスの不活化及び除去を目的とした精製を施す等、感染症に対する安全対策を講じていることから、ブタ膵臓由来トリプシンおよびブタ皮由来ゼラチンを経由して本剤にインフルエンザウイルス(H1N1)が混入する可能性は極めて低いものと考える。	今後とも感染症情報の収集に努めるとともに、必要に応じて本剤の安全対策に関する検討を行なう。

NNPL2009－infl002

Archive Number 20090425.1557
Published Date 25-APR-2009
Subject PRO/AH/EDR> Influenza A (H1N1) virus, human - N America (02)

INFLUENZA A (H1N1) VIRUS, HUMAN - NORTH AMERICA (02)
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A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

Update:
[1] and [2] Strain identity
[3] Pandemic warning
[4] Outbreak in NY ?

******
[1] Strain identity
Date: Fri 24 Apr 2009
Source: CIDRAP News [edited]
<http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/news/apr2409swine.h

Labs confirm same swine flu in deadly Mexican outbreaks

Samples from a deadly respiratory illness outbreak in Mexico match swine influenza isolates from patients in the United States who had milder illnesses, an official from the US Centers for Disease Control and Prevention (CDC) said today [24 Apr 2009], fueling speculation that the World Health Organization (WHO) could be on the verge of raising the global pandemic alert level. Richard Besser, MD, CDC's acting director, told reporters today during a press teleconference that the development is worrisome. "Our concern has grown since yesterday, based on what we've learned," he said. "We do not know if this will lead to the next pandemic, but our scientists are monitoring it and take the threat very seriously."

The swine flu A/H1N1 strain has been confirmed in one more US citizen, a child from San Diego who has recovered, raising the total number of US cases to 8, Besser said. The virus contains gene segments from 4 different influenza types: North American swine, North American avian, human, and Eurasian swine.

WHO said today that Mexican officials have reported 3 separate events. In the Federal District, the number of cases rose steadily through April, and as of yesterday, more than 854 cases of pneumonia, 59 of them fatal, had been reported in Mexico City. The illness outbreak in Mexico City prompted the country's health minister, Jose Cordova, to cancel classes in Mexico City today and advise students and adults to avoid crowded public places and large events, Bloomberg News reported. Mexican officials also reported 24 cases with 3 deaths from an influenza-like illness in San Luis Potosi, in the central part of the country, and 4 cases with no deaths in Mexicali, near the US border, WHO reported.

The virus in Mexico has primarily struck otherwise healthy young adults, WHO said, which is a departure from seasonal influenza, which typically affects the very young and very old. CDC's laboratory analyzed 14 samples from severely ill Mexican patients and found that 7 of them had the same swine flu mix as the virus that infected the US patients. Besser called the analysis preliminary, however, and said that CDC doesn't yet have enough information to draw conclusions. "We still don't have enough information

about the extent of the spread or the illness spectrum." WHO said today that Canada's national laboratory has confirmed swine flu A/H1N1 in 18 isolates from Mexican patients, 12 of which were genetically identical to the swine flu viruses from California.

WHO and CDC both said they were sending representatives to Mexico to assist local authorities, and WHO said it has alerted its Global Alert and Response Network. Besser said that WHO will likely convene an expert panel to discuss raising the pandemic alert level from 3 (human infection with new influenza subtype with only rare human-to-human spread) to 4 (small clusters with localized human-to-human transmission). He said the experts will consider 3 factors: the novelty of the virus, disease severity, and how easily transmission of the virus is sustained. Global health officials might consider a containment strategy such as dispatching antiviral medications to affected parts of Mexico in an attempt to stop the spread of the virus, but Besser said that such a measure might not work, because there are signs that the virus has already spread from human to human over long distances. "A focused, well defined area is not something we've seen here," he said. CDC officials have said the swine flu A/H1N1 virus is susceptible to the newer antivirals oseltamivir (Tamiflu) and zanamivir (Relenza), but not the older ones, amantadine and rimantadine. Jeff McLaughlin, a spokesman for GlaxoSmithKline, the maker of Relenza, told CIDRAP News that the company is watching the swine flu developments closely. Terry Hurley, a spokesman for Roche, which produces Tamiflu, said its "rapid response stockpile" is on 24-hour standby, as usual, for deployment to WHO, which has not yet requested it.

The threat from the swine flu virus serves as a reminder for individuals and businesses to think about their own level of preparedness, Besser said. "This is a time for people to be thinking about that teachable moment." So far, federal officials have not changed their travel recommendations to California, Texas, or Mexico, though they have issued an advisory about the increased health risk in certain parts of Mexico, urging travelers to take standard precautions such hand washing, staying home when sick, and using good coughing and sneezing hygiene.

[byline: Lisa Schnirring]

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communicated by:
ProMED-mail
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[The "swine" influenza A(H1N1) virus associated with current outbreaks of respiratory illness in the southern region of the USA and in Mexico appears to be a complex reassortant containing genome components from avian, human, and swine virus sources. Such a virus is unique and it is too early to conclude that this virus has originated in swine.

According to the CDC website (<http://www.cdc.gov/swineflu/>) swine influenza (swine flu) is a respiratory disease of pigs caused by type A influenza viruses that regularly cause outbreaks of influenza among pigs. Swine flu viruses do not normally infect humans; however, human infections with swine flu do occur, and cases of human-to-human spread of swine flu viruses has been documented. From December 2005 through February 2009, a total of 12 human infections with swine influenza were reported from 10 states in the United States. Since March 2009, a number of confirmed human cases of the new strain of swine influenza A (H1N1) virus infection in California, Texas, and Mexico have been identified.

Whatever the origin of the current outbreak virus it is likely that the designation swine influenza virus will stick. - Mod.CP]

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[2] Strain identity
Date: Fri 24 Apr 2009
Source: CBC News [abbreviated and edited]
<http://www.cbc.ca/health/story/2009/04/24/health-flu-mexico090424.html>

Canadian lab confirms human swine flu cases in Mexico

"Today we have received results which confirm that the virus is human swine influenza," Leona Aglukkaq told a press conference in Ottawa, Ontario, Canada. A handful of cases of flu-like illness in Canadian residents who recently returned from Mexico are being monitored; however, "there have been no confirmed cases of human swine influenza yet" here, said Dr David Butler-Jones, Canada's chief public health officer.

Mexico sent 51 specimens for testing to Canada's National Microbiology Laboratory on Wednesday [21 Apr 2009]. 16 positives of swine flu were found among the samples. Mexican health minister Jose Angel Cordova said on Friday that 20 people were killed in the outbreak and 1004 were infected throughout the country, prompting WHO to convene an emergency meeting on Saturday. Officials closed schools, museums and libraries in Mexico City on Friday to limit spread of the virus.

Dr Rich Besser, acting head of the US Centers for Disease Control (CDC), said early analysis of Mexican samples of the virus showed it is very similar to those responsible for 8 American cases, one confirmed on Friday. All the US victims have recovered. Canada is working with Mexican and US health officials to confirm that the virus in both countries is linked and is in fact a new strain of influenza A H1N1 human swine virus, he added.

"This is an interesting virus. It's a brand new virus, not only to humans but to the world," said Dr Frank Plummer, scientific director of the Winnipeg lab. "About 80 per cent of the virus is highly related to a North American body [?] of swine flu that's been around for a number of years, but about 20 per cent of it comes from an Eurasian variety of swine flu 1st seen in Thailand, so it's recombined [re-assorted ?] to create something totally new. How it did that, where it did it, when it did it, I don't think we know yet."

CDC said the current strain of swine flu includes genetic material from 4 sources: North American swine influenza viruses, North American avian influenza viruses, human influenza virus, and swine influenza viruses found in Asia and Europe -- a new combination that has not been recognized anywhere in the world before. There appears to be human-to-human spread in both the US and Mexico over a wide geographic area at this point, but investigators are still checking for direct contact with swine.

WHO spokesperson Gregory Hartl said the agency needs to determine whether the outbreaks constitute an international public health threat. Hartl also said 12 of 18 samples taken from victims in Mexico showed the virus had a genetic structure identical to that of the virus found in California earlier this week. But he said the agency needs more information before it changes its pandemic alert level, which currently stands at 3 on a scale of one to 6. The virus was 1st reported earlier this week as US health officials scrambled to deal with the diagnoses of 7 people with the never-before-seen strain in Texas and California. The states share a border with Mexico not far from a town where 2 deaths were reported.

Hartl said health officials are dealing with 3 separate events in Mexico, with most of the cases in and around the capital, Mexico City. Most of the cases have occurred in healthy young adults, he added. "Because these cases are not happening in the very old or the very young, which is normal with seasonal influenza, this is an unusual event and a cause for heightened concern," Hartl said in an interview from WHO headquarters in Geneva. It is also rare to see such high flu activity so late in the season, he said. "The end of April, especially in a place like Mexico, you would think that we would see quite a steep decline," said Hartl.

On Thursday [23 Apr 2009], Canadian health officials issued advice warning travellers who have recently returned from Mexico to be on alert for flu-like symptoms that could be connected to the illness.

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[3] *Pandemic warning*
Date: Sat 25 Apr 2009
Source: MSNBC [edited]
<http://www.msnbc.msn.com/id/30398682>

Health officials prepare for swine flu "pandemic"

A new swine flu strain that has killed as many as 68 people and sickened more than 1000 across Mexico has "pandemic potential," the WHO chief said on Saturday [25 Apr 2009], and it may be too late to contain the sudden outbreak. CDC has stepped up surveillance across the United States. "We are worried," said CDC's Dr Anne Schuchat. "We don't think we can contain the spread of this virus," said Schuchat, interim deputy director for the Science and Public Health Program. "We are likely to find it in many other places." Because cases have been detected in California, Texas, and in several sites in Mexico, officials now must work to detect infections and reduce their severity, if possible. "It's time to prepare, time to think ahead and to be prepared for some uncertainty," she told reporters in a telephone briefing on Saturday.

Two dozen new suspected cases were reported Saturday [25 Apr 2009] in Mexico City alone. Schools were closed and all public events suspended in the capital until further notice -- including more than 500 concerts and other gatherings in the metropolis of 20 million. A hot line fielded 2366 calls in its 1st hours from frightened city residents who suspected they might have the disease. Soldiers and health workers handed out masks at subway stops, and hospitals dealt with crowds of people seeking help.

WHO's director-general, Margaret Chan, said the outbreak of the never-before-seen virus is a very serious situation and has "pandemic potential". But she said it is still too early to tell if it would become a pandemic. "The situation is evolving quickly," Chan said in a telephone news conference in Geneva. "A new disease is by definition poorly understood. "This virus is a mix of human, pig, and bird strains that prompted the WHO to meet Saturday to consider declaring an international *public health emergency -- a step that could lead to travel advisories*, trade restrictions and border closures. Spokesman Gregory Hartl said a decision would not be made on Saturday.

Scientists have warned for years about the potential for a pandemic from viruses that mix genetic material from humans and animals. Another reason to worry is that authorities said the dead so far don't include vulnerable infants and elderly. The Spanish flu pandemic, which killed at least 40 million people worldwide in 1918-19, also 1st struck otherwise healthy young adults. This swine flu and regular flu can have similar symptoms -- mostly fever, cough, and sore throat, though some of the US victims who recovered also experienced vomiting and diarrhea. But unlike with regular flu, humans don't have natural immunity to a virus that includes animal genes -- and new vaccines can take months to bring into use.

But experts at WHO and CDC say the nature of this outbreak may make containment impossible. Already, more than 1000 people have been infected in as many as 14 of Mexico's 32 states, according to daily newspaper El Universal. Tests show 20 people have died of the swine flu, and 48 other deaths were probably due to the same strain.

CDC and Canadian health officials were studying samples sent from Mexico, and airports around the world were screening passengers from Mexico for symptoms of the new flu strain, saying they may quarantine passengers. But CDC officials dismissed the idea of trying that in the United States. They noted there had been no direct contact between the cases in the San Diego and San Antonio areas, suggesting the virus had already spread from one geographic area through other undiagnosed people. "Anything that would be about containing it right now would purely be a political move," said Michael Osterholm, a University of Minnesota pandemic expert.

Mexican President Felipe Calderon said his government only discovered the

nature of the virus late on Thursday, with the help of international laboratories. "We are doing everything necessary," he said in a brief statement. But the government had said for days that its growing flu caseload was nothing unusual, so the sudden turnaround angered many who wonder if Mexico missed an opportunity to contain the outbreak.

Across Mexico's capital, residents reacted with fatalism and confusion, anger, and mounting fear at the idea that their city may be ground zero for a global epidemic. Authorities urged people to stay home if they feel sick and to avoid shaking hands or kissing people on the cheeks.

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[4] Suspected outbreak in New York
Date: Fri 24 Apr 2009
Source: WCBS TV News [edited]
<http://wcbstv.com/health/swine.flu.nyc.2.994071.html>

Possible swine flu outbreak at NYC prep school

New York City health officials say that about 75 students at a Queens high school have fallen ill with flu-like symptoms and testing is under way to rule out the strain of swine flu that has killed dozens in Mexico. The Health Department's Dr Don Weiss said on Friday [24 Apr 2009] that a team of agency doctors and investigators were dispatched to the private St Francis Preparatory School the previous day after students reported fever, sore throat, cough, aches, and pains. No one has been hospitalized.

