資料2

感染症定期報告に関する今後の対応について

平成１６年度第５回
運営委員会確認事項
（平成１６年９月１７日）

1 基本的な方針

運営委員会に報告する資料においては、

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

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

2 具体的な方法

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

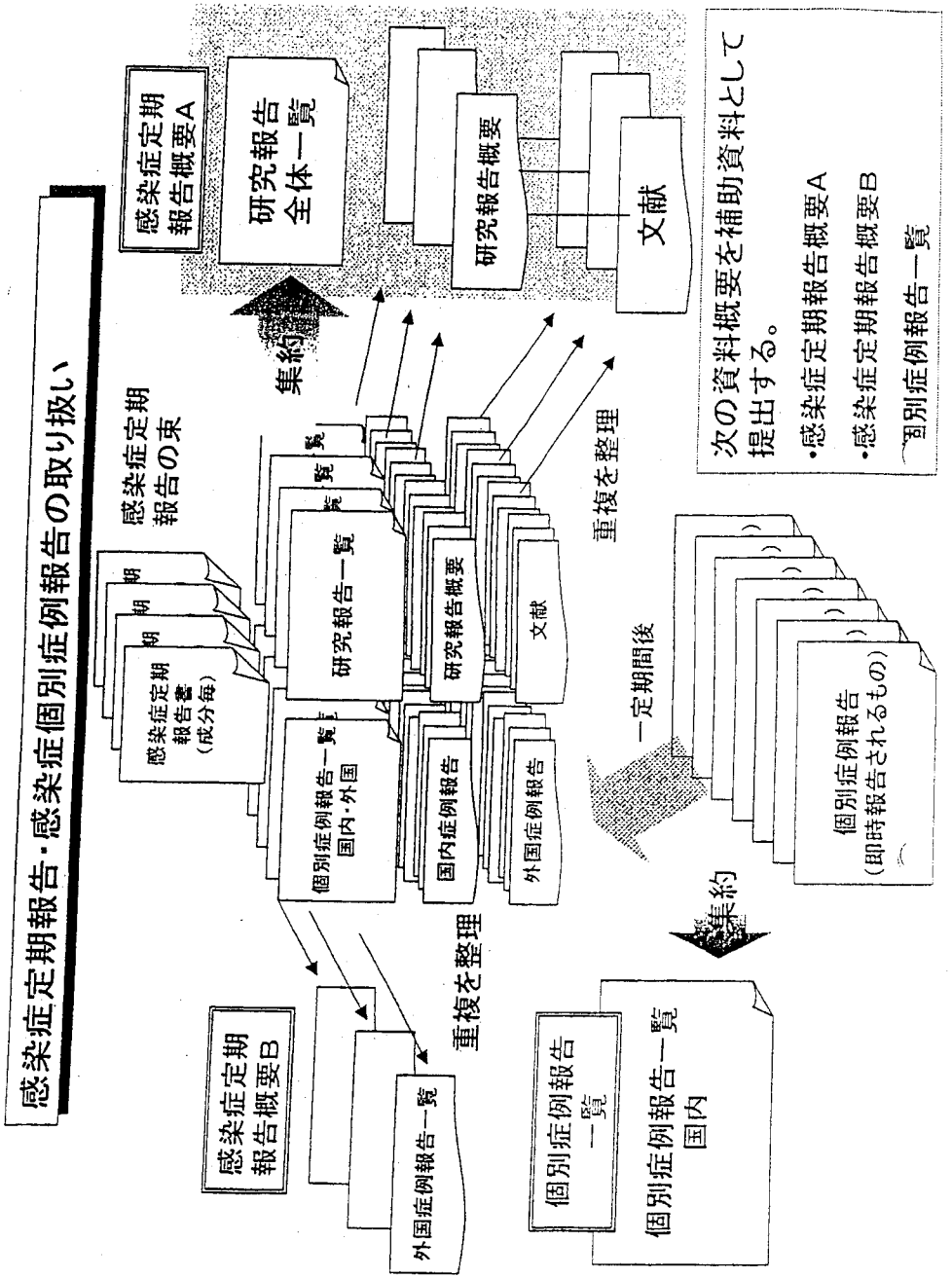
① 研究報告は、同一文献による重複を廃した別紙のような形式の一覧表を作成し、当該一覧表に代表的なものの報告様式（別紙様式第2）及び該当文献を添付した「資料概要A」を事務局が作成し、送付する。

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

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

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

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



感染症定期報告概要

（平成２１年７月２８日）

平成２１年３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３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(2008/3/1～2009/5/29)

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
90130	2009/4/24	90139	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。	1
90103	2009/3/26	81038	B型肝炎	J Hepatol 2008; 48: 1022-1025	スロヴェニアで、HBs抗原陰性で抗HBc抗体陽性、抗HBs抗体低力価陽性、HBV DNA陽性の濃厚赤血球と新鮮凍結血漿を輸血された59歳の患者が4ヶ月後に急性B型肝炎を発症した。また同じ供血血液由来のRCCの輸血を受けた71歳の患者も7ヶ月後にHBV感染を認めた。2例ともドナーと同じ配列を有するジェノタイプDが感染していた。潜在性B型肝炎ウイルス感染者の血液は抗HBs抗体が陽性にかかわらず、感染性を有した。	
90130	2009/4/24	90139	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。	
90154	2009/5/27	90197	B型肝炎	Transfusion 2008; 48: 1602-1608	供血時には血清検査陰性であったが、その後HBV DNAが検出された供血者由来の血液成分を輸血された2名の免疫不全患者について調べた。受血者1はHBVワクチン接種を受け、抗HBsキャリアであったが、赤血球輸血後13ヵ月で急性B型肝炎を発症するまで他のHBVマーカーは全て陰性であった。供血者とHBVシークエンスが一致したため、輸血関連感染と確認された。受血者2は血小板輸血を受けたが、感染していなかった。	
90140	2009/4/27	90151	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。	2
90130	2009/4/24	90139	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。	
90130	2009/4/24	90139	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。	3
90130	2009/4/24	90139	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。	
90130	2009/4/24	90139	C型肝炎	Clin Infect Dis 2008; 47: 931-934	ニューヨーク市のEast Harlemのクリニックから18歳以上で血中HCV PCR陽性の吸引用麻薬常習者38名の鼻汁検体および吸引に使用したストローを入手し、血液およびHCV RNAの存在の有無を調べた。鼻汁検体28例(74%)、ストロー3例(8%)から血液が検出され、鼻汁検体5例(13%)、ストロー2例(5%)でHCV RNAが検出された。HCVウイルスの鼻腔内伝播のウイルス学的妥当性が示された。	
90130	2009/4/24	90139	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。	4
90130	2009/4/24	90139	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。	5
90130	2009/4/24	90139	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。	6
90103	2009/3/26	81038	E型肝炎	Transfusion 2008; 48: 1368-1375	2004年9月20日に39歳日本人男性から献血された血液はALT高値のため不適当とされ、HEV陽性であった。当該ドナーの遡及調査の結果、9月6日にも献血を行い、HEV RNAを含有する血小板が輸血されていた。当該ドナーと親戚は8月14日にブタの焼肉を食べており、父親は9月14日に急性肝炎を発症し、E型劇症肝炎で死亡した。他に7名がHEV陽性であった。レシピエントは輸血22日目にALTが上昇し、HEVが検出された。	
90130	2009/4/24	90139	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。	7
90100	2009/3/19	81013	E型肝炎	Vox Sanguinis 2008; 95(Suppl.1): 282-283	2005年の中国の4都市(Beijing、Urmuchi、KunmingおよびGuangzhou)における供血検体のHEV感染率を調べた。その結果、ルーチン検査(抗HCV、抗HIV1/2、HBsAg、梅毒およびALT)陰性供血者の約1%は抗HEV IgMまたはHEV Ag陽性で、HEV感染の可能性があった。また、ALTスクリーニングは中国のHEV感染血排除に役立つ可能性があった。	
90116	2009/3/30	81068	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陽性率は非常に低い。	8
90116	2009/3/30	81068	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。	9
90145	2009/5/1	90184	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。	10
90145	2009/5/1	90184	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。	