The handful of sick students who remained at the school were tested for a variety of flu strains. If they're found to have a known human strain that would rule out swine flu. Results could take several days. In the meantime, the school says it's postponing an evening event and sanitizing the building over the weekend.

Mexican authorities said 60 people may have died from a swine flu virus in Mexico, and world health officials worry it could unleash a global flu epidemic. Mexico City closed schools, museums, libraries, and state-run theaters across the metropolis on Friday in hopes of containing the outbreak that has sickened more than 900. The US Centers for Disease Control and Prevention (CDC) said tests show some of the Mexico victims died from the same new strain of swine flu that sickened 8 people in Texas and California. It's a frightening new strain that combines genetic material from pigs, birds and humans.

WHO was looking closely at the 60 deaths -- most of them in or near Mexico's capital. It wasn't yet clear what flu they died from, but spokesman Thomas Abraham said "We are very, very concerned. We have what appears to be a novel virus and it has spread from human to human," he said. "It's all hands on deck at the moment."

WHO raised its internal alert system on Friday, preparing to divert more money and personnel to dealing with the outbreak. President Felipe Calderon cancelled a trip and met with his Cabinet to coordinate Mexico's response. The government has 500 000 flu vaccines and planned to administer them to health workers, the highest risk group. There are no vaccines available for the general public in Mexico, and authorities urged people to avoid hospitals unless they had a medical emergency, since hospitals are centers of infection. Some Mexican residents have started wearing blue surgical masks for extra protection, reports CBS News correspondent Adrienne Bard. The federal health minister has warned people not to go near anyone with a

respiratory infection and to avoid kissing -- a traditional Mexican greeting.

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communicated by:
ProMED-mail rapporteur Mary Marshall

[If infection by the novel swine flu virus is confirmed, it will represent a dramatic extension of the range of the outbreak virus from the southern states and Mexico to the north east of the United States. There is no reason to conclude at present, however, that this is anything other than an outbreak of seasonal influenza virus infection (or for that matter another common respiratory virus). - Mod.CP]

[see also:
Influenza A (H1N1) virus, swine, human - N America 20090425.1552
Acute respiratory disease - Mexico, swine virus susp 20090424.1546
Influenza A (H1N1) virus, swine, human - USA (02): (CA, TX) 20090424.1541
Influenza A (H1N1) virus, swine, human - USA: (CA) 20090422.1516
Influenza A (H1N1) virus, swine, human - Spain 20090220.0715
2008

Influenza A (H1N1) virus, swine, human - USA (TX) 20081125.3715
2007

Influenza A (H2N3) virus, swine - USA 20071219.4079
2006

Influenza, swine, human - USA (IA): November 2006 20070108.0077]

.....cp/ejp/sh

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研究報告の概要

CDC は過去のワクチン研究で集めた保存血清サンプルを用いて、2005～06 年、2006～07 年、2007～08 年あるいは 2008～09 年の季節性インフルエンザワクチンの接種前後の小児および成人コホートにおける新型インフルエンザ A ウイルスと交差反応を起こす抗体量をマイクロ中和（MN）法及び赤血球凝集抑制（HI）法により評価した。
その結果、ワクチン接種前では、新型インフルエンザ A ウイルスとの交差反応を起こす抗体量は小児の間では存在しなかった。ワクチン接種前の成人では、18-64 歳で 6-9%、60 歳以上で 33%の人に交差反応を起こす抗体が検出された。
過去にどの 4 種類の 3 価の季節性不活化インフルエンザワクチン又は弱毒化生インフルエンザワクチンの小児への接種において、新型インフルエンザ A との交差反応を起こす抗体産生反応を引き出せなかった。成人では、季節性不活化ワクチンの接種は新型インフクエンザ A(H1N1)と交差反応を起こす抗体産生反応は 18-64 歳では 2 倍に増加させた（季節性の H1N1 に対しての交差反応性抗体産生反応は 12-19 倍増加）。60 歳以上では新型インフルエンザ A と交差反応を起こす抗体産生反応の増加は見られなかった。これらのデータは、最近(2005 年～2009 年)の季節性インフルエンザワクチンは新型インフルエンザ A に対する感染防御抗体反応を起こしそうもないことを示唆する。

報告企業の意見

60 歳以上の人の 33%で新型インフルエンザ A に対する抗体が検出されたこと及び季節性インフルエンザワクチンの接種では小児及び 60 歳以上の人では抗体産生が得られず、成人においても抗体産生が 2 倍の増加にとどまったとする報告である。
インフルエンザ A (H1N1) はオルソミクソウイルス科に属するビリオンは球形で、直径 80～120nm の脂質エンベロープを有する比較的大きな RNA ウイルスである。万一、インフルエンザ A (H1N1) が原料血漿に混入したとしても BVD をモデルウイルスとしたウイルスバリデーション試験成績から、製造工程にて十分に不活化・除去されると考えている。

今後の対応

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。

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Weekly May 22, 2009 / Vol. 58 / No. 19

Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine

As of May 19, 2009, a total of 5,469 confirmed or probable cases* of human infection with a novel influenza A (H1N1) virus had been documented in 47 states and the District of Columbia (*1,2*). In addition, the virus had spread to 41 countries (*3*), with a total of 4,774 cases reported in countries outside the United States. Because producing a novel influenza A (H1N1) virus vaccine will take several months (*4*), determining whether receipt of seasonal influenza vaccine might offer any protection against the novel influenza A (H1N1) virus is important. Therefore, using stored serum specimens collected during previous vaccine studies, CDC assessed the level of cross-reactive antibody to the novel influenza A (H1N1) virus in cohorts of children and adults before and after they had been vaccinated with the 2005–06, 2006–07, 2007–08, or 2008–09 influenza season vaccines. The results indicated that before vaccination, no cross-reactive antibody to the novel influenza A (H1N1) virus existed among children. Among adults, before vaccination, cross-reactive antibody was detected in 6%–9% of those aged 18–64 years and in 33% of those aged >60 years. Previous vaccination of children with any of four seasonal trivalent, inactivated influenza vaccines (TIV) or with live, attenuated influenza vaccine (LAIV) did not elicit a cross-reactive antibody response to the novel influenza A (H1N1) virus. Among adults, vaccination with seasonal TIV resulted in a twofold increase in cross-reactive antibody response to the novel influenza A (H1N1) virus among those aged 18–64 years, compared with a twelvefold to nineteenfold increase in cross-reactive antibody response to the seasonal H1N1 strain; no increase in cross-reactive antibody response to the novel influenza A (H1N1) virus was observed among adults aged >60 years. These data suggest that receipt of recent (2005–2009) seasonal influenza vaccines is unlikely to elicit a protective antibody response to the novel influenza A (H1N1) virus.

Serum specimens were provided to CDC from academic, government, and industry partners for use as part of the public health response to the emergence of the novel influenza A (H1N1) virus. The specimens had been collected from healthy human participants, with written, informed consent. All participants had been vaccinated either 1) intramuscularly with licensed TIV developed for the northern hemisphere 2005–06, 2006–07, 2007–08, or 2008–09 influenza seasons or 2) intranasally with licensed LAIV developed for the northern hemisphere 2005–06 or 2006–07 influenza seasons. The serum specimens were grouped for influenza serology testing by the age of participants and formulation of the vaccines.

Microneutralization (MN) and hemagglutination inhibition (HI) assays were performed at CDC, according to standard MN and HI procedures (*5,6*). As with vaccine production, the seasonal influenza A (H1N1) viruses used in this study (A/New Caledonia/20/1999 [2005–06 and

* Case definitions available at http://www.cdc.gov/h1n1flu/casedef.htm.

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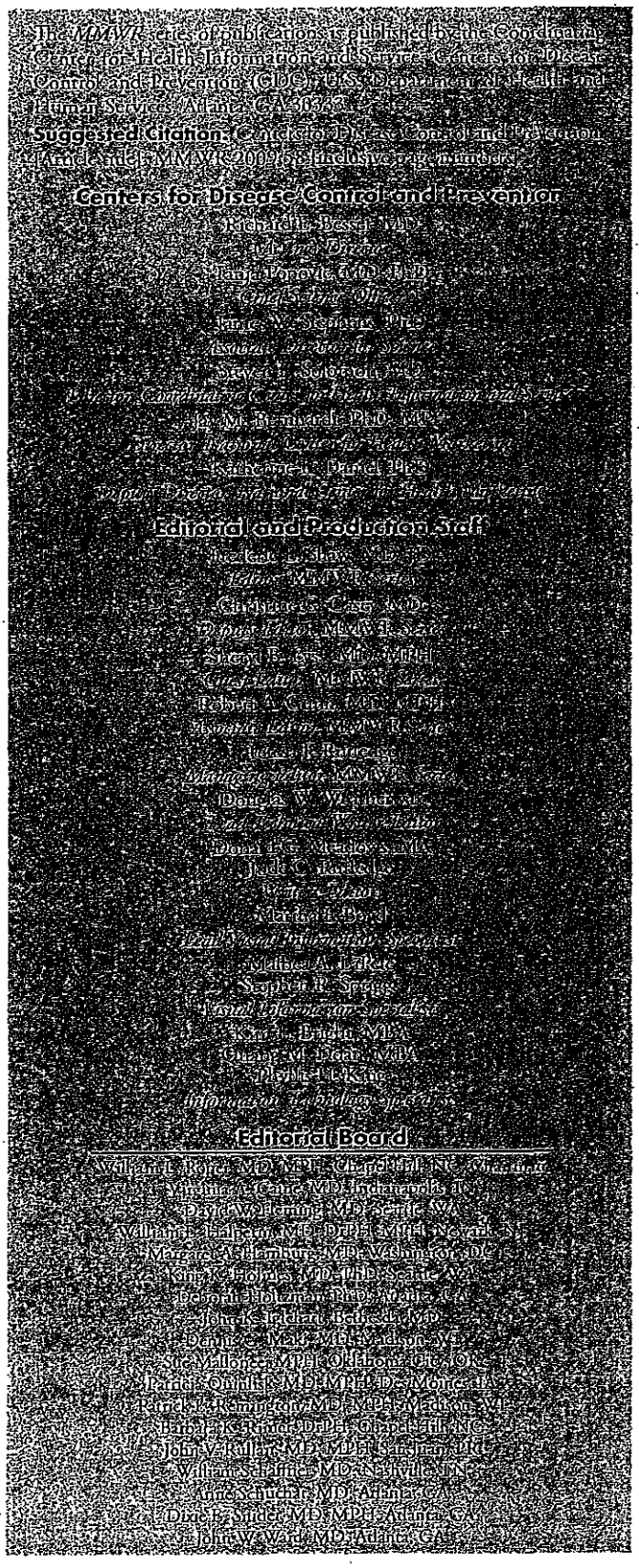
DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION



2006–07], A/Solomon Islands/3/2006 [2007–08], and A/Brisbane/59/2007 [2008–09]) were propagated in embryonated chicken eggs. The novel influenza A (H1N1) virus used in the study was A/California/04/2009, which was grown in Madin-Darby canine kidney cells. All procedures were performed in a biosafety level 2 laboratory using biosafety level 3 practices.† The HI assay was performed using 0.5% turkey red blood cells. Serum specimens were treated with receptor-destroying enzymes. Sera containing nonspecific agglutinins were heme-adsorbed and tested at an initial dilution of 1:10. For the MN assay, serum specimens were heat inactivated (at 133°F [56°C], for 30 minutes) and tested at an initial dilution of 1:10. For calculation of geometric mean titer (GMT) estimates, a titer of <10 was assigned a value of 5, and a titer of ≥1280 was assigned a value of 1280. Statistical significance was determined using a paired t-test.

An initial comparison between the HI and MN assays was made for panels of sera from children aged 6 months to 9 years (n = 28), adults aged 18–59 years (n = 30), and adults aged >60 years (n = 42). Although the estimated correlation between HI and MN titers was high (r = 0.82) for the seasonal vaccine strains, the MN assay generally yielded higher titers and detected more seroconversions (i.e., fourfold or greater increases in antibody titers) to A/California/04/2009 than the HI assay. Therefore, the MN assay was used to assess the level of cross-reactive antibody to A/California/04/2009 in populations before and after vaccination with seasonal influenza vaccines. Although serum HI antibody titers of 40 are associated with at least a 50% reduction in risk for influenza infection or disease in populations (*7*), no such correlate of protection exists for MN antibody titers. Therefore, a linear regression model was used to predict the MN titer for seasonal influenza A (H1N1) viruses that corresponded to an HI titer of 40 and to measure titer achievement against the seasonal vaccine strain and the novel influenza A (H1N1) virus. In the pediatric population, an HI titer of 40 corresponded to an MN titer of 40, whereas in the adult population the corresponding MN titer was ≥160.

Among 79 children ranging in age from 6 months to 9 years, little evidence was found of prevaccination cross-reactive antibodies to A/California/04/2009 (Table 1). In addition, after vaccination with seasonal TIV, no seroconversions to A/California/04/2009 virus were detected, whereas seroconversions to the seasonal vaccine strains were detected in 67%–100% of children. Children vaccinated with LAIV also had no seroconversions to the A/California/04/2009 virus.

† Biosafety level information is available at http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm.

TABLE 1. Cross-reactive microneutralization (MN) antibody response to novel influenza A (H1N1) virus* in pediatric recipients (aged 6 months–9 years) of seasonal influenza vaccines

Vaccine	Influenza season	Influenza virus	Age group	No.	% with fourfold or greater increase in antibody titer†	% with MN titer of ≥40§		Geometric mean titer (GMT)¶			
						Prevaccination	Postvaccination	Prevaccination (95% CI**)		Postvaccination (95% CI)		Postvaccination to prevaccination ratio
TIV††	2005–2007§§	A/New Caledonia/20/1999	6 mos–9 yrs	33	67	42	94	31	(21–46)	255	(172–378)	8
		A/California/04/2009			0	0	0	5	(4–6)	6	(6–7)	1
	2007–08	A/Solomon Is/3/2006	5–9 yrs	13	85	54	100	42	(22–80)	575	(303–1093)	14
		A/California/04/2009			0	8	8	10	(7–15)	12	(8–17)	1
	2008–09	A/Brisbane/59/2007	6 mos–3 yrs	9	100	0	100	5	(4–7)	285	(202–402)	57
		A/California/04/2009			0	0	0	5	(—)	5	(—)	1
LAIV¶¶	2005–2007§§	A/New Caledonia/20/1999	6 mos–9 yrs	24	25	46	79	33	(17–63)	73	(38–139)	2
		A/California/04/2009			0	0	4	5	(4–6)	6	(5–7)	1

* A/California/04/2009.
† A fourfold or greater increase in antibody titer indicates seroconversion (a response to the vaccine).
§ A linear regression model was used to predict the MN titer for seasonal H1N1 viruses that corresponded to a hemagglutination inhibition (HI) antibody titer of 40. (Serum HI antibody titers of 40 are associated with at least a 50% decrease in risk for influenza infection or disease [7]). In pediatric populations, an HI titer of 40 corresponds with an MN titer of 40.
¶ A titer of 1280 was used for all samples with a titer of ≥1280. The dilution of sera in the first well is based on the combination of a 1:10 serum dilution with an equal volume of diluted virus for a final serum dilution referred to as 1:10. In the statistical models, study participants were treated as random effects sampled from a larger population of study participants, and duplicate samples were treated as random effects nested within each study participant.
** Confidence interval.
†† Trivalent, inactivated influenza vaccine.
§§ 2005–06 and 2006–07 influenza seasons.
¶¶ Live, attenuated influenza vaccine.

Consistent with previous reports (*4*), vaccination of adults with seasonal TIV resulted in seroconversion to the seasonal influenza A (H1N1) vaccine strain in 74% of adults aged 18–64 years, 78% of adults aged 18–40 years, and 54% of adults aged >60 years (Table 2). In contrast, seroconversion to the A/California/04/2009 virus was detected in 19% of adults aged 18–64 years and 3% of adults aged >60 years who received the 2007–08 vaccine and in 12% of adults aged 18–40 years who received the 2008–09 vaccine. Compared with responses to the seasonal influenza A (H1N1) vaccine virus, postvaccination to prevaccination GMT ratios for the response to A/California/04/2009 virus were fivefold to tenfold lower among all adults. However, 6% of adults aged 18–40 years, 9% of adults 18–64 years, and 33% of adults aged >60 years had prevaccination MN titers of ≥160. After vaccination with seasonal vaccine, 7% of adults aged 18–40 years, 25% of adults aged 18–64 years, and 43% of adults aged >60 years had postvaccination titers of ≥160 to A/California/04/2009. The prevaccination GMT of adults aged >60 years against the novel 2009 H1N1 strain was significantly higher than against the seasonal 2007–08 H1N1 vaccine component ($p<0.001$).

Reported by: *J Katz, PhD, K Hancock, PhD, V Veguilla, MPH, W Zhong, PhD, XH Lu, MD, H Sun, MD, E Butler, MPH, L Dong, MD, PhD, F Liu, MD, PhD, ZN Li, MD, PhD, J DeVos, MPH, P Gargiullo, PhD, N Cox, PhD, Influenza Div, National Center for Immunization and Respiratory Diseases, Coordinating Center for Infectious Diseases, CDC.*

Editorial Note: The results in this report suggest that vaccination with recent (2005–2009) seasonal influenza vaccines is unlikely to provide protection against the novel influenza A (H1N1) virus. Although vaccination of adults with seasonal TIV generally resulted in a small increase in antibodies against the novel influenza A (H1N1) virus, whether such levels of cross-reactive antibody provide any protection against infection with novel influenza A (H1N1) virus is unknown. These results are consistent with the substantial degree of genetic divergence of the novel influenza A (H1N1) virus of swine origin from recent seasonal human H1N1 viruses; A/California/04/09 shares only 72%–73% amino acid identity in the HA1 portion of the hemagglutinin molecule with the seasonal viruses used in this study. For comparison, the amino acid sequence identity in the HA1 portion among seasonal vaccine strains used in this study is 97%–98%.

Although the number of sera from children tested in this analysis was small, results indicate that U.S. children are largely serologically naïve to the novel influenza A (H1N1) virus and that vaccination with seasonal TIV or LAIV does not elicit any measurable level of cross-reactive antibody to the novel virus. Results among adults suggest that some degree of preexisting immunity to the novel H1N1 strains exists, especially among adults aged >60 years. One possible explanation is that some adults in this age group have had previous exposure, either through infection or vaccination, to an influenza A (H1N1) virus that is genetically and antigenically more closely related

TABLE 2. Cross-reactive microneutralization (MN) antibody response to novel influenza A (H1N1) virus* in adult recipients of seasonal influenza vaccines

Vaccine	Influenza season	Influenza virus	Age group (yrs)	No.	% with fourfold or greater increase in antibody titer†	% with MN titer of ≥160§		Geometric mean titer (GMT)¶		
						Prevaccination	Postvaccination	Prevaccination (95% CI**)	Postvaccination (95% CI)	Postvaccination to prevaccination ratio
TIV††	2007–08	A/Solomon Is/3/2006	18–64	134	74	28	92	48 (40–59)	561 (462–682)	12
		A/California/04/2009			19	9	25	28 (23–34)	53 (43–66)	2
	2008–09	A/Brisbane/59/2007	18–40	83	78	20	88	29 (22–38)	546 (418–713)	19
		A/California/04/2009			12	6	7	11 (9–14)	21 (16–26)	2
	2007–08	A/Solomon Is/3/2006	>60	63	54	14	54	31 (22–42)	143 (105–194)	5
		A/California/04/2009			3	33	43	92 (71–121)	97 (74–127)	1

* A/California/04/2009.
† A fourfold or greater increase in antibody titer indicates seroconversion (a response to the vaccine).
§ A linear regression model was used to predict the MN titer for seasonal H1N1 viruses that corresponded to a hemagglutination inhibition (HI) antibody titer of 40. (Serum HI antibody titers of 40 are associated with at least a 50% decrease in risk for influenza infection or disease [7]). In adult populations, an HI titer of 40 corresponds with an MN titer of ≥160.
¶ A titer of 1280 was used for all samples with a titer of ≥1280. The dilution of sera in the first well is based on the combination of a 1:10 serum dilution with an equal volume of diluted virus for a final serum dilution referred to as 1:10. In the statistical models, study participants were treated as random effects sampled from a larger population of study participants, and duplicate samples were treated as random effects nested within each study participant.
** Confidence interval.
†† Trivalent, inactivated influenza vaccine.

to the novel influenza A (H1N1) virus than are contemporary seasonal H1N1 strains. Ongoing assessment of the cross-reactive antibody response among persons in different age groups might identify a particular age group that would allow further clarification of the cross-reactive serologic response. Development of a strain-specific vaccine against the novel influenza A (H1N1) virus is needed for optimal protection against the virus among persons of all ages.

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Federal and State Cigarette Excise Taxes — United States, 1995–2009

On April 1, 2009, the largest federal cigarette excise tax increase in history went into effect, bringing the combined federal and average state excise tax for cigarettes to $2.21 per pack and achieving the *Healthy People 2010* (HP2010) objective (27-21a) to increase the combined federal and average state cigarette excise tax to at least $2 per pack (*1*). This report summarizes changes in the federal excise tax, as well as state excise taxes for all 50 states and the District of Columbia (DC) from December 31, 1995 to April 1, 2009.* The findings indicate that the federal excise tax increased from 24 cents per pack in 1995 to $1.01 per pack in 2009, and the average state excise tax increased from 32.7 cents per pack to $1.20 per pack during the same period.† These increases represent a 321% increase in the federal excise tax and a 267% increase in the average state excise tax since 1995. Price increases should be combined with other evidence-based policy and clinical

* For this report, DC is included among results for states.
† The federal tax of $50.33 for cigarettes is levied per 1,000 cigarettes. When calculated per pack of 20 cigarettes, this is $1.0066 per pack. For this study, this fractional tax is referred to as $1.01 per pack.

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年4月22日	該当なし	
一般的名称	別紙のとおり	研究報告の公表状況	MMWR. 2009;58:1-3	公表国 米国	
販売名（企業名）	別紙のとおり				

研究報告の概要

問題点：南カリフォルニア周辺郡において、ヒトからヒトへ感染した可能性のある新しいブタインフルエンザA株（H1N1）感染事例が報告された。

2009年4月17日、CDCは、南カリフォルニア周辺郡に住む小児の熱性呼吸器疾患症例2例がブタインフルエンザA(H1N1)ウイルス感染によるものであったと判断した。2症例から検出されたウイルスは、遺伝子的に非常に近く、アマンタジン及びリマンタジンに耐性を示し、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は接触しておらず、感染源は不明である。感染源の確認と、類似するブタインフルエンザウイルスに感染した患者が他にいないかどうかの確認が行われている。
このウイルスはヒトインフルエンザAの新しいサブタイプではないが、このブタインフルエンザA（H1N1）の新株はヒトインフルエンザA（H1N1）ウイルスとは本質的に異なっており、感染しやすいヒトが多い可能性があり、季節性インフルエンザワクチンH1N1株では予防できない可能性が懸念される。2症例にはブタへの暴露がないことから、この新しいインフルエンザウイルスがヒトからヒトへ感染した可能性が高い。

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。

使用上の注意記載状況・その他参考事項等

記載なし

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－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P 1500 注射用
報告企業の意見	インフルエンザウイルス粒子は 70～120nm の球形または多形性で、8 本の分節状マイナス一本鎖 RNA を核酸として有する。エンベロープの表面に赤血球凝集素(HA)とノイラミダーゼ(NA)のスパイクを持ち、その抗原性により 16 種類の HA 亜型および 9 種類の NA 亜型に分類される。 今回の新型インフルエンザの原因ウイルスは、1930 年代以降に発見された米国由来のブタインフルエンザウイルス、ヒトインフルエンザウイルス (H3N2)、鳥インフルエンザウイルスの 3 つのウイルスの遺伝子がブタインフルエンザとして再集合してできたウイルスに、さらにユーラシア大陸由来のブタインフルエンザウイルスの遺伝子の一部の分節が再集合して加わったものであると推察されている。新型インフルエンザは、これまでのところ限られた知見しか得られていないが、そのヒトからヒトへの感染伝播経路は従来の季節性インフルエンザに準ずると考えられている。すなわち、感染・発病者の咳やくしゃみとともに口から発せられる飛沫による飛沫感染が主な感染経路であり、患者との直接、間接の接触による接触感染も感染経路としての可能性がある。臨床症状であるが、これまでのところ、この新型インフルエンザのヒトへの病原性は、高病原性鳥インフルエンザウイルス A/H5N1 のヒト感染例とは異なって、ヒトに対する病原性はそれほど高くはないと考えられている。(http://idsc.nih.go.jp/idwr/douko/2009d/17douko.html) 弊所の血漿分画製剤の製造工程には、冷エタノール分画工程、ウイルス除去膜ろ過工程あるいは加熱工程等の原理の異なるウイルス除去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。今回報告したインフルエンザウイルスは、エンベロープの有無、核酸の種類等からモデルウイルスとしては BVDV が該当すると考えられるが、上記バリデーションの結果から、弊所の血漿分画製剤の製造工程が BVDV の除去・不活化効果を有することを確認している。また、これまでに当該製剤によるインフルエンザウイルス感染の報告例は無い。 以上の点から、当該製剤はインフルエンザ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

MMWR

Dispatch

April 21, 2009 / 58 (Dispatch);1-3

Swine Influenza A (H1N1) Infection in Two Children --- Southern California, March--April 2009

On April 17, 2009, CDC determined that two cases of febrile respiratory illness occurring in children who resided in adjacent counties in southern California were caused by infection with a swine influenza A (H1N1) virus. The viruses from the two cases are closely related genetically, resistant to amantadine and rimantadine, and contain a unique combination of gene segments that previously has not been reported among swine or human influenza viruses in the United States or elsewhere. Neither child had contact with pigs; the source of the infection is unknown. Investigations to identify the source of infection and to determine whether additional persons have been ill from infection with similar swine influenza viruses are ongoing. This report briefly describes the two cases and the investigations currently under way. Although this is not a new subtype of influenza A in humans, concern exists that this new strain of swine influenza A (H1N1) is substantially different from human influenza A (H1N1) viruses, that a large proportion of the population might be susceptible to infection, and that the seasonal influenza vaccine H1N1 strain might not provide protection. The lack of known exposure to pigs in the two cases increases the possibility that human-to-human transmission of this new influenza virus has occurred. Clinicians should consider animal as well as seasonal influenza virus infections in their differential diagnosis of patients who have febrile respiratory illness and who 1) live in San Diego and Imperial counties or 2) traveled to these counties or were in contact with ill persons from these counties in the 7 days preceding their illness onset, or 3) had recent exposure to pigs. Clinicians who suspect swine influenza virus infections in a patient should obtain a respiratory specimen and contact their state or local health department to facilitate testing at a state public health laboratory.