90130	2009/4/24	90139	インフルエンザ	ProMED-mail20080825.2648	タミフル耐性型の「通常の」季節性インフルエンザが急速に拡大しており、南アフリカでは今年の冬(2008～2009年)のインフルエンザに効果がないおそれがある。WHOのデータによると同国でH1N1株に感染した107名に関する検査の結果、全員がタミフルに耐性の突然変異株を保有していた。2008年4月1日から8月20日に南半球の12カ国のH1N1インフルエンザ感染患者由来検体788例中242例(31%)がタミフル耐性に関係があるH274Y突然変異を有していた。	
90130	2009/4/24	90139	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。	
90136	2009/4/27	90147	ウイルス感染	PNAS 2008; 105: 14124-14129	新規ヒトカルジオウイルス7株についての報告。	
90125	2009/4/23	90119	ウイルス感染	Proc Natl Acad Sci USA 2008; 105: 14124-14129	インフルエンザ様疾患の小児の呼吸分泌物中から、汎ウイルスマイクロアレイ法を用いて、初めてヒトカルディオウイルスを同定した。系統遺伝学的分析から、このウイルスはTheilerのネズミ脳脊髄炎ウイルス亜型に属し、Saffoldウイルスと最も近縁であった。また、胃腸疾患患者群498名から得た751例の糞便検体中6検体からカルディオウイルスが検出された。	
90129	2009/4/23	90123	ウイルス感染	ProMED-mail20081028.3409	2008年10月初旬に南アフリカでアレナウイルスによる感染のアウトブレイクが同定された。9月12日から10月24日までに計5例が報告され、5例中4例が死亡し、1例は入院中である。死亡した4例では発病から死亡まで9～12日間であった。塩基配列分析より、ユニークな旧世界アレナウイルスが原因であることが明らかとなった。現在のところ新たな疑い症例はない。	
90117	2009/4/1	90003	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。	11
90130	2009/4/24	90139	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。	12
90147	2009/5/20	90188	ウイルス感染	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。	13
90148	2009/5/22	90189	ウイルス感染	WHO/EPR 2008年10月13日	南アフリカとザンビア出身者の最近の死亡例3例はアレナウイルス科のウイルスが原因あることが、NICDおよびCDCで行われた検査の結果明らかとなった。詳細な分析が継続されている。一方、南アフリカでは患者と密接に接触した看護師が感染し、入院中である。	
90147	2009/5/20	90188	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。	14

90117	2009/4/1	90003	ウイルス性脳炎	ProMED-mail20080828.2697	インド東部のウッタルプラデシ州で小児を死亡させている原因不明のウイルスは、インド保健省の専門家らにより急性脳炎症候群と診断された。同州の13の地区では、数週間におよそ600人の患者が発生し150人が死亡したと報告され、その数は増加すると見られている。血液検査で日本脳炎陽性となった患者は5%以下であった。日本脳炎とエンテロウイルスとの混合感染の可能性について調査中である。	
90116	2009/3/30	81068	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。	
90099	2009/3/19	81012	エボラ出血	OIE (December 23, 2009)	フィリピンマニラの農場で2008年10月にブタで始めてエボラレストンウイルスが確認され、2009年1月には当該農場の労働者少なくとも1名で抗体陽性を示した。同ウイルスのブタからヒトへの感染を示す初の報告。	15
90136	2009/4/27	90147	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。	16
90130	2009/4/24	90139	クロイツフェルト・ヤコブ病	Emerg Infect Dis 2009; 15: 265-271	孤発性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。	17
90116	2009/3/30	81068	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。	
90117	2009/4/1	90003	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。	18
90100	2009/3/19	81013	チクングニヤウイルス感染	Transfusion 2008; 48: 1333-1341	2005年から2007年に、チクングニヤウイルス(CHIKV)はレユニオン島で大流行し、供血は2006年1月に中断された。大流行中のウイルス血症血供血の平均リスクは、10万供血あたり132と推定された。2006年2月の最流行時におけるリスクは、10万供血あたり1500と最高であった。この期間中、757000人の住民のうち推定312500人が感染した。2006年1月から5月の平均推定リスク(0.7%)は、CHIKV NAT検査による血小板供血のリスク(0.4%)と同じオーダーであった。	
90100	2009/3/19	81013	デング熱	Transfusion 2008; 48: 1342-1347	高力価の培養デングウイルス セロタイプ2をアルブミンおよび免疫グロブリンの各種製造工程(低温エタノール分画、陽イオン交換クロマトグラフィー、低温殺菌、S/D処理およびウイルスろ過)前の検体に加え、各工程での同ウイルスのクリアランスをVero E6細胞培養におけるTCID50アッセイおよびRT-PCRで測定した。その結果、全ての工程が不活化・除去に有効であることが示された。	

90100	2009/3/19	81013	デング熱	Transfusion 2008; 48: 1348-1354	2005年9月20日～12月4日のブエルトルコの米国赤十字におけるすべての供血16521検体中のデングウイルス(DENV) RNAをTMA(transcription-mediated amplification)法で測定したところ、12検体(0.07%)がTMA陽性であった。4検体は、RT-PCR(DENVセロタイプ2および3)陽性であった。RT-PCR陽性4検体中3検体でウイルスを培養することができた。TMA陽性12検体中1検体がIgM陽性であった。1:16に希釈した場合は5検体のみTMA陽性であった	
90112	2009/3/27	81052	パベシア症	Clin Infect Dis 2008; 48: 25-30	FDAはBPDR(生物学的製剤逸脱報告システム)により、2005年に2例、2006年に3例、2007年に3例の輸血によるパベシア症感染報告を受けていた。受血者は輸血後2.5～7週で症状が進行し、2ヶ月以内に死亡した。	19
90103	2009/3/26	81038	パルボウィルス	Lab Hematol 2007; 13: 34-38	血漿交換、コルチコステロイドおよびコリンエステラーゼ阻害剤による治療を受けていた重症筋無力症患者が、アルブミンを用いた血漿交換を行った2週後にパルボウイルスB19感染による赤芽球減少症と診断された。アルブミン由来感染かどうかを確定することはできなかったが、アルブミンなどの血液製剤によるB19感染を除外することはできない。	
90145	2009/5/1	90184	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。	20
90145	2009/5/1	90184	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。	21
90129	2009/4/23	90123	マラリア	CDC/MMWR 2009; 58: 229-232	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。	22
90145	2009/5/1	90184	マラリア	Emerg Infect Dis 2008; 14: 1434-1436	2007年にマレー半島でフィンランドの旅行者が、通常はサルにおけるマラリアの原因となるニ日熱マラリア原虫に感染した。ニ日熱マラリア原虫はヒトマラリアを引き起こす第5のマラリア原虫種として確立された。この疾病は生命を脅かす危険があり、臨床医と臨床検査技師は旅行者においてこの病原体を更に注意すべきである。	
90145	2009/5/1	90184	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。	
90145	2009/5/1	90184	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。	23
90097	2009/3/26	80995	リケッチア症	ProMED-mail20080728.2306	オランダ・ブラバント州の公衆衛生局が行った調査でQ熱の症例報告数が急激に増加し、2008年7月21日付けで491症例が報告されている。感染症管理センター長によると、実際の感染者数は報告された症例数の10倍であると思われる。2007年まではQ熱はオランダではほとんど存在しなかった。	