Case Reports

Patient A. On April 13, 2009, CDC was notified of a case of respiratory illness in a boy aged 10 years who lives in San Diego County, California. The patient had onset of fever, cough, and vomiting on March 30, 2009. He was taken to an outpatient clinic, and a nasopharyngeal swab was collected for testing as part of a clinical study. The boy received symptomatic treatment, and all his symptoms resolved uneventfully within approximately 1 week. The child had not received influenza vaccine during this influenza season. Initial testing at the clinic using an investigational diagnostic device identified an influenza A virus, but the test was negative for human influenza subtypes H1N1, H3N2, and H5N1. The San Diego County Health Department was notified, and per protocol, the specimen was sent for further confirmatory testing to reference laboratories, where the sample was verified to be an unsubtypable influenza A strain. On April 14, 2009, CDC received clinical specimens and determined that the virus was swine influenza A (H1N1). The boy and his family reported that the child had had no exposure to pigs. Investigation of potential animal exposures among the boy's contacts is continuing. The patient's mother had respiratory symptoms without fever in the first few days of April 2009, and a brother aged 8 years had a respiratory illness 2 weeks before illness onset in the patient and had a second illness with cough, fever, and rhinorrhea on April 11, 2009. However, no respiratory specimens were collected from either the mother or brother during their acute illnesses. Public health officials are conducting case and contact investigations to determine whether illness has occurred among other relatives and contacts in California, and during the family's travel to Texas on April 3, 2009.

Patient B. CDC received an influenza specimen on April 17, 2009, that had been forwarded as an unsubtypable influenza A virus from the Naval Health Research Center in San Diego, California. CDC identified this specimen as a swine influenza A (H1N1) virus on April 17, 2009, and notified the California Department of Public Health. The source of the specimen, patient B, is a girl aged 9 years who resides in Imperial County, California, adjacent to San Diego County. On March 28, 2009, she had onset of cough and fever (104.3°F [40.2°C]). She was taken to an outpatient facility that was participating in an influenza surveillance project, treated with amoxicillin/clavulanate potassium and an antihistamine, and has since recovered uneventfully. The child had not received influenza vaccine during this influenza season. The patient and her parents reported no exposure to pigs, although the girl did attend an agricultural fair where pigs were exhibited approximately 4 weeks before illness onset. She reported that she did not see pigs at the fair and went only to the amusement section of the fair. The Imperial County Public Health Department and the California Department of Public Health are now conducting an investigation to determine possible sources of infection and to identify any additional human cases. The patient's brother aged 13 years had influenza-like symptoms on April 1, 2009, and a male cousin aged 13 years living in the home had influenza-like symptoms on March 25, 2009, 3 days before onset of the patient's symptoms. The brother and cousin were not tested for influenza at the time of their illnesses.

Epidemiologic and Laboratory Investigations

As of April 21, 2009, no epidemiologic link between patients A and B had been identified, and no additional cases of infection with the identified strain of swine influenza A (H1N1) had been identified. Surveillance data from Imperial and San Diego

counties, and from California overall, showed declining influenza activity at the time of the two patients' illnesses. Case and contact investigations by the county and state departments of health in California and Texas are ongoing. Enhanced surveillance for possible additional cases is being implemented in the area.

Preliminary genetic characterization of the influenza viruses has identified them as swine influenza A (H1N1) viruses. The viruses are similar to each other, and the majority of their genes, including the hemagglutinin (HA) gene, are similar to those of swine influenza viruses that have circulated among U.S. pigs since approximately 1999; however, two genes coding for the neuraminidase (NA) and matrix (M) proteins are similar to corresponding genes of swine influenza viruses of the Eurasian lineage (*1*). This particular genetic combination of swine influenza virus segments has not been recognized previously among swine or human isolates in the United States, or elsewhere based on analyses of influenza genomic sequences available on GenBank.* Viruses with this combination of genes are not known to be circulating among swine in the United States; however, no formal national surveillance system exists to determine what viruses are prevalent in the U.S. swine population. Recent collaboration between the U.S. Department of Agriculture and CDC has led to development of a pilot swine influenza virus surveillance program to better understand the epidemiology and ecology of swine influenza virus infections in swine and humans.

The viruses in these two patients demonstrate antiviral resistance to amantadine and rimantadine, and testing to determine susceptibility to the neuraminidase inhibitor drugs oseltamivir and zanamivir is under way. Because these viruses carry a unique combination of genes, no information currently is available regarding the efficiency of transmission in swine or in humans. Investigations to understand transmission of this virus are ongoing.

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Editorial Note:

In the past, CDC has received reports of approximately one human swine influenza virus infection every 1–2 years in the United States (*2,3*). However, during December 2005–January 2009, 12 cases of human infection with swine influenza were reported; five of these 12 cases occurred in patients who had direct exposure to pigs, six in patients reported being near pigs, and the exposure in one case was unknown (*1,4,5*). In the United States, novel influenza A virus infections in humans, including swine influenza infections, have been nationally notifiable conditions since 2007. The recent increased reporting might be, in part, a result of increased influenza testing capabilities in public health laboratories, but genetic changes in swine influenza viruses and other factors also might be a factor (*1,4,5*). Although the vast majority of human infections with animal influenza viruses do not result in human-to-human transmission (*2,3*), each case should be fully investigated to be certain that such viruses are not spreading among humans and to limit further exposure of humans to infected animals, if infected animals are identified. Such investigations should include close collaboration between state and local public health officials with animal health officials.

The lack of known exposure to pigs in the two cases described in this report increases the possibility that human-to-human transmission of this new influenza virus has occurred. Clinicians should consider animal as well as seasonal influenza virus infections in the differential diagnosis of patients with febrile respiratory illness who live in San Diego and Imperial counties or have traveled to these areas or been in contact with ill persons from these areas in the 7 days before their illness onset. In addition, clinicians should consider animal influenza infections among persons with febrile respiratory illness who have been near pigs, such as attending fairs or other places where pigs might be displayed. Clinicians who suspect swine influenza virus infections in humans should obtain a nasopharyngeal swab from the patient, place the swab in a viral transport medium, and contact their state or local health department to facilitate transport and timely diagnosis at a state public health laboratory. CDC requests that state public health laboratories send all influenza A specimens that cannot be subtyped to the CDC, Influenza Division, Virus Surveillance and Diagnostics Branch Laboratory.

Interim guidance on infection control, treatment, and chemoprophylaxis for swine influenza is available at http://www.cdc.gov/flu/swine/recommendations.htm. Additional information about swine influenza is available at http://www.cdc.gov/flu/swine/index.htm.

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* Available at http://www.ncbi.nlm.nih.gov/Genbank.

別紙様式第2-1
番号7

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2009年5月12日	新医薬品等の区分 該当なし	厚生労働省処理欄
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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

新型インフルエンザA(H1N1)の致死率は1957年のアジア風邪並みの約0.4%で、感染力も季節性のインフルエンザより高いとする分析結果を、英ロンドン大等からなる国際チームがまとめた。
新型インフルエンザA(H1N1)ウイルスは世界的に急速に広がっている。パンデミックになる可能性の判断は限られたデータでは難しいが、適切な保健対応を伝達するためには不可欠である。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の評価を実施した。4月後半までにメキシコで23,000人(範囲：6,000～32,000)が感染し、その時報告された死亡例から致死率(CFR)は0.4%(範囲：0.3～1.5%)と我々は推測する。不確定ではあるが、臨床的重症度は1918年の世界的に流行したインフルエンザより低いが、1957年のインフルエンザと同等であると思われる。感染力を示すR_0は遺伝的分析で中央値1.2人であったのに対して、3つの異なる疫学的分析では、1.4～1.6人であった。この推定値の範囲は4月後半にメキシコで起こったヒトーヒト感染が14～73回繰り返されたことと一致する。感染力は、季節性インフルエンザより実際は高く、過去の世界的に流行したインフルエンザの低い方のR_0値に匹敵する。

報告企業の意見	今後の対応
新型インフルエンザA(H1N1)の致死率は1957年のアジア風邪並みの約0.4%で、感染力も季節性のインフルエンザより高いとする報告である。 インフルエンザA(H1N1)はオルソミクソウイルス科に属し、ビリオンは球形で、直径80～120nmの脂質エンベロープを有する比較的大きなRNAウイルスである。万一、インフルエンザA(H1N1)が原料血漿に混入したとしてもBVDをモデルウイルスとしたウイルスバリデーション試験成績から、製造工程にて十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、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。

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REPORTS

Submitted on May 5, 2009
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Pandemic Potential of a Strain of Influenza A (H1N1) : Early Findings

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‡All authors are members of this collaboration.

A novel influenza A (H1N1) virus has spread rapidly across the globe. Judging its pandemic potential is difficult with limited data, but nevertheless essential to inform appropriate health responses. By analyzing the outbreak in Mexico, early data on international spread, and viral genetic diversity, we make an early assessment of transmissibility and severity. Our estimates suggest that 23,000 (range 6,000-32,000) individuals had been infected in Mexico by late April, giving an estimated case fatality ratio (CFR) of 0.4% (range 0.3% to 1.5%) based on confirmed and suspect deaths reported to that time. In a community outbreak in the small community of La Gloria, Veracruz no deaths were attributed to infection, giving an upper 95% bound on CFR of 0.6%. Thus while substantial uncertainty remains, clinical severity appears less than that seen in 1918 but comparable with that seen in 1957. Clinical attack rates in children in La Gloria were twice that in adults (<15 years-of-age: 61%, ≥15: 29%). Three different epidemiological analyses gave R_0 estimates in the range 1.4-1.6, while a genetic analysis gave a central estimate of 1.2. This range of values is, consistent with 14 to 73 generations of human-to-human transmission having occurred in Mexico to late April.

Transmissibility is therefore substantially higher than seasonal flu, and comparable with lower estimates of R_0 obtained from previous influenza pandemics.

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番号1

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4月28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）	－					
研究報告の概要	メキシコや米国で発生した豚インフルエンザの人への大量感染を受け，世界保健機関（WHO）は27日，世界の警戒水準（フェーズ）を現行の「3」から，豚インフルエンザウイルスが人から人への感染力を十分に得た段階を示す「4」に初めて引き上げた．新型インフルエンザ発生を認定したことになる． 人への感染はメキシコ以外に米国，カナダ，さらにスペイン，英国でも確認され，欧州に広がった．メキシコでは27日までに感染が確認されたが，感染の疑いがある死者は149人となった．					使用上の注意記載状況等・その他参考事項等
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”および“重大な感染症情報”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．			

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MedDRA/J Ver. 12.0J

30 29

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NMP2009-0001

日本が見える
2009/04/28 06:07　【共同通信】

27日、メキシコ市でマスクを着け地下鉄の出口に向かう人たち(AP＝共同)

新型インフルエンザ発生　WHO、警戒水準4へ引き上げ

【ジュネーブ27日共同】メキシコや米国で発生した豚インフルエンザの人への大量感染を受け、世界保健機関(WHO)は27日、世界の警戒水準(フェーズ)を現行の「3」から、豚インフルエンザウイルスが人から人への感染力を十分に得た段階を示す「4」に初めて引き上げた。新型インフルエンザ発生を認定したことになる。日本を含む各国に感染が広がり、世界的大流行となる恐れがある。

これを受け日本政府は、麻生太郎首相を本部長とする対策本部の設置を決めた。検疫強化をはじめウイルスの国内侵入防止と在外邦人支援の対策を進める。

米国やメキシコを中心に、国際的な人の移動が制限されるとみられ、景気低迷にあえぐ世界経済への影響が懸念される。

WHOは28日に開く予定だった緊急委員会を前倒しし、27日に開催、警戒水準引き上げを決めた。水準引き上げは25日の緊急委員会でも検討したが「さらに情報が必要」と見送っていた。

人への感染はメキシコ以外に米国、カナダ、さらにスペイン、英国でも確認され、欧州に広がった。メキシコでは27日までに感染が確認されたか、感染の疑いがある死者は149人となった。

ワクチン開発には半年程度かかるとされる。

20世紀には3回のインフルエンザの世界的流行があり、1918年発生の「スペイン風邪」では世界で約4000万人が死亡した。

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NMP2009-0002

World Health Organization
Regional Office for Europe

Confirmed cases of swine influenza A (H1N1) virus in three countries in the WHO European Region

On 27 April 2009, National Focal Points (NFPs) for the International Health Regulations (IHR) informed WHO/Europe about the detection of four confirmed cases of swine influenza A (H1N1) virus infection: two cases each in Spain and the United Kingdom. On 28 April 2009, the NFP of Israel reported an additional confirmed case.