90153	2009/5/25	90196	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。	24
90117	2009/4/1	90003	レトロウイルス	第56回日本ウイルス学会学術集会(2008年10月27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。	25
90145	2009/5/1	90184	リケッチア症	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。	26
90116	2009/3/30	81068	異型クロイツフェルト・ヤコブ病	2008年プリオン研究会 2008年8月29-30日	CJDサーベイランス委員会による調査では1999年4月から2008年2月までの9年間に日本国内で1069例がプリオン病と判定された。うち孤発性CJDが821例(76.8%)、遺伝性プリオン病が171例(16.0%)、硬膜移植後CJD74例(6.9%)、変異型CJD1例(0.1%)、分類不能2例(0.2%)であった。日本のプリオン病剖検率は欧米諸国より著明に低かった。孤発性CJDの病型は欧米に比べMM2型が多かったが、非典型例が多く剖検されている可能性が考えられた。	
90116	2009/3/30	81068	異型クロイツフェルト・ヤコブ病	2008年プリオン研究会 2008年8月29-30日 ポスター11	ウイルス除去膜濾過工程を含んでいる製剤(血液凝固第VIII因子製剤:プラノバ20N濾過、抗HBs人免疫グロブリン製剤:プラノバ35N濾過)について、263K株感染ハムスターより得たSUS処理PrPScを用いて、その除去効果を検証した。その結果、SUS処理PrPScは濾過膜の孔径よりも小さいにもかかわらず、プラノバ35Nやプラノバ20Nで除去された。PrPScが凝集したり、膜へ吸着したためと考えられる。	
90116	2009/3/30	81068	異型クロイツフェルト・ヤコブ病	2008年プリオン研究会 2008年8月29-30日 ポスター18	スクレイピー263K感染ハムスター脳乳剤を脳内接種したハムスターにおける血中PrPres経時的変化を追跡したところ、PK抵抗性3F4反応性蛋白バンドは、感染後4～6週で認められ、10週ではほぼ消失した。発症末期では血中PrPresと見られる蛋白バンドは認められなかった。PrPresをマーカーとした血液検査は感染後発症前～発症中期までに限定される可能性が示唆された。	
90112	2009/3/27	81052	異型クロイツフェルト・ヤコブ病	American Society of Hematology/Press Releases 2008年8月28日	Blood誌のprepublished onlineに掲載されたヒツジにおける研究によると、輸血によるBSE伝播のリスクは驚くほど高い。エジンバラ大学で行われた9年間の研究は、BSEまたはスクレイピーに感染したヒツジからの輸血による疾病伝播率を比較した。その結果、BSEおよびスクレイピーとも輸血によりヒツジに効率よく伝播された。症状を呈する前のドナーから採取された血液によっても伝播することが示された。	
90116	2009/3/30	81068	異型クロイツフェルト・ヤコブ病	Blood. Prepublished online 2008年7月22日	ヒツジを用いた感染実験において、BSEは36%、スクレイピーは43%と予想以上に高い輸血伝播率を示した。高い伝播率および臨床的に陽性のレシピエントにおける比較的短期間の一定した潜伏期間は、血中の感染性力価が高いことおよびTSEが輸血により効率的に伝播することを示唆する。血液製剤によるヒトでのvCJD伝播を研究するために、ヒツジが有用なモデルであることが示された。	

90100	2009/3/19	81013	異型クロイツフェルト・ヤコブ病	Cell 2008; 134: 757-768	マウスPrPScと混合させることによって折り畳み異常が起こったハムスターPrPCは、野生型ハムスターに対して感染性を起こす新規なプリオンを生成した。同様の結果は、反対方向でも得られた。PMCA増幅を繰り返すとin vitro産生プリオンの順応が起こる。このプロセスは、in vivoでの連続継代に観察される株の安定化を暗示させる。種の壁と株の生成がPrP折り畳み異常の伝播によって決定されることが示唆される。	
90100	2009/3/19	81013	異型クロイツフェルト・ヤコブ病	Emerg Infect Dis 2008; 14: 1406-1412	263Kスクレイピーの臨床症状を呈するハムスター22匹の尿にTSE感染性があることが示された。これらの動物の腎臓と膀胱のホモジネートは20000倍以上希釈してもTSE感染性があった。組織学的、免疫組織化学的分析では、腎臓における疾患関連PrPの散発的な沈着以外、炎症や病変は見られなかった。尿中のTSE感染性が、自然のTSEの水平感染に何らかの役割を果たす可能性がある。	
90118	2009/4/15	90068	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。	27
90144	2009/4/30	90183	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。	28
90138	2009/4/27	90149	異型クロイツフェルト・ヤコブ病	J. Hosp. Infect. 2009; 72: 65-70	新規のプリオン不活化法として、Bacillus lentusサブチリシン遺伝子を変異させて得られたアルカリプロテアーゼ:MC3の報告。MC3はプロテイナーゼKよりも高い分解能を示し、MC3消化の感染性マウス脳ホモジネート(iMBH)投与マウスの生存率は、非分解iMBH投与マウスと比較して極めて高かった。	29
90132	2009/4/24	90141	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。	30
90136	2009/4/27	90147	異型クロイツフェルト・ヤコブ病	News-Medical.Net 2008 Dec 22	Amorfix Life Sciences社(カナダ)が開発した血漿中におけるvCJDプリオンタンパク質の検査法。脳ホモジネートを1/1,000,000まで希釈した検体を検出することが可能である。	31
90116	2009/3/30	81068	異型クロイツフェルト・ヤコブ病	PLoS ONE 2008; 3: e2878	野生型マウスおよびヒトPrPを発現しているトランスジェニックマウスに、輸血関連vCJD感染第1号症例由来の脳材料を接種し、輸血によるヒト-ヒト間の2次感染後のvCJD病原体の性質について調べた。その結果、潜伏期間、臨床症状、神経病理学的特徴およびPrP型について、vCJD(輸血)接種群はvCJD(BSE)接種群と類似していた。vCJD病原体は、ヒトにおける2次感染により、有意な変化が起こらないことが明らかとなった。	
90100	2009/3/19	81013	異型クロイツフェルト・ヤコブ病	PLoS ONE 2008; 3: e3017	非定型BSE(BASE)に感染した無症候のイタリアの乳牛の脳ホモジネートをカニクイザルに脳内接種した。BASE接種サルは生存期間が短く、古典的BSEまたはvCJD接種サルとは異なる臨床的展開、組織変化、PrPresパターンを示した。感染牛と同じ国の孤発性CJD患者でPrPが異常なウエスタンブロットを示す4例のうち3例のPrPresに同じ生化学的特徴を認めた。BASEの宿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。	
90130	2009/4/24	90139	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。	32
90148	2009/5/22	90189	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。	33
90145	2009/5/1	90184	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。	34
90145	2009/5/1	90184	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。	35
90145	2009/5/1	90184	寄生虫感染	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。	36
90100	2009/3/19	81013	狂犬病	ProMED-mail20080826.2660	1990年から2007年の中国における狂犬病発生傾向を調べた研究によると、最近8年間でヒト狂犬病症例数が急激に増加したことが明らかとなった。ヒト狂犬病は1990年から1996年の間は全国的な狂犬病ワクチン接種プログラムにより抑制され、わずか159症例が報告されただけであるが、2006年は3279症例と激増した。	
90145	2009/5/1	90184	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。	
90097	2009/3/26	80995	細菌感染	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。	
90145	2009/5/1	90184	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。	37
90132	2009/4/24	90141	真菌感染	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、2007年に減少した。アリゾナ州は毎年米国のコクシジオイデス症全体の約60%を占めており、1999年の1,812例(37/10万人)から2006年の5,535例(91/10万人)と実質的な増加を示した。米国全体では、1996年の1,697例から2006年の8,917例に増加した。	38

医薬品 研究報告 調査報告書

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研究報告の概要

○加熱および高静水圧によるA型肝炎ウイルスの不活化:実験株間の差異

背景および目的:感染した血液製剤によるA型肝炎ウイルス(HAV)の伝播が報告されている。HAV細胞馴化株(Cell-adapted HAV strains)は、通常、血液製剤製造時のウイルス不活化の確認に用いられるが、これらは不活化処理に対する感度が異なると考えられる。ウイルス・バリデーションに適切なHAV細胞馴化株を選ぶため、2種類の物理的不活化処理法下(加熱および高静水圧)で、4株間の不活化効率を比較した。

材料および方法:本試験で使用したHAV細胞馴化株は、KRM238、KRM003(subgenotype IIIB)、KRM031(IA)、TKM005(IB)であった。60℃(～10時間)の加熱、または高静水圧下(～420 MPa)にて、これらの株に処理を行った。immunofocus-staining法でHAV感染力の低下を測定した。

結果:加熱(60℃10時間)処理はHAV感染性を3～5 $\log_{10}$の範囲で低下させたが、KRM238およびTKM005は他2株と比べ不活性化が困難であった。高静水圧処理(420 MPa)も感染性を3～5 $\log_{10}$の範囲で低下させ、KRM031は他の株と比べて不活性化が容易であった。

結論:加熱処理および高静水圧処理によりHAV細胞馴化株間の不活化効果の差が明らかとなり、処理によって各株の反応は異なった。KRM238は不活化が困難で、他の細胞株よりも細胞培養での複製が良好であるため、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候補と考えられる。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
加熱およ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3～5 $\log_{10}$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であったとの報告である。 これまで、本剤によるHAV感染の報告はない。さらに最終製品についてHAV-NAT陰性であることを確認している事から本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、本剤の重要なウイルス除去・不活化工程である液状加熱に抵抗性のある遺伝子型の存在が示唆されたので、今後もウイルスの検出や不活化する方策について情報の収集に努める。なお、日本赤十字社は、輸血感染症対策として、問診で肝炎の既往があった場合、A型肝炎については治癒後6ヶ月間、家族に発症した人がいる場合は1ヶ月間献血不適としている。

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ORIGINAL PAPER

Inactivation of hepatitis A virus by heat and high hydrostatic pressure: variation among laboratory strains

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Vox Sanguinis

Background and Objectives Hepatitis A virus (HAV) transmission via contaminated blood products has been reported. Cell-adapted HAV strains are generally used to confirm virus inactivation in manufacturing blood products, but the strains may differ in their sensitivity to inactivation treatment. To select an appropriate cell-adapted HAV strain for virus validation, we compared the inactivation efficiency among four strains under two different physical inactivation treatments: heat and high hydrostatic pressure.

Materials and Methods The cell-adapted HAV strains used here were KRM238, KRM003 (subgenotype IIIB), KRM031 (IA), and TKM005 (IB). The strains were treated at 60°C for up to 10 h or under high hydrostatic pressure (up to 420 MPa). The reduction in HAV infectivity was measured by an immunofocus-staining method.

Results The heat treatment at 60°C for 10 h reduced HAV infectivity in the range of 3 to 5 $\log_{10}$ among the strains; KRM238 and TKM005 were harder to inactivate than the other two. The high hydrostatic pressure treatment at 420 MPa also reduced infectivity in the range of 3 to 5 $\log_{10}$ among the strains, and KRM031 was easier to inactivate than the other strains.

Conclusion Heat treatment and high hydrostatic pressure treatment revealed differences in inactivation efficiencies among cell-adapted HAV strains, and each strain reacted differently depending on the treatment. KRM238 may be the best candidate for virus validation to ensure the safety of blood products against viral contamination, as it is harder to inactivate and it replicates better in cell culture than the other strains.

Key words: heat inactivation, hepatitis A virus, high hydrostatic pressure inactivation, variation among strains, virus validation.

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Introduction

Hepatitis A virus (HAV), which is responsible for acute viral hepatitis, is transmitted primarily by the fecal-oral route, either through the ingestion of contaminated food or water or through person-to-person contact [1,2]. On the other hand, parenteral HAV transmission has also been reported via contaminated blood [3] or blood products [4,5]. Moreover, *in vivo* HAV infection via blood reportedly has a much higher HAV infection efficiency than does oral HAV infection [6]. In developed countries such as Japan, HAV infections have become less common, owing to improved hygiene resulting from the maintenance of water and sewage facilities. Infections in early childhood are relatively rare, and thus the majority

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Table 1 Characteristics of HAV strains used

Strain	Subgenotype	Source	Year of recovery	Number of passages on African green monkey kidney cells	Titre of stock virus (FFU/ml)	Reference	Accession no.
KRM238	IIIB	Outbreak	1977	59	$1{\cdot}5 \times 10^8$	[21]	AB300205
KRM003	IIIB	Sporadic	1979	72	$1{\cdot}5 \times 10^8$	[15,18]	AB425339
KRM031	IA	Outbreak	1977	47	$1{\cdot}5 \times 10^8$	[15]	AB300206
TKM005	IB	Travel-associated	1981	48	$0{\cdot}5 \times 10^8$	[15]	AB300207

of adults remain susceptible to infection, because they lack the immunity to HAV [7]. As this could potentially facilitate massive outbreaks of hepatitis A in the general population, treatment to inactivate HAV in blood and blood products should be improved.

Previous results have demonstrated that, because HAV is a non-enveloped virus, it is quite resistant against chemical inactivation approaches, such as solvent/detergent treatments used in the preparation of blood products [8]. HAV can be inactivated however by pasteurization [9], γ-irradiation [10], and short wavelength ultraviolet light irradiation [11].