The five people with confirmed cases in the WHO European Region presented with mild illness and had recently returned from travel in Mexico. As of 27 April 2009, 43 additional people in 8 countries in the Region were under investigation for infection.

Situation in the European Region

The reports of confirmed cases from Israel, Spain and the United Kingdom reflect important steps taken by the national authorities to ensure early detection and response in association with the evolving situation in the Americas. National authorities are advised to intensify surveillance efforts for the early detection of people who may be infected with swine influenza A (H1N1) virus and may transmit the infection to others.

On 27 April 2009, the WHO Regional Director for Europe, Dr Marc Danzon, informed the health ministers, chief medical officers and NFPs in the Region of WHO/Europe's response. He acknowledged that cooperation between WHO and national and international counterparts was crucial in preparing for and responding to the potential spread of swine influenza A (H1N1) virus in the European Region.

WHO/Europe is working closely with the Directorate-General for Health and Consumers of the European Commission and the European Centre for Disease Prevention and Control. Similarly, WHO is in close consultation with development partners, United Nations agencies and other international organizations (including those involved in trade and travel), and manufacturers of vaccines, drugs, diagnostic equipment and personal protection equipment.

Global situation

The five cases in the WHO European Region are the first confirmed cases identified outside the Americas. The WHO headquarters web pages on swine influenza offer additional information on the global situation, including Canada, Mexico and the United States of America.

Change in pandemic alert level

On 27 April 2009, the second meeting of the Emergency Committee was convened as stipulated under the IHR. Following the Committee's advice, the WHO Director-General, Dr Margaret Chan, decided to change the current phase of pandemic alert from level 3 to level 4.

This decision was based primarily on epidemiological data demonstrating human-to-human transmission and the ability of the virus to cause community-level outbreaks. As further information becomes available, WHO may decide either to revert to phase 3 or to raise the level of alert further.

The outcome of the Emergency Committee's meeting included recommendations to countries not to close borders or to restrict international travel. It is considered prudent for people who are ill to delay international travel and for those developing symptoms following international travel to seek medical attention. In addition, WHO will facilitate the process needed to develop a vaccine effective against the A (H1N1) virus.

WHO published interim guidance for the surveillance of human infection with swine influenza A (H1N1) virus, including case definition and requirements for reporting to WHO, on 27 April 2009.

Back to normal view

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年5月16日	該当なし	
一般的名称	別紙のとおり	研究報告の公表状況	新型インフルエンザに関する報道発表資料（厚生労働省、2009年5月16日）	公表国：日本	
販売名（企業名）	別紙のとおり				

研究報告の概要

問題点：国内で最初の新型インフルエンザ（インフルエンザA/H1N1）患者が確認された。

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/HINI)が疑われる患者の発生について(第5報)

患者Aは、兵庫県神戸市在住の10代後半の男性。本人には海外渡航歴はない。5月11日に悪寒を訴え、5月12日に37.4℃の発熱があり医師の診察を受け、インフルエンザ簡易検査でA型陽性、B型陰性であった。医師がソ連型と香港型を区別するため、検体を神戸市環境保健研究所に提出した。検体は5月12日に神戸市環境保健研究所に到着し5月15日に検査が行われた。結果が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)が否定できない可能性のある事例として、厚生労働省新型インフルエンザ対策推進本部に連絡があった。

5月16日午前0時すぎ、感染症の予防及び感染症の患者に対する医療に対する法律（平成10年法律第114号。以下、「感染症法」という。）に基づき、神戸市内の医療機関から神戸市に対して、新型インフルエンザが疑われる患者としての届出があり、午前3時30分ごろ、患者は感染症法に基づき、神戸市内の感染指定医療機関に入院した。

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。

使用上の注意記載状況・その他参考事項等

記載なし

MedDRA/J ver.12.0

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P 1500 注射用
報告企業の意見	インフルエンザウイルス粒子は 70～120nm の球形または多形性で、8 本の分節状マイナス一本鎖 RNA を核酸として有する。エンベロープの表面に赤血球凝集素(HA)とノイラミダーゼ(NA)のスパイクを持ち、その抗原性により 16 種類の HA 亜型および 9 種類の NA 亜型に分類される。 今回の新型インフルエンザの原因ウイルスは、1930 年代以降に発見された米国由来のブタインフルエンザウイルス、ヒトインフルエンザウイルス (H3N2)、鳥インフルエンザウイルスの 3 つのウイルスの遺伝子がブタインフルエンザとして再集合してできたウイルスに、さらにユーラシア大陸由来のブタインフルエンザウイルスの遺伝子の一部の分節が再集合して加わったものであると推察されている (http://idsc.nih.go.jp/idwr/douko/2009d/17douko.html)。神戸市における新型インフルエンザの臨床像は、患者の大半は入院を要する臨床状況ではなかった。5 月 19 日現在、人工換気を行う対象者は無く、また、死亡例も発生していない。臨床的な観点から大半は直ぐに退院となり、自宅における健康観察を行う対象となっている。5 月 19 日現在、長期的な予後については不明だが、現時点までの状況では、季節性のインフルエンザと臨床像において類似しており、全例を入院させる医学的必要性はないことが示唆される (http://www.mhlw.go.jp/kinkyu/kenkou/influenza/090520-01.html)。 当所の血漿分画製剤の製造工程には、冷エタノール分画工程、ウイルス除去膜ろ過工程あるいは加熱工程等の原理の異なるウイルス除去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。今回報告したインフルエンザウイルスは、エンベロープの有無、核酸の種類等からモデルウイルスとしては BVDV が該当すると考えられるが、上記バリデーションの結果から、当所の血漿分画製剤の製造工程が BVDV の除去・不活化効果を有することを確認している。また、これまでに当該製剤によるインフルエンザウイルス感染の報告例は無い。 以上の点から、当該製剤はインフルエンザ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

ひと、くらし、みらいのために
厚生労働省
Ministry of Health, Labour and Welfare

Press Release

平成21年5月16日
新型インフルエンザ対策推進本部
照会先：メディア班
(電　話) 03(3595)3040
内線(8778、8779、8780)

報道関係者　各位

【第五報】
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)が疑われる患者の発生について

5月15日夜10時頃、兵庫県神戸市から連絡のあった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(患者A)について、国立感染症研究所からの検査結果の報告がございましたので、お知らせします。

○ 検査結果(国立感染症研究所)

A型	(＋)
ヒトH1	(＋)
ヒトH3	(－)
新型H1	(＋)

このことから、当該疑われる患者Aは、新型インフルエンザの患者であることが確定しました。
患者Aに関する情報、その他の患者に関する情報、今後の対応は、以下のとおりです。

1. 患者Aに関する情報

(1)　概要

患者Aは、兵庫県神戸市在住の 10 代後半の男性。本人には海外渡航歴はない。5月11 日に悪寒を訴え、5月12日に 37. 4℃の発熱があり、医師の診察を受け、インフルエンザ簡易検査でA型陽性、B型陰性であった。医師がソ連型と香港型を区別するため、検体を神戸市環境保健研究所に提出した。検体は5月12日に神戸市環境保健研究所に到着し5月15日に検査が行われた。結果が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)が否定できない可能性のある事例として、厚生労働省新型インフルエンザ対策推進本部に連絡があった。

5月16日午前0時すぎ、感染症の予防及び感染症の患者に対する医療に関する法律(平成 10 年法律第 114 号。以下、「感染症法」という。)に基づき、神戸市内の医療機関から神戸市に対して、新型インフルエンザが疑われる患者としての届出があり、午前3時30分ごろ、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。

(2)　患者の状況

5月15日の時点において、咽頭痛および咳がある。体温は36℃台。5月12日より抗インフルエンザ薬(リレンザ)を使用している。

2. その他の患者の状況

○ 神戸市が行った積極的疫学調査(患者Aの行動及び接触者の状況についての調査)により、患者と同じ学校に通う2名については、現在、神戸市内の感染症指定医療機関に入院しており、今後、国立感染症研究所において、PCR検査を実施する予定。

患者B:兵庫県神戸市在住の10代後半の男性。患者Aと同じ高校に通っている。5月15 日に発熱し、医師の診察を受け、インフルエンザ簡易検査で、A型陽性、B型陰性であった。その後、神戸市内にある感染症指定医療機関に入院したところ、同病院から新型インフルエンザが疑われる患者として届出があった。神戸市環境保健研究所で行われたPCR検査で、A型(+)、新型H1(+)であったため、新型インフルエンザの可能性がある。

5月15日の時点で、咽頭痛および頭痛がある。体温は、39. 7℃。5月15日より抗インフルエンザ薬(リレンザ)を使用している。

患者C:兵庫県神戸市在住の10代後半の女性。患者Aと同じ高校に通っている。5月12 日に発熱し、5月13日に医師の診察を受け、インフルエンザ簡易検査でA型陽性、B型陰性であった。5月16日に神戸市内にある感染症指定医療機関に入院したところ、同病院から新型インフルエンザが疑われる患者として届出があった。神戸市環境保健研究所で行われたPCR検査で、A型(+)、新型H1(+)であったため、新型インフルエンザの可能性がある。

5月15日の時点で、鼻汁はあるがほぼ回復している。

3. 今後の対応

○ 感染症指定医療機関に入院している患者に対しては、神戸市において、適切な入院医療が提供されます。

○ 神戸市は、3名の患者について、積極的疫学調査を実施し、濃厚接触者を特定し、その行動や状況について、把握に努めています。

○ 厚生労働省は、16日朝、神戸市に担当官を派遣し、神戸市と協力しながら、疫学調査や情報収集に当たっております。

○ 今回、国内で最初の新型インフルエンザ患者が確認されたことを踏まえ、今後、都道府県等を通じて、感染拡大の防止、発熱外来や入院医療機関など医療体制の確保等に全力を尽くすこととしております。

B　個別症例報告概要

○　総括一覧表
○　報告リスト

個別症例報告のまとめ方について

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

血対課ID	受理日	番号	報告者名	一般名	生物由来成分名	原材料名	原産国	含有区分	文献	症例	適正使用措置
90156	2009/6/2	90236	日本赤十字社	解凍人赤血球濃厚液	解凍人赤血球濃厚液	人血液	日本	有効成分	有	無	有
90157	2009/6/18	90249	ベネシス	ポリエチレングリコール処理抗破傷風人免疫グロブリン 乾燥抗破傷風人免疫グロブリン	破傷風抗毒素	人血液	米国	有効成分	有	無	無
90158	2009/6/18	90251	日本赤十字社	人赤血球濃厚液	人赤血球濃厚液	人血液	日本	有効成分	有	有	有
90159	2009/6/18	90252	日本赤十字社	洗浄人赤血球浮遊液	洗浄人赤血球浮遊液	人血液	日本	有効成分	有	有	有
90160	2009/6/18	90253	日本赤十字社	－	合成血	人血液	日本	有効成分	有	無	有
90161	2009/6/18	90254	日本赤十字社	人全血液	人全血液	人血液	日本	有効成分	有	無	有
90162	2009/6/18	90255	日本赤十字社	抗HBs人免疫グロブリン	抗HBs人免疫グロブリン	人血液	日本	有効成分	有	無	無
90163	2009/6/25	90272	化学及血清療法研究所	乾燥ペプシン処理人免疫グロブリン	ペプシン処理人免疫グロブリンG分屑	ヒト血液	日本	有効成分	有	無	無
90164	2009/6/25	90273	化学及血清療法研究所	乾燥ペプシン処理人免疫グロブリン	ペプシン	ブタ胃粘膜	米国、カナダ	製造工程	有	無	無
90165	2009/6/26	90275	バクスター	乾燥イオン交換樹脂処理人免疫グロブリン	人免疫グロブリンG	人血漿	米国	有効成分	有	有	無
90166	2009/6/26	90276	バクスター	乾燥イオン交換樹脂処理人免疫グロブリン	人血清アルブミン	人血漿	米国	添加物	有	有	無
90167	2009/7/10	90294	富士フイルムRIファーマ	テクネチウム大凝集人血清アルブミン(99Tc)	テクネチウム大凝集人血清アルブミン(99mTc)	ヒト血液	日本	有効成分	有	無	無
90168	2009/7/13	90295	化学及血清療法研究所	乾燥スルホ化人免疫グルブリン	スルホ化人免疫グルブリンG	ヒト血液	米国、日本	有効成分	有	無	無
90169	2009/7/17	90297	CSLベーリング	乾燥濃縮人アンチトロンビンIII	乾燥濃縮人アンチトロンビンIII	ヒト血液	米国、ドイツ、オーストリア	有効成分	無	無	無
90170	2009/7/17	90298	CSLベーリング	乾燥濃縮人アンチトロンビンIII	乾燥濃縮人アンチトロンビンIII	ヒト血液	米国、ドイツ、オーストリア	有効成分	有	有	無
90171	2009/7/28	90312	ベネシス	人ハプトグロビン	人ハプトグロビン	人血液	日本	有効成分	有	無	無