Because environmental HAV strains that have just isolated from human generally grow poorly in cell culture, cell-adapted HAV strains are generally used to test virus inactivation. As extensive genetic variation is found among cell-adapted strains [12], the strains may differ in their sensitivity to inactivation treatments. But no studies have considered the variation among cell-adapted HAV strains in testing the efficiency of inactivation treatments.

HAV strains recovered from different parts of the world have been classified into six genotypes (I–VI). Genotypes I, II and III are found in humans, and each of them is further divided into subgenotypes A and B. Most human HAV strains belong to genotypes I and III [13–15]. Subgenotype IA appears to be the predominant virus of hepatitis A cases worldwide, whereas subgenotypes IB and IIIA have been found in Scandinavia and in the Mediterranean region [16,17]. Subgenotype IIIB is unique to Japan [15,18].

To select an appropriate HAV laboratory strain for use in virus validation, we compared the rates of inactivation efficiency among cell-adapted HAV strains by using two different physical inactivation treatments – heat treatment at 60°C and high hydrostatic pressure treatment – among four cell-adapted HAV strains belonging to three subgenotypes. Heat treatment was used as a conventional inactivation treatment for blood products. High hydrostatic pressure treatment is a promising new virus-inactivating technique that is applicable to human immunodeficiency virus in blood products [19] and has been applied to HAV in food [20]. It is expected to be useful for inactivating a broad range of micro-organisms in blood products under conditions without applying high temperatures.

Materials and methods

Virus strains and propagation

Four laboratory HAV strains (KRM238, KRM003, KRM031, and TKM005) were isolated from patients with hepatitis A in Japan [15,21], and these strains were adapted by numerous passages on African green monkey kidney cells. Table 1 shows each strain's subgenotype, passage history, and stock virus titre. All four strains were propagated on an established African green monkey kidney cell line, GL37 [18].

GL37 cells were grown in Eagle's minimum essential medium supplemented with 10% fetal bovine serum (FBS) and 50 μg/ml gentamycine. To prepare the virus stocks, GL37 cells were infected at a multiplicity of infection of 0·1 focus forming units (FFU) per cell in Eagle's minimum essential medium containing 2% FBS, and were incubated for 2 weeks at 36·5°C in the presence of 5% CO_2. The infected cells were harvested by replacing the medium with phosphate-buffered saline containing 2% FBS. Virus stocks were obtained as supernatants of centrifugation at 2380 *g* for 5 min after release of the viruses by three freeze-thaw cycles and sonication of infected cells. The virus stocks were then stored at −80°C until use.

Infectivity assay

The infectious titre of each HAV strain was measured by the immunofocus-staining method described previously [21]. Briefly, a 100 μl portion of the virus dilution was inoculated into duplicate GL37 cells cultures in six-well plates at 36·5°C in the presence of 5% CO_2. After 60 min adsorption, 5 ml of the medium containing 0·6% agarose and 2% FBS was overlaid on each well. The plates were incubated at 36·5°C in the presence of 5% CO_2 for 9 days. The cells were fixed with 80% methanol containing 0·03% H_2O_2 after removal of the agarose medium. HAV foci were revealed by anti-HAV rabbit serum and horseradish peroxidase-conjugated anti-rabbit immunoglobulin G (IgG) (MBL, Nagoya, Japan) followed by colour development with DAB substrate solution (0·5 mg/ml diaminobenzidine, 0·03% $(NH_4)_2Ni(SO_4)_2$, 0·03% $CoCl_2$, and 0·03% H_2O_2 in phosphate-buffered saline).

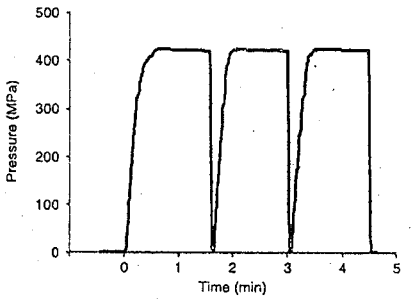

Fig. 1 The pattern of pressure change with high hydrostatic pressure at 420 MPa. Samples were treated at 25–30°C by three cycles of pressurization at the indicated pressure for 1 min followed by immediate release of the pressure. Essentially similar patterns were obtained at other hydrostatic pressures.

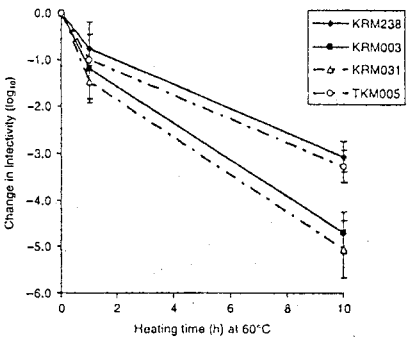

Fig. 2 Inactivation of HAV strains by heat at 60°C. The cell-adapted strains in 25% human serum albumin were treated by heat at 60°C for the indicated times. Data are the means of two or three replicates. Error bars represent the 95% confidence intervals. Change in infectivity (log_{10}) = log_{10} (titre of treated samples) − log_{10} (titre of untreated samples).

Heat treatment

The samples used for the heat treatment were prepared by adding one volume of each virus stock to 9 volumes of 25% human serum albumin (Benesis Corporation, Osaka, Japan). The samples were divided into microcentrifuge tubes in amounts of approximately 0·8 ml, and the tubes were sealed. The samples were heated at 60°C for 1 or 10 h and were then cooled on ice rapidly to arrest the heating process.

Two or three independent trials were conducted for all samples. The 95% confidence limits of these data were statistically determined and assessed; the difference was significant if it was over the 95% confidence limits.

High hydrostatic pressure treatment

The samples used for the high hydrostatic pressure treatment were prepared by adding one volume of each virus stock to 9 volumes of 5% human serum albumin. The samples were divided into ultra-centrifuge tubes (Beckman Coulter, Fullerton, CA, USA) in amounts of approximately 1·5 ml, and the tubes were sealed. The sealed tubes were placed in the chamber of a laboratory-sized high hydrostatic pressure instrument designed for food processing (Echigo Seika, Co., Ltd, Niigata, Japan). High hydrostatic pressure was controlled by water filled in the chamber. The samples were treated at 25–30°C by repeating three cycles of pressurization at the indicated pressure for 1 min and then immediately releasing the pressure. Three different pressures (300, 350, or 420 MPa) were used. At 420 MPa, the pattern of pressure change with treatment is shown in Fig. 1.

Two or three independent trials were conducted for all samples. The 95% confidence limits of these data were statistically determined and assessed; the difference was significant if it was over the 95% confidence limits.

Results

Inactivation by heat treatment at 60°C

The four cell-adapted HAV strains were treated in 25% human serum albumin with heat at 60°C for 1 or 10 h. The infectious titres of HAV in the samples were measured after heat treatment, and the reduction in HAV infectivity was then calculated. For all four strains, infectivity was reduced by approximately 1 log_{10} after heat treatment at 60°C for 1 h, indicating that HAV was resistant to heat inactivation as compared, for example, to poliovirus, which Barrett *et al.* reported was much more thermolabile than HAV [22].

With heat treatment at 60°C for 10 h, the reduction of HAV infectivity ranged from approximately 3 to 5 log_{10} among the four strains, as shown in Fig. 2. The reduction in the infectivity of KRM238 was 3·1 log_{10}, that of KRM003 was 4·7 log_{10}, that of KRM031 was 5·1 log_{10}, and that of TKM005 was 3·3 log_{10}. In other words, two strains (KRM238 and TKM005) were more resistant to inactivation by heat treatment than the other two (KRM003 and KRM031). There was 2·0 log_{10} difference between the most resistant strain KRM238 and the most sensitive strain KRM031. There was 1·6 log_{10} of variation in the inactivation rate between KRM238 and KRM003, even though they belong to the same IIIB strain subgenotype. These differences mentioned here were significant.

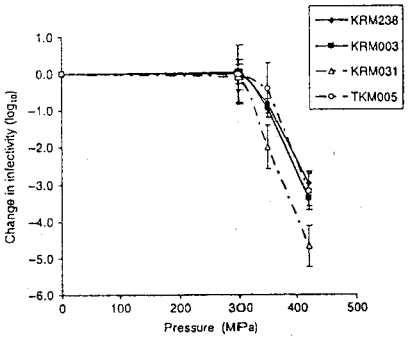

Fig. 3 Inactivation of HAV strains by high hydrostatic pressure. The cell-adapted strains in 5% human serum albumin were treated at the indicated pressures by repeating three cycles. Data are the means of two or three replicates. Error bars represent the 95% confidence intervals. Change in infectivity (log_{10}) = log_{10} (titre of treated samples) − log_{10} (titre of untreated samples).

Inactivation by high hydrostatic pressure treatment

The four cell-adapted HAV strains were treated in 5% human serum albumin with high hydrostatic pressure at 300, 350, or 420 MPa. The infectious titres of HAV in the samples were measured after the treatment, and the reduction in HAV infectivity was then calculated.

None of the HAV strains were inactivated by high hydrostatic pressure of less than 300 MPa, but all of the strains began to show inactivation at pressures exceeding 300 MPa. At 420 MPa, the reduction of HAV infectivity ranged from approximately 3 to 5 log_{10} among the strains, as shown in Fig. 3. The reduction in the infectivity of KRM238 was 3·0 log_{10}, that of KRM003 was 3·4 log_{10}, that of KRM031 was 4·7 log_{10}, and that of TKM005 was 3·2 log_{10}. There was at least 1·3 log_{10} difference, which was significant, between the resistant strains and the sensitive strain KRM031. In other words, high hydrostatic pressure inactivation was more effective against KRM031 than against the other three strains. As with heat inactivation, high hydrostatic pressure inactivation showed variation among the strains.

Accumulative effects of inactivation by heat and pressurization

To evaluate efficiency of two such inactivation treatments in the manufacture of blood products, the combined effects of inactivation by heat at 60°C for 10 h and by high hydrostatic pressure at 420 MPa are calculated by addition as shown in Table 2.

With either treatment, the degree of variation in infectivity reduction between resistant and sensitive strains was approximately 2 log_{10}. KRM238 and TKM005 well resisted inactivation by either heat or high hydrostatic pressure.

The combined reduction in the infectivity of KRM238 was 6·1 log_{10}, that of KRM003 was 8·1 log_{10}, that of KRM031 was 9·8 log_{10}, and that of TKM005 was 6·5 log_{10}.

Discussion

Cell-adapted strains are useful in studies aimed at validating the virus-inactivation procedures used in manufacturing. We report here on variation in inactivation rates – whether by heat treatment or high hydrostatic pressure treatment – among laboratory HAV strains. As shown in Table 2, if both inactivation treatments could be combined, the variation between resistant and sensitive strains would increase. For example, the most sensitive strain, KRM031, showed an estimated total reduction of 9·8 log_{10} via the combined treatments; on the other hand, the most resistant strain, KRM238, showed only a 6·1 log_{10} reduction. The maximum variation among the HAV strains after combined treatment inactivation was predicted to be about 3·7 log_{10}. To ensure the safety of

Table 2 Inactivation among HAV strains by heat and pressurization

	Reduction in infectivity (log_{10})		
HAV strain	By heat at 60°C for 10 h	By high hydrostatic pressure at 420 MPa	By combination[b] of heat and high hydrostatic pressure
KRM238	3·1 (± 0·3 2)[a]	3·0 (± 0·25)	6·1
KRM003	4·7 (± 0·4 5)	3·4 (± 0·22)	8·1
KRM031	5·1 (± 0·6 1)	4·7 (± 0·56)	9·8
TKM005	3·3 (± 0·3 5)	3·2 (± 0·52)	6·5

[a]Parentheses indicate 95% confidential limits.
[b]Expected values calculated by addition.

manufactured blood products, it is important to avoid overestimating HAV-inactivation rates. Thus, the HAV strain that is most resistant to inactivation treatment should be used in virus validation.

Considering that KRM238 grows better in cell culture than TKM005 (Table 1), it can be concluded that, among the four strains used here, KRM238 is the best candidate for virus-validation to ensure the safety of blood products against viral contamination. In general, the evaluation of inactivation processes will depend on the strains used for testing.

Our results also indicated that we should evaluate carefully the efficiency of inactivation by selecting an appropriate strain that is resistant to inactivation treatment, and that a strain that is resistant to one particular inactivation treatment may not always be resistant to another. Here, KRM003 was easily inactivated by heat treatment, showing a 4·7 log_{10} reduction, but was more stubborn against high hydrostatic pressure, which resulted in only a 3·4 log_{10} reduction. Indeed, when a novel inactivation treatment is applied to the manufacture of blood products to prevent viral contamination, inactivation treatment must be validated carefully. In other words, the efficiency of inactivation should be evaluated not only by using a strain that has shown resistance to the standard inactivation treatment, but also by selecting an appropriate strain that is resistant to a newer inactivation treatment. A test strain of virus validation for a newer inactivation should be selected carefully for avoiding a risk of overestimating the resistance of the test strain to a newer inactivation.

Pressurization has emerged as a new technique for inactivating pathogenic viruses in blood plasma and plasma-derived products, as pressurization at 400 MPa exerted no effect on the recovery of biologically active plasma proteins, with the exception of factor XIII [19]. Most enveloped viruses are markedly inactivated at pressures below 400 MPa, as summarized by Grove *et al.* [23]. However, small RNA viruses can vary widely in their sensitivity to high pressure. For example, HAV and poliovirus are both members of the picornavirus family, but they exhibit quite different susceptibilities. HAV is inactivated by 3–5 log_{10} of infectivity at 420 MPa, whereas poliovirus remains essentially unaffected even at 600 MPa [24]. At this point in time, the mechanism underlying virus inactivation by pressurization is still poorly understood.

Heat inactivation is currently used to inactivate enveloped viruses in particular, such as human immunodeficiency virus, hepatitis B virus and hepatitis C virus, in blood products. Moreover, non-enveloped viruses such as HAV and poliovirus differ greatly in terms of their sensitivity to heat inactivation [22]. As with pressurization, in heat treatment the mechanism underlying inactivation of non-enveloped viruses remains unclear.