90172	2009/7/28	90317	日本メジフィジックス	放射性医薬品基準ガラクトシル人血清アルブミンジエチレントリアミン五酢酸テクネチウム(99mTc)注射液	ガラクトシル人血清アルブミンジエチレントリアミン五酢酸テクネチウム(99mTc)	生物学的製剤基準人血清アルブミン	日本	有効成分	有	無	無
90173	2009/7/29	90337	日本製薬	乾燥人血液凝固第IX因子複合体	血液凝固第IX因子複合体	人血液	日本	有効成分	有	無	無
90174	2009/7/30	90352	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	ルリオクトコグ アルファ(遺伝子組換え)	遺伝子組換えチャイニーズハムスター卵巣細胞株	該当なし	有効成分	有	有	無
90175	2009/7/30	90353	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	アプロチニン	ウシ肺	ニュージーランド	製造工程	有	有	無
90176	2009/7/30	90354	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	インスリン(抗第VIII因子モノクローナル抗体製造用)	ウシ膵臓	米国	製造工程	有	有	無
90177	2009/7/30	90355	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	ウシ血清アルブミン	ウシ血液	米国	製造工程	有	有	無
90178	2009/7/30	90356	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	ウシ胎児血清(抗第VIII因子モノクローナル抗体製造用)	ウシ血液	オーストラリア	製造工程	有	有	無
90179	2009/7/30	90357	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	培養補助剤(抗第VIII因子モノクローナル抗体製造用-1)	ウシ血液	米国	製造工程	有	有	無
90180	2009/7/30	90358	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	培養補助剤(抗第VIII因子モノクローナル抗体製造用-2)	ウシ肝臓	米国又はカナダ	製造工程	有	有	無
90181	2009/7/30	90359	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	人血清アルブミン	人血漿	米国	添加物	有	有	無
90182	2009/7/30	90360	バクスター	加熱人血漿たん白	人血清アルブミン	人血漿	米国	有効成分	有	無	無
90183	2009/8/6	90365	富士フイルムRIファーマ	ヨウ化血清アルブミン(131I)	ヨウ化人血清アルブミン(131I)	ヒト血液	日本	有効成分	有	無	無
90184	2009/8/21	90380	日本製薬	加熱人血漿たん白 人血清アルブミン(5%) 人血清アルブミン(20%) 人血清アルブミン(25%) 乾燥ポリエチレングリコール処理人免疫グロブリン トロンビン 乾燥濃縮人アンチトロンビンIII 人免疫グロブリン 乾燥人血液凝固第IX因子複合体	ヘパリン	ブタ腸粘膜	ブラジル	製造工程 添加物・製造工程	無	有	無
90185	2009/8/24	90387	ノボノルディスクファーマ	エプタコグ アルファ(活性型)(遺伝子組換え)	ブタ膵臓由来トリプシン	ブタ膵臓(抽出物)	不明	製造工程	有	無	無

90186	2009/8/24	90388	ノボノルディスクファーマ	エプタゴク アルファ(活性型)(遺伝子組換え)	エプタゴクアルファ(活性型)(遺伝子組換え)	エプタゴクアルファ(活性型)(遺伝子組換え	不明	有効成分	無	有	無
90187	2009/8/24	90389	ノボノルディスクファーマ	エプタゴク アルファ(活性型)(遺伝子組換え)	ウシ胎仔血清	ウシ血液	ニュージーランド、オーストラリア、米国及びカナダ	製造工程	無	有	無
90188	2009/8/24	90390	ノボノルディスクファーマ	エプタゴク アルファ(活性型)(遺伝子組換え)	ウシ新生仔血清	ウシ血液	ニュージーランド	製造工程	無	有	無
90189	2009/8/24	90391	CSLベーリング	人血清アルブミン 破傷風抗毒素 フィブリノゲン加第XIII因子 乾燥濃縮人アンチトロンビンIII	ヘパリンナトリウム	ブタ腸粘膜	中国	製造工程	無	有	無
90190	2009/8/24	90392	CSLベーリング	人C1-インアクチベーター	人C1-インアクチベーター	ヒト血液	米国、ドイツ、オーストリア	有効成分	有	無	無
90191	2009/8/26	90395	化学及血清療法研究所	乾燥濃縮人血液凝固第VIII因子	血液凝固第VIII因子	ヒト血液	日本	有効成分	有	無	無
90192	2009/8/28	90408	バクスター	ルリオクトコグ アルファ(遺伝仕組換え)	ルリオクトコグ アルファ(遺伝仕組換え)	遺伝子組換えチャイニーズハムスター卵巣細胞株	-	有効成分	無	無	無

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	肝炎ウイルスキャリアー	米国	不明	不明	1993	不明	症例報告	当該製品	識別番号： 08000002 (完了報告) 報告日：2008年12月22日 MedDRA: Version(11.1)
	12-2	感染症および寄生虫症	Ｃ型肝炎	米国	女性	48	2008/12/09	未回復	症例報告	当該製品	識別番号： 08000034 (完了報告) 報告日：2008年 1月19日 MedDRA: Version(11.1)
	12-3	感染症および寄生虫症	Ｃ型肝炎	米国	女性	不明	不明	不明	症例報告	当該製品	識別番号： 09000004 (完了報告) 報告日：2008年 5月18日 MedDRA: Version(12.0)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第11回	11-1	臨床検査	Ｂ型肝炎抗体陽性	米国	男性	17	2008/05	不明	症例報告	当該製品	識別番号： 08000007（完了報告） 報告日：2008年6月5日 MedDRA: Version(11.0)
	11-2	感染症および寄生虫症	Ｃ型肝炎	米国	女性	不明	2008	不明	症例報告	当該製品	識別番号： 08000018（追加報告） 報告日：2008年11月12日 第11回症例番号11-2において10月17日に報告したものの追加報告 MedDRA: Version(11.1)
	11-2	感染症および寄生虫症	Ｃ型肝炎	米国	女性	不明	2008	不明	症例報告	当該製品	識別番号： 08000018（完了報告） 報告日：2008年10月17日 MedDRA: Version(11.0)
	11-3	感染症および寄生虫症	Ｂ型肝炎	スペイン	女性	不明	2008/6/3	未回復	症例報告	外国製品	識別番号： 08000026（完了報告） 報告日：2008年10月31日 MedDRA: Version(11.1)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期 (年/月/日)	転帰	出典	区分	備考
		器官別大分類	基本語								
第10回		0*	0	0	0	0	0	0	0	0	* 当該調査期間に対象となる感染症報告はなかった
第9回		0	0	0	0	0	0	0	0	0	
第8回		0	0	0	0	0	0	0	0	0	
第7回	7-1	臨床検査	ＨＩＶ抗体陽性	米国	不明	小児	不明	不明	症例報告	外国製品	識別番号： 06000022 (完了報告) 報告日：2006年8月24日 MedDRA: Version (9.0)
第6回	5-1	感染症および寄生虫症	Ｃ型肝炎	米国	男性	51歳	2005年9月	未回復	症例報告	当該製品	識別番号： 05000456 (追加報告) 報告日：2006年2月15日 第6回症例番号5-1は前回報告における第5回症例番号5-1において報告したものの追加報告 MedDRA: Version (8.1)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第５回	5-1	感染症および寄生虫症	Ｃ型肝炎	米国	男性	51歳	2005年9月	未回復	症例報告	当該製品	識別番号： 05000456(追加報告) 報告日：2005年11月11日 MedDRA: Version(8.1)
	5-1	感染症および寄生虫症	Ｃ型肝炎	米国	男性	51歳	2005年9月	未回復	症例報告	当該製品	識別番号： 05000456(完了報告) 報告日：2005年10月27日 MedDRA: Version(8.1)
	1-3	感染症および寄生虫症	Ｃ型肝炎	米国	男性	26歳	2002/11/19	不明	症例報告	当該製品	識別番号：03000006(追加報告) 報告日：2005年7月4日 第2回症例番号1-3において報告したものの追加報告 MedDRA: Version(8.0)
	1-3	感染症および寄生虫症	Ｂ型肝炎	米国	男性	26歳	2002/10/4	不明	症例報告	当該製品	識別番号：03000006(追加報告) 報告日：2005年7月4日 第2回症例番号1-3において報告したものの追加報告 MedDRA: Version(8.0)
	4-1	臨床検査	HTLV-1血清学的検査陽性	フランス	男性	6歳	2005年	不明	症例報告	当該製品	識別番号： 05000001(追加報告) 報告日：2005年6月27日 第4回症例番号4-1において報告したものの追加報告 MedDRA: Version(8.0)
	4-1	臨床検査	HTLV-2血清学的検査陽性	フランス	男性	6歳	2005年	不明	症例報告	当該製品	識別番号： 05000001(追加報告) 報告日：2005年6月27日 第4回症例番号4-1において報告したものの追加報告 MedDRA: Version(8.0)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第４回	4-1	臨床検査	HTLV-1 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001（追加報告） 報告日：2005 年 4 月 25 日 MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-1 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001（完了報告） 報告日：2005 年 4 月 7 日 MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-2 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001（追加報告） 報告日：2005 年 4 月 25 日） MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-2 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001（完了報告） 報告日：2005 年 4 月 7 日 MedDRA: Version (8.0)
	4-2	感染症および寄生虫症	Ｃ型肝炎	フランス	男性	不明	不明	不明	症例報告	外国製品	識別番号：04000129 報告日：2005 年 3 月 31 日） MedDRA: Version (8.0)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第３回	3-1	感染症および寄生虫症	Ｃ型肝炎	米国	女性	37歳	2004/5/21	不明	症例報告	当該製品	識別番号：04000023 報告日：2004年6月30日 MedDRA: Version(7.0)
	3-2	臨床検査	Ｂ型肝炎抗体陽性	米国	女性	63歳	2004/7/27	不明	症例報告	当該製品	識別番号：04000059 報告日：2004年9月7日 MedDRA: Version(7.0)
	3-2	臨床検査	Ａ型肝炎抗体陽性	米国	女性	63歳	2004/8/16	不明	症例報告	当該製品	識別番号：04000059 報告日：2004年9月7日 MedDRA: Version(7.0)
	3-3	臨床検査	Ｂ型肝炎抗体陽性	米国	女性	50歳代	2004/9月	不明	症例報告	当該製品	識別番号：04000082 報告日：2004年10月20日 MedDRA: Version(7.1)
	3-3	臨床検査	Ａ型肝炎抗体陽性	米国	女性	50歳代	2004/9月	不明	症例報告	当該製品	識別番号：04000082 報告日：2004年10月20日 MedDRA: Version(7.1)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第２回	1-3	感染症および寄生虫症	Ｃ型肝炎	米国	男性	26歳	2003/8/30	軽快	症例報告	当該製品	識別番号：03000006 報告日：2004年1月7日 第1回症例番号1-3において報告したもの（FAX報告）の完了報告 MedDRA: Version(6.1)
	2-2	感染症および寄生虫症	Ｃ型肝炎	ドイツ	女性	6歳	1994/6/21	未回復	症例報告	外国製品	識別番号：04000013 報告日：2004年5月27日 MedDRA: Version(7.0)
第１回	1-1	臨床検査	Ｃ型肝炎ウイルス	米国	男性	不明	不明	未回復	症例報告	外国製品	識別番号：D03-31 報告日：2003年8月6日 MedDRA: Version(6.1)
	1-2	臨床検査	Ｃ型肝炎ウイルス	米国	男性	不明	不明	未回復	症例報告	外国製品	識別番号：A03-32 報告日：2003年8月6日 MedDRA: Version(6.1)
	1-3	感染症および寄生虫症	Ｃ型肝炎	米国	男	26歳	2003/8/30	軽快	症例報告	当該製品	FAX報告 報告日：2003年11月19日 （識別番号：03000006 2003年11月28日） MedDRA: Version(6.1)