The cell-adapted HAV strains exhibited disparate sensitivities to the two different treatments used in this study. These findings are important in terms of ensuring safety in the manufacture of blood products. Further studies will be needed in order to validate the inactivation procedures for naturally occurring viral strains.

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別紙様式第２－１

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分		総合機構処理欄
一般的名称	赤血球、血小板					公表国	
販売名（企業名）	－	研究報告の公表状況		Transfusion medicine (Oxford, England) (England) Dec 2008, 18 (6) p379-81		英国	

研究報告の概要	2006年11月、大阪赤十字社血液センターにおいて、繰り返し供血していた69歳の女性が20-NATでHBV DNA陽性であることが判明し、ルーチンの検査ではHBsAg、抗HBs抗体と抗HBc抗体は陰性で、EIA法による抗HBc抗体だけが陽性であり、供血者が抗HBc抗体低値の不顕性HBV感染者であることを示していた。 この供血者の凍結標本を調査したところ、1999年10月1日以降に供血された血清が個別（ID）-NATでHBV DNA陽性であり、13の供血のうち、11が輸血に使用されていた。 受血者のHBV検査記録を収集したが、4例は既に原疾患で死亡しており、2例は記録がなかった。残りの5例のうち3例では輸血前後で、2例では輸血後のみHBV検査が行われており、HBV感染のサインを示唆する情報はなかったが、HBV感染が起きたかどうか決定するには不十分である。 神奈川赤十字社血液センターは、繰り返し血小板を提供していたID-NATのHBV検出臨界付近でウイルス量が揺れ動いていた不顕性HBV感染症の症例からの200mlの血漿を含む濃厚血小板液でのHBV感染症を報告している。日赤血液センターによる最近のルックバック研究では、不顕性HBV陽性の供血者から得られた33の血液成分中の1つ（450mlの新鮮凍結血漿の輸注）でHBV感染症を起こしており、ミニプールNATのウインドピリオドの間に供血された22の血液成分中11の輸注でのHBV感染を明らかにした。 不顕性HBV感染者から血液成分の潜在的な危険を明確にするためには、さらに多くの症例が詳細に分析される必要があり、血液成分中のHBVの総輸注量、HBV免疫抗体の保有状態、受血者の免疫状況、HBV遺伝子型そして／あるいは突然変異の存在は算定されるべきである。	使用上の注意記載状況・その他参考事項等 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、・・・・・陰性で、かつALT（GPT）値でスクリーニングを実施している。さらに、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。
報告企業の意見	今後の対応	
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である。 当社血漿分画製剤の製造工程におけるHBVのモデルウイルスに対するウイルスクリアランス指数は9以上である。なお、原料血漿はミニプール血漿におけるNAT検査でHBV DNA陰性を確認しており、最終製品においてもHBV DNA陰性を確認している。	今後ともにB型肝炎ウイルス感染に関する安全性情報に留意していく。	

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LETTER TO THE EDITOR

Transfusions of red blood cells from an occult hepatitis B virus carrier without apparent signs of transfusion-transmitted hepatitis B infection

Dear Sir

To minimize the risk of transfusion-transmitted hepatitis B virus (HBV) infections, the Japanese Red Cross (JRC) Blood Centers have adopted a multistep screening system to identify donors at risk of HBV infection. First, donors are examined for the hepatitis B surface antigen (HBsAg) by performing reverse passive haemagglutination tests with a sensitivity of 3 ng mL^{-1}. HBsAg-negative donations are screened for antibodies against HBsAg and the hepatitis B core antigen (anti-HBs and anti-HBc, respectively) by particle haemagglutination and haemagglutination inhibition (HI) tests, respectively. Donations with a high anti-HBs titre ($\geq 2^4$ dilution equivalent to 200 mIU mL^{-1}) or a low or zero anti-HBc titre ($\leq 2^4$ dilution) are defined as 'seronegative'. The cut off value for anti-HBc tests is relatively high compared to that of enzyme-linked immunoassays (EIAs) because HBV DNA was not detected by an in-house polymerase chain reaction (PCR) in donors who tested negative for HBsAg and positive for anti-HBc at an HI titre less than 2^5 (Iizuka *et al.*, 1992). Since the introduction of nucleic acid amplification test (NAT) technology, all seronegative donations are pooled (initially, at a pool size of 500 and a current pool size of 20, i.e. 20-NAT) and subjected to NAT (Ampli-NAT, Roche, IN, USA). If the 20-NAT tests positive, the pooled donations are further subjected to individual NAT (ID-NAT) to identify the blood donation that contains the viral genome. The 95% confidence interval of the detection range for HBV in ID-NAT is 22–60 copies of HBV per millilitre (Meng *et al.*, 2001). Donors who did not fall within the algorithm would be either categorized in the window period of 20 NAT or assigned an occult HBV status with a low viral load (reviewed by Raimondo *et al.*, 2007).

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In November 2006, the Osaka Red Cross Blood Center, Japan, identified a repeat donor, namely, a 69-year-old female, whose donation was found to be positive for HBV DNA when tested by the latest 20-NAT. According to the guidelines for the safety of transfusion in the JRC Blood Centers, the serological status of the donation was re-evaluated. The donated blood was found to be negative for HBsAg, anti-HBs and anti-HBc by routine testing methods and positive for only anti-HBc when tested using EIA (AxSYM; Abbott Laboratories, Abbott Park, IL, USA), indicating that the donor was an occult HBV carrier with a low anti-HBc titre. We retrieved frozen aliquots of previous donations by this donor and found that sera donated on and after 1 October 1999 tested positive for HBV DNA when tested by ID-NAT. The amount of HBV DNA in these donations was less than 100 copies per millilitre, except for two donations (Table 1). From the 13 donations made by this donor in the abovementioned period, 11 components were transfused into recipients (recipient number 1–11 in Table 1). We collected the HBV test records of some of the recipients from the medical institutions where each recipient had been hospitalized. Recipients 3, 6, 7 and 9 had succumbed to their primary disease, and no records were available for recipients 10 and 11. Of the remaining five cases, the HBV test was performed at both the pre- and post-transfusion stages in recipients 1, 4 and 5, but recipients 2 and 8 were tested only at the post-transfusion stage. Recipient 1 was a 70-year-old female who had tested negative for HBsAg and anti-HBc by EIA 2 days prior to transfusion. She was transfused with packed red blood cells (RBCs) and tested negative for HBsAg, anti-HBs and anti-HBc by EIA and negative for HBV DNA by PCR 7 months after the transfusion. These data suggest that the latest RBC component from this occult HBV donor did not cause transfusion-transmitted HBV infection. In recipients 2 and 8, the post-transfusion EIA test results for HBsAg were reported negative. Recipient 4 tested negative for HBsAg by EIA at 11 days before