00165	2009/6/26	バクスター	乾燥イオン交換樹脂処理人免疫グロブリン	人免疫グロブリンG	

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	肝炎ウイルスキャリアー	米国	不明	不明	1993	不明	症例報告	当該製品	識別番号： 08000002（完了報告） 報告日：2008年12月22日 MedDRA: Version(11.1)
	12-2	感染症および寄生虫症	Ｃ型肝炎	米国	女性	48	2008/12/09	未回復	症例報告	当該製品	識別番号： 08000034（完了報告） 報告日：2008年 1月19日 MedDRA: Version(11.1)
	12-3	感染症および寄生虫症	Ｃ型肝炎	米国	女性	不明	不明	不明	症例報告	当該製品	識別番号： 09000004（完了報告） 報告日：2008年 5月18日 MedDRA: Version(12.0)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第11回	11-1	臨床検査	Ｂ型肝炎抗体陽性	米国	男性	17	2008/05	不明	症例報告	当該製品	識別番号： 08000007（完了報告） 報告日：2008年6月5日 MedDRA: Version(11.0)
	11-2	感染症および寄生虫症	Ｃ型肝炎	米国	女性	不明	2008	不明	症例報告	当該製品	識別番号： 08000018（追加報告） 報告日：2008年11月12日 弟11回症例番号11-2において10月17日に報告したものの追加報告 MedDRA: Version(11.1)
	11-2	感染症および寄生虫症	Ｃ型肝炎	米国	女性	不明	2008	不明	症例報告	当該製品	識別番号： 08000018（完了報告） 報告日：2008年10月17日 MedDRA: Version(11.0)
	11-3	感染症および寄生虫症	Ｂ型肝炎	スペイン	女性	不明	2008/6/3	未回復	症例報告	外国製品	識別番号： 08000026（完了報告） 報告日：2008年10月31日 MedDRA: Version(11.1)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第10回		0*	0	0	0	0	0	0	0	0	* 当該調査期間に対象となる感染症報告はなかった
第9回		0	0	0	0	0	0	0	0	0	
第8回		0	0	0	0	0	0	0	0	0	
第7回	7-1	臨床検査	ＨＩＶ抗体陽性	米国	不明	小児	不明	不明	症例報告	外国製品	識別番号： 06000022 (完了報告) 報告日：2006年8月24日 MedDRA: Version (9.0)
第6回	5-1	感染症および寄生虫症	Ｃ型肝炎	米国	男性	51歳	2005年9月	未回復	症例報告	当該製品	識別番号： 05000456 (追加報告) 報告日：2006年2月15日 第6回症例番号5-1は前回報告における第5回症例番号5-1において報告したものの追加報告 MedDRA: Version (8.1)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第５回	5-1	感染症および寄生虫症	Ｃ型肝炎	米国	男性	51歳	2005年９月	未回復	症例報告	当該製品	識別番号：　05000456（追加報告） 報告日：2005年11月11日 MedDRA: Version（8.1）
	5-1	感染症および寄生虫症	Ｃ型肝炎	米国	男性	51歳	2005年９月	未回復	症例報告	当該製品	識別番号：　05000456（完了報告） 報告日：2005年10月27日 MedDRA: Version（8.1）
	1-3	感染症および寄生虫症	Ｃ型肝炎	米国	男性	26歳	2002/11/19	不明	症例報告	当該製品	識別番号：03000006（追加報告） 報告日：2005年７月４日 第２回症例番号1-3において報告したものの追加報告　MedDRA: Version（8.0）
	1-3	感染症および寄生虫症	Ｂ型肝炎	米国	男性	26歳	2002/10/4	不明	症例報告	当該製品	識別番号：03000006（追加報告） 報告日：2005年７月４日 第２回症例番号1-3において報告したものの追加報告　MedDRA: Version（8.0）
	4-1	臨床検査	HTLV-1血清学的検査陽性	フランス	男性	6歳	2005年	不明	症例報告	当該製品	識別番号：　05000001（追加報告） 報告日：2005年６月27日 第４回症例番号4-1において報告したものの追加報告　MedDRA: Version（8.0）
	4-1	臨床検査	HTLV-2血清学的検査陽性	フランス	男性	6歳	2005年	不明	症例報告	当該製品	識別番号：　05000001（追加報告） 報告日：2005年６月27日 第４回症例番号4-1において報告したものの追加報告　MedDRA: Version（8.0）

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第４回	4-1	臨床検査	HTLV-1 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001 (追加報告) 報告日：2005 年 4 月 25 日 MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-1 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001 (完了報告) 報告日：2005 年 4 月 7 日 MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-2 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001 (追加報告) 報告日：2005 年 4 月 25 日) MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-2 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001 (完了報告) 報告日：2005 年 4 月 7 日 MedDRA: Version (8.0)
	4-2	感染症および寄生虫症	Ｃ型肝炎	フランズ	男性	不明	不明	不明	症例報告	外国製品	識別番号： 04000129 報告日：2005 年 3 月 31 日) MedDRA: Version (8.0)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第３回	3-1	感染症および寄生虫症	Ｃ型肝炎	米国	女性	37 歳	2004/5/21	不明	症例報告	当該製品	識別番号：04000023 報告日：2004 年 6 月 30 日 MedDRA: Version(7.0)
	3-2	臨床検査	Ｂ型肝炎抗体陽性	米国	女性	63 歳	2004/7/27	不明	症例報告	当該製品	識別番号：04000059 報告日：2004 年 9 月 7 日 MedDRA: Version(7.0)
	3-2	臨床検査	Ａ型肝炎抗体陽性	米国	女性	63 歳	2004/8/16	不明	症例報告	当該製品	識別番号：04000059 報告日：2004 年 9 月 7 日 MedDRA: Version(7.0)
	3-3	臨床検査	Ｂ型肝炎抗体陽性	米国	女性	50 歳代	2004/9 月	不明	症例報告	当該製品	識別番号：04000082 報告日：2004 年 10 月 20 日 MedDRA: Version(7.1)
	3-3	臨床検査	Ａ型肝炎抗体陽性	米国	女性	50 歳代	2004/9 月	不明	症例報告	当該製品	識別番号：04000082 報告日：2004 年 10 月 20 日 MedDRA: Version(7.1)

別紙様式第4

別紙(3)

感染症発生症例一覧

	番号	感染症の種類器官別大分類	基本語	発生国	性別	年齢	発現時期	転帰	出典	区分	備考
第13回		報告なし									
第12回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	77	2009/1/5	不明	症例報告	外国製品	識別番号3-08000039 報告日:2009年02月17日
第11回	1	感染症および寄生虫症	HIV感染	ドイツ	男	35	不明	不明	症例報告	外国製品	識別番号3-08000029 報告日:2009年02月17日
	1	感染症および寄生虫症	B型肝炎	ドイツ	男	35	不明	不明	症例報告	外国製品	識別番号3-08000029 報告日:2009年02月17日
第10回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	24	2008/1/10	不明	症例報告	外国製品	識別番号3-07000026 報告日:2008年4月1日
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	60	2007/4/13	不明	症例報告	外国製品	識別番号3-08000005 報告日:2008年5月29日
第9回		報告なし									
第8回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日：2006年12月20日
	1	臨床検査	C型肝炎抗体陽性	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日：2006年12月20日
	1	臨床検査	C型肝炎RNA陽性	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日：2006年12月20日
第7回		報告なし									
第6回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号:3-05000494 報告日:2005年12月27日
	1	感染症および寄生虫症	輸血後肝炎	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号:3-05000494 報告日:2005年12月27日
	1	臨床検査	抗HBs抗体陽性	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号:3-05000494 報告日:2005年12月27日
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	識別番号:3-06000004 報告日:2006年5月18日
第5回		報告なし									
第4回	1	感染症および寄生虫症	ウイルス性肝炎	ドイツ	女	55	1995年	不明	症例報告	外国製品	識別番号:3-04000122 報告日:2005年6月8日
第3回		報告なし									
第2回		報告なし									
第1回	1	感染症および寄生虫症	C型肝炎	ドイツ	男	64歳	2003/7/2	後遺症	症例報告	外国製品	識別番号D03-51 報告日:2003年10月10日
	1	臨床検査	C型肝炎抗体陽性	ドイツ	男	64歳	2003/7/2	後遺症	症例報告	外国製品	識別番号D03-51 報告日:2003年10月10日
	1	臨床検査	C型肝炎RNA陽性	ドイツ	男	64歳	2003/7/2	後遺症	症例報告	外国製品	識別番号D03-51 報告日:2003年10月10日
	2	感染症および寄生虫症	サイトメガロウイルス感染	ドイツ	男	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003年11月19日
	2	臨床検査	サイトメガロウイルス抗体陽性	ドイツ	男	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003年11月19日
	2	臨床検査	サイトメガロウイルス抗体陽性	ドイツ	男	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003年11月19日

別紙様式第4

別紙(4)

感染症発生症例一覧

	番号	感染症の種類器官別大分類	基本語	発生国	性別	年齢	発現時期	転帰	出典	区分	備考
第12回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	77	2009/1/5	不明	症例報告	外国製品	識別番号3-08000039 報告日:2009年02月17日
第11回	1	感染症および寄生虫症	HIV感染	ドイツ	男	35	不明	不明	症例報告	外国製品	識別番号3-08000029 報告日:2009年02月17日
	1	感染症および寄生虫症	B型肝炎	ドイツ	男	35	不明	不明	症例報告	外国製品	識別番号3-08000029 報告日:2009年02月17日
第10回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	24	2008/1/10	不明	症例報告	外国製品	識別番号3-07000026 報告日:2008年4月1日
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	60	2007/4/13	不明	症例報告	外国製品	識別番号3-08000005 報告日:2008年5月29日
第9回	報告なし										
第8回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日:2006年12月20日
	1	臨床検査	C型肝炎抗体陽性	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日:2006年12月20日
	1	臨床検査	C型肝炎RNA陽性	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日:2006年12月20日
第7回	報告なし										
第6回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号:3-05000494 報告日:2005年12月27日
	1	感染症および寄生虫症	輸血後肝炎	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号:3-05000494 報告日:2005年12月27日
	1	臨床検査	抗HBs抗体陽性	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号:3-05000494 報告日:2005年12月27日
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	識別番号:3-06000004 報告日:2006年5月18日
第5回	報告なし										
第4回	1	感染症および寄生虫症	ウイルス性肝炎	ドイツ	女	55	1995年	不明	症例報告	外国製品	識別番号:3-04000122 報告日:2005年6月8日
第3回	報告なし										
第2回	報告なし										
第1回	1	感染症および寄生虫症	C型肝炎	ドイツ	男	64歳	2003/7/2	後遺症	症例報告	外国製品	識別番号D03-51 報告日:2003年10月10日
	1	臨床検査	C型肝炎抗体陽性	ドイツ	男	64歳	2003/7/2	後遺症	症例報告	外国製品	識別番号D03-51 報告日:2003年10月10日
	1	臨床検査	C型肝炎RNA陽性	ドイツ	男	64歳	2003/7/2	後遺症	症例報告	外国製品	識別番号D03-51 報告日:2003年10月10日
	2	感染症および寄生虫症	サイトメガロウイルス感染	ドイツ	男	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003年11月19日
	2	臨床検査	サイトメガロウイルス抗体陽性	ドイツ	男	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003年11月19日
	2	臨床検査	サイトメガロウイルス抗体陽性	ドイツ	男	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003年11月19日
	2	臨床検査	サイトメガロウイルス検査陽性	ドイツ	男	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003年11月19日

	番号	感染症の種類器官別大分類	基本語	発生国	性別	年齢	発現時期	転帰	出典	区分	備考
	3	臨床検査	C型肝炎RNA陽性	ドイツ	女	71歳	2003/6/27	後遺症	症例報告	外国製品	識別番号D03-41 報告日:2003年9月11日
	4	感染症および寄生虫症	HIV感染	ドイツ	男	67歳	2000/4頃	後遺症	症例報告	外国製品	識別番号D03-47 報告日:2003年10月3日
	5	感染症および寄生虫症	C型肝炎	ドイツ	男	不明	不明	後遺症	症例報告	外国製品	識別番号D03-40 報告日:2003年9月11日

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90170	2009/7/17	CSL ベーリング	乾燥濃縮人アンチトロンビンIII	乾燥濃縮人アンチトロンビンIII

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	HIV感染	フランス	男	49歳	不明	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
	12-2	感染症および寄生虫症	C型肝炎	フランス	男	49歳	1996	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
第11回	該当なし										
第10回	10-1	感染症および寄生虫症	C型肝炎	米国	男	43歳	1990	未回復	症例報告	当該製品	識別番号：07000020 報告日：2008年1月18日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎表面抗原陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎DNA測定値陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
第9回	該当なし										
第8回	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月9日 MedDRA: Version(9.1)
	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月27日 2007年4月9日に提出した症例番号8-1の追加報告 MedDRA: Version(9.1)

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	HIV感染	フランス	男	49歳	不明	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
	12-2	感染症および寄生虫症	C型肝炎	フランス	男	49歳	1996	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
第11回	該当なし										
第10回	10-1	感染症および寄生虫症	C型肝炎	米国	男	43歳	1990	未回復	症例報告	当該製品	識別番号：07000020 報告日：2008年1月18日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎表面抗原陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎DNA測定値陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
第9回	該当なし										
第8回	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月9日 MedDRA: Version(9.1)
	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月27日 2007年4月9日に提出した症例番号8-1の追加報告 MedDRA: Version(9.1)

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	HIV感染	フランス	男	49歳	不明	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
	12-2	感染症および寄生虫症	C型肝炎	フランス	男	49歳	1996	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
第11回	該当なし										
第10回	10-1	感染症および寄生虫症	C型肝炎	米国	男	43歳	1990	未回復	症例報告	当該製品	識別番号：07000020 報告日：2008年1月18日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎表面抗原陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎DNA測定値陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
第9回	該当なし										
第8回	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月9日 MedDRA: Version(9.1)
	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月27日 2007年4月9日に提出した症例番号8-1の追加報告 MedDRA: Version(9.1)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第７回											
第６回	5-1	臨床検査	HIV 検査陽性	韓国	男	5 歳	2004/9/15	未回復	症例報告	当該製品	識別番号：05000406 報告日：2006 年 2 月 6 日 第 6 回症例番号 5-1 は前回報告における第 5 回症例番号 5-1 において報告したものの取り下げ報告 MedDRA: Version(8.0)
	6-1	臨床検査	B 型肝炎抗原陽性	アメリカ	男	66 歳	2005/12/9	未回復	症例報告	当該製品	識別番号：05000495 報告日：2006 年 2 月 2 日 MedDRA: Version(8.1)
第５回	5-1	臨床検査	HIV 検査陽性	韓国	男	5 歳	2004/9/15	未回復	症例報告	当該製品	識別番号：05000406 報告日：2005 年 8 月 18 日 MedDRA: Version(8.0)
第４回	該当なし										
第３回	3-1	臨床検査	C 型肝炎陽性	米国	男	14 歳	2001/11/30	不明	症例報告	当該製品	識別番号：04000072 報告日：2004 年 12 月 13 日 MedDRA: Version(7.1)
	3-2	臨床検査	C 型肝炎陽性	米国	男	10 歳	2002/9/11	不明	症例報告	当該製品	識別番号：04000073 報告日：2004 年 12 月 13 日 MedDRA: Version(7.1)
第２回	2-1	臨床検査	A 型肝炎抗体陽性	フランス	不明	50 歳	不明	不明	症例報告	当該製品	識別番号：03000021 報告日：2004 年 2 月 18 日 MedDRA: Version(6.1)

注）第１回は該当なし。

90176	2009/7/30	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	インスリン（抗第Ⅷ因子モノクローナル抗体製造用）	

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感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	HIV感染	フランス	男	49歳	不明	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
	12-2	感染症および寄生虫症	C型肝炎	フランス	男	49歳	1996	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
第11回	該当なし										
第10回	10-1	感染症および寄生虫症	C型肝炎	米国	男	43歳	1990	未回復	症例報告	当該製品	識別番号：07000020 報告日：2008年1月18日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎表面抗原陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎DNA測定値陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
第9回	該当なし										
第8回	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月9日 MedDRA: Version(9.1)
	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月27日 2007年4月9日に提出した症例番号8-1の追加報告 MedDRA: Version(9.1)

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感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	HIV感染	フランス	男	49歳	不明	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
	12-2	感染症および寄生虫症	C型肝炎	フランス	男	49歳	1996	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
第11回	該当なし										
第10回	10-1	感染症および寄生虫症	C型肝炎	米国	男	43歳	1990	未回復	症例報告	当該製品	識別番号：07000020 報告日：2008年1月18日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎表面抗原陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎DNA測定値陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
第9回	該当なし										
第8回	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月9日 MedDRA: Version(9.1)
	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月27日 2007年4月9日に提出した症例番号8-1の追加報告 MedDRA: Version(9.1)

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感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	HIV感染	フランス	男	49歳	不明	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
	12-2	感染症および寄生虫症	C型肝炎	フランス	男	49歳	1996	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
第11回	該当なし										
第10回	10-1	感染症および寄生虫症	C型肝炎	米国	男	43歳	1990	未回復	症例報告	当該製品	識別番号：07000020 報告日：2008年1月18日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎表面抗原陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎DNA測定値陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
第9回	該当なし										
第8回	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月9日 MedDRA: Version(9.1)
	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月27日 2007年4月9日に提出した症例番号8-1の追加報告 MedDRA: Version(9.1)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第７回											
第６回	5-1	臨床検査	HIV 検査陽性	韓国	男	5 歳	2004/9/15	未回復	症例報告	当該製品	識別番号：05000406 報告日：2006 年 2 月 6 日 第 6 回症例番号 5-1 は前回報告における第 5 回症例番号 5-1 において報告したものの取り下げ報告 MedDRA: Version (8.0)
	6-1	臨床検査	B 型肝炎抗原陽性	アメリカ	男	66 歳	2005/12/9	未回復	症例報告	当該製品	識別番号：05000495 報告日：2006 年 2 月 2 日 MedDRA: Version (8.1)
第５回	5-1	臨床検査	HIV 検査陽性	韓国	男	5 歳	2004/9/15	未回復	症例報告	当該製品	識別番号：05000406 報告日：2005 年 8 月 18 日 MedDRA: Version (8.0)
第４回	該当なし										
第３回	3-1	臨床検査	C 型肝炎陽性	米国	男	14 歳	2001/11/30	不明	症例報告	当該製品	識別番号：04000072 報告日：2004 年 12 月 13 日 MedDRA: Version (7.1)
	3-2	臨床検査	C 型肝炎陽性	米国	男	10 歳	2002/9/11	不明	症例報告	当該製品	識別番号：04000073 報告日：2004 年 12 月 13 日 MedDRA: Version (7.1)
第２回	2-1	臨床検査	A 型肝炎抗体陽性	フランス	不明	50 歳	不明	不明	症例報告	当該製品	識別番号：03000021 報告日：2004 年 2 月 18 日 MedDRA: Version (6.1)

注）第１回は該当なし。

90179	2009/7/30	バクスター	ルリオクトコグ アルファ（遺伝子組換え）		培養補助剤（抗第Ⅷ因子モノクローナル抗体製造用-1）

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	HIV感染	フランス	男	49歳	不明	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
	12-2	感染症および寄生虫症	C型肝炎	フランス	男	49歳	1996	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
第11回	該当なし										
第10回	10-1	感染症および寄生虫症	C型肝炎	米国	男	43歳	1990	未回復	症例報告	当該製品	識別番号：07000020 報告日：2008年1月18日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎表面抗原陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎DNA測定値陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
第9回	該当なし										
第8回	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月9日 MedDRA: Version(9.1)
	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月27日 2007年4月9日に提出した症例番号8-1の追加報告 MedDRA: Version(9.1)

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	12-1	感染症および寄生虫症	HIV感染	フランス	男	49歳	不明	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
	12-2	感染症および寄生虫症	C型肝炎	フランス	男	49歳	1996	不明	症例報告	当該製品	識別番号：08000041 報告日：2008年3月18日 MedDRA: Version(12.0) 本例は2回目の報告であるが最新の1行に集約し、更新した。
第11回	該当なし										
第10回	10-1	感染症および寄生虫症	C型肝炎	米国	男	43歳	1990	未回復	症例報告	当該製品	識別番号：07000020 報告日：2008年1月18日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎表面抗原陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
	10-2	臨床検査	B型肝炎DNA測定値陽性	韓国	男	不明	2008/3/8	未回復	症例報告	当該製品	識別番号：08000003 報告日：2008年4月21日 MedDRA: Version(10.1)
第9回	該当なし										
第8回	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月9日 MedDRA: Version(9.1)
	8-1	臨床検査	C型肝炎抗体陽性	日本	男	11歳	2007/3/8	未回復	症例報告	当該製品	識別番号：07000005 報告日：2007年4月27日 2007年4月9日に提出した症例番号8-1の追加報告 MedDRA: Version(9.1)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第７回											
第６回	5-1	臨床検査	HIV 検査陽性	韓国	男	5 歳	2004/9/15	未回復	症例報告	当該製品	識別番号：05000406 報告日：2006 年 2 月 6 日 第 6 回症例番号 5-1 は前回報告における第 5 回症例番号 5-1 において報告したものの取り下げ報告 MedDRA: Version (8.0)
	6-1	臨床検査	B 型肝炎抗原陽性	アメリカ	男	66 歳	2005/12/9	未回復	症例報告	当該製品	識別番号：05000495 報告日：2006 年 2 月 2 日 MedDRA: Version (8.1)
第５回	5-1	臨床検査	HIV 検査陽性	韓国	男	5 歳	2004/9/15	未回復	症例報告	当該製品	識別番号：05000406 報告日：2005 年 8 月 18 日 MedDRA: Version (8.0)
第４回	該当なし										
第３回	3-1	臨床検査	C 型肝炎陽性	米国	男	14 歳	2001/11/30	不明	症例報告	当該製品	識別番号：04000072 報告日：2004 年 12 月 13 日 MedDRA: Version (7.1)
	3-2	臨床検査	C 型肝炎陽性	米国	男	10 歳	2002/9/11	不明	症例報告	当該製品	識別番号：04000073 報告日：2004 年 12 月 13 日 MedDRA: Version (7.1)
第２回	2-1	臨床検査	A 型肝炎抗体陽性	フランス	不明	50 歳	不明	不明	症例報告	当該製品	識別番号：03000021 報告日：2004 年 2 月 18 日 MedDRA: Version (6.1)

注）第１回は該当なし。

90181	2009/7/30	バクスター	ルリオクトコグ アルファ（遺伝子組換え）			人血清アルブミン

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発生国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	77	2009/1/5	不明	症例報告	外国製品	識別番号3-08000039 報告日:2009年02月17日
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	77	2009/1/5	不明	症例報告	外国製品	識別番号3-08000040 報告日:2009年02月17日
	3	感染症および寄生虫症	C型肝炎	ドイツ	男	66	2009/5/1	不明	症例報告	外国製品	識別番号3-09000009 報告日:2009年07月22日
第11回	1	感染症および寄生虫症	HIV感染	ドイツ	男	35	不明	不明	症例報告	外国製品	識別番号3-08000029 報告日:2009年02月17日 *
	1	感染症および寄生虫症	B型肝炎	ドイツ	男	35	不明	不明	症例報告	外国製品	識別番号3-08000029 報告日:2009年02月17日 *
第10回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	24	2008/1/10	不明	症例報告	外国製品	識別番号3-07000026 報告日:2008年4月1日
	2	臨床検査	C型肝炎抗体陽性	日本	女	37	2007/9/11	不明	症例報告	当該製品	識別番号1-07000251 報告日:2008年4月30日
	3	感染症および寄生虫症	B型肝炎	ドイツ	男	24	2008/1/10	不明	症例報告	外国製品	識別番号3-07000031 報告日:2008年3月25日
	4	感染症および寄生虫症	C型肝炎	ドイツ	女	60	2007/4/13	不明	症例報告	外国製品	識別番号3-08000005 報告日:2008年5月29日
第9回	1	感染症および寄生虫症	B型肝炎	日本	女	33	2007/8/7	回復	症例報告	当該製品	識別番号1-07000093 報告日:2007年10月11日
第8回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	61	2007年1月	不明	症例報告	外国製品	識別番号3-06000032 報告日:2007年3月30日
	1	臨床検査	C型肝炎陽性	ドイツ	女	61	2007年1月	不明	症例報告	外国製品	識別番号3-06000032 報告日:2007年3月30日
第7回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日:2006年12月20日
	1	臨床検査	C型肝炎抗体陽性	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日:2006年12月20日
	1	臨床検査	C型肝炎RNA陽性	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日:2006年12月20日
第6回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	識別番号3-06000004 報告日:2006/5/18
第5回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号3-05000494 報告日:2005/12/27
	1	感染症および寄生虫症	輸血後肝炎	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号3-05000494 報告日:2005/12/27
	1	臨床検査	抗HBs抗体陽性	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号3-05000494 報告日:2005/12/27
	2	感染症および寄生虫症	B型肝炎	ドイツ	女	77	2005/9/28	未回復	症例報告	外国製品	識別番号3-05000493 報告日:2005/12/27
第4回	1	感染症および寄生虫症	C型肝炎	ドイツ	不明	不明	不明	不明	症例報告	外国製品	識別番号3-04000125 報告日:2005/5/27
	2	感染症および寄生虫症	ウイルス性肝炎	ドイツ	女	55	1995年	不明	症例報告	外国製品	識別番号3-04000122 報告日:2005/6/8
第3回	1	臨床検査	C型肝炎陽性	ドイツ	男	68	2004/08	不明	症例報告	外国製品	識別番号3-04000088 報告日:2004/11/22

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発生国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第12回	報告なし										
第11回	1	臨床検査	C型肝炎抗体陽性	ドイツ	女	66	2008/10/14	不明	症例報告	外国製品	識別番号3-08000030 報告日:2008年12月2日
第10回	報告なし										
第9回	報告なし										
第8回	報告なし										
第7回	報告なし										
第6回	報告なし										
第5回	報告なし										
第4回	報告なし										
第3回	報告なし										
第2回	報告なし										
第1回	1	感染症および寄生虫症	サイトメガロウイルス感染	ドイツ	男性	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003/11/19
	1	臨床検査	サイトメガロウイルス抗体陽性	ドイツ	男性	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003/11/19
	1	臨床検査	サイトメガロウイルス抗体陽性	ドイツ	男性	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003/11/19
	1	臨床検査	サイトメガロウイルス検査陽性	ドイツ	男性	0歳	2003/6末	死亡	症例報告	外国製品	識別番号3-03000005 報告日:2003/11/19

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90190	2009/8/24	CSLベーリング	人CI-インアクチベーター	人CI-インアクチベーター