Table 1. HBV status of the donor and recipients

Donor					Recipients				Pretransfusion		Post-transfusion	
Date of donation	Pooled NAT	ID-NAT	Copy number per mL	Component	Recipient number	Age (years)	Primary diseases*	HBsAg	Anti-HBc	HBsAg	Other markers
1 November 2006	+†	+	ND	—¶							
22 May 2006	–†	+	<100	RBCs	1	70	(1)	–	–	–	–, anti-HBs; –, anti-HBc; –, HBV DNA
15 April 2006	–†	+	140	RBCs	2	NA	(2)	NA	NA	–**	
26 September 2005	–†	+	210	RBCs	3	NA	NA	–	NA	–**	
27 June 2005	–†	+	<100	—¶							
10 April 2005	–†	+	<100	RBCs	4	86	NA	–	NA	–	–, HBV DNA
15 February 2004	–‡	+	<100	RBCs	5	60	(3)	–	NA	–	
15 September 2003	–‡	+	<100	—¶							
21 March 2003	–‡	+	<100	RBCs	6	69	(4)	–	NA	–**	
1 March 2002	–‡	+	<100	RBCs	7	51	(5)	NA	NA	–**	
1 July 2002	–‡	+	<100	RBCs	8	41	(6)	NA	NA	–	
15 January 2001	–‡	+	<100	RBCs	9	57	(7)	NA	NA	–**	
1 October 1999	–§	+	<100	RBCs	10	NA	NA	NA	NA	NA	
15 April 1999	–§	–	ND	RBCs	11	NA	NA	NA	NA	NA	

NA, not applicable; ND, not determined.
*Primary Diseases: (1), perforation of sigmoid diverticulum; (2), transverse colon cancer; (3), bleeding gastric ulcer; (4), operative diseases; (5) operative diseases; (6), gastric ulcer; and (7), ovarian cancer.
†20-pooled.
‡50-pooled.
§500-pooled.
¶Not used.
**Decease by the primary disease.

transfusion with RBCs. Furthermore, she tested negative for HBsAg at both 17 and 19 months after the transfusion. In addition, PCR results for this patient were negative for HBV DNA 21 months after transfusion. In recipient 5, it was reported that both pre- and post-transfusion sera tested negative for HBsAg by EIA. Although no further reports suggesting any signs of HBV transmission in recipients 2, 4, 5, and 8 have been filed with our blood centre, the HBV test records of these four recipients are insufficient to determine whether transfusion-transmitted HBV infection occurred.

Kanagawa Red Cross Blood Center, Japan, recently reported a case of transfusion-transmitted HBV infection caused by an individual with an occult HBV infection who had repeatedly donated platelets and whose viral load fluctuated around the limit of HBV detection level by the ID-NAT (Inaba *et al.*, 2006). It is noteworthy that the component transfused in this case was a platelet concentrate containing approximately 200 mL of plasma; on the other hand, in our subjects, the transfused component was packed RBCs including 10–15 mL of plasma. A more recent look-back study on transfusion-transmitted HBV infection conducted by the JRC Blood Center identified that only one of the 33 components obtained from occult HBV donors caused the HBV infection (Satake *et al.*, 2007). This particular patient was transfused with 450 mL of fresh frozen plasma. The same study also demonstrated that 11 of the 22 components donated during the mini-pool NAT window period resulted in transfusion-transmitted HBV infection. Although the results of recipient 1 in our case appear to be consistent with those in the look-back study, data available in the literature suggest that occult HBV infection is transmissible, especially in endemic areas (reviewed by Liu *et al.*, 2006). To clarify the potential risks of blood components from occult HBV donors, many more cases need to be analysed in detail, where the total amount of HBV in the component transfused, the presence or absence of HBV antibodies in the component, the immunological status of the recipient, the HBV genotype and/or the presence of mutation(s) should be assessed.

The peculiar criterion of seronegative used in the JRC Blood Centers was a practical solution to exclude donors with a risk of HBV infection, without excessively reducing the size of the donor pool. This criterion was introduced because the prevalence of HBV infection, when serological testing was introduced, was relatively higher in Japan than in other industrialized countries. Our serological screening, however, has failed to identify a few occult HBV carriers with a low anti-HBc titre and a low viral DNA. JRC has been re-evaluating the efficacy of our screening strategy by follow-up surveys, including the present study, and exploring options to be adopted to minimize the risk not only by the occult HBV carrier but also by donors in the 20-NAT window period.

Although we consider that the current possibility of HBV transmission by occult HBV carriers with a low anti-HBc titre is limited in Japan, this consideration cannot be generalized to countries with different HBV prevalence as mentioned above. Once the cut off value of the anti-HBc titre confirming the HBV-DNA-negative status of the donor blood is more rigorously determined, our serological screening algorithm may be an acceptable option in areas of intermediate or high HBV endemicity where NAT is unavailable.

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別紙様式第2−1　No. 19

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. 2. 18	該当なし		
一般的名称	乾燥濃縮人血液凝固第Ⅷ因子		研究報告の公表状況	小松 陽樹、乾 あやの、十河 剛、藤澤 知雄. 第40回日本小児感染症学会総会・学術集会; 2008 Nov 15-16; 名古屋市.	公表国	日本	使用上の注意記載状況・その他参考事項等
販売名（企業名）	クロスエイトM250（日本赤十字社） クロスエイトM500（日本赤十字社） クロスエイトM1000（日本赤十字社）						クロスエイトM250 クロスエイトM500 クロスエイトM1000
研究報告の概要	○母子感染以外のHBV感染によるHBV DNAの解析 【目的】小児における母子感染以外のHBV感染の実態を分子疫学的に把握する。 【方法】成人および小児HBVキャリア82名中で、母親がHBsAg陰性かつ患児以外にHBVキャリアが存在する7家族を対象とし、HBV全遺伝子解析を行い、分子系統樹を用い感染源を検索した。 【成績】HBsAg陽性例は、父親が4家族、兄弟のみが2家族（両親はHBVマーカー陰性）、祖母が1家族であった。血清が得られた7家族中3家族（2家族；父親HBsAg陽性、1家族；祖母HBsAg陽性）を対象にHBV遺伝子解析を行った。Family1は長女3歳がHBVキャリアと判明し、父親および長男5歳がHBsAg陽性、母親はHBsAb陽性であった。Family2は次男4歳がHBVキャリアと判明し、長男9歳、長女2歳がHBsAg陽性、母親がHBsAb陽性であった。Family3は、12歳女児がB型劇症肝炎と診断され、祖母がHBVキャリア、同居の従弟が同時期にB型急性肝炎と診断された。分子系統樹解析ではいずれも家族でも高い相同性を示し、それぞれ1つのクラスターを形成したため同じ感染源であると考えられた。 【考察】アジア諸国の中でHBV浸淫度が比較的低いと考えられる本邦でも、母子感染以外のHBV感染経路は無視できない。7家族中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。 【結語】母子感染など感染リスクが高い集団に対してのみワクチン接種を行う"target strategy"ではこのような水平感染を完全に防止することは不可能であり、本邦でuniversal vaccinationが必要と考えられた。						血液を原料とすることに由来する感染症伝播等 vCJD等の伝播のリスク
	報告企業の意見		今後の対応				
	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および小児HBVキャリア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との報告である。 これまで、本剤によるHBV感染の報告はない。また本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。さらに最終製品についてHBV-NAT陰性であることを確認していることから、特別の対応を必要としないと考える。		今後も引き続き情報の収集に努める。なお、日本赤十字社では献血時のスクリーニング法としてより感度の高い化学発光酵素免疫測定法（CLEIA）および新NATシステムを導入し、陽性血液を排除している。				

(3)

【研究奨励賞】

E-20　母子感染以外の HBV 感染による HBV DNA の解析

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済生会横浜市東部病院こどもセンター

【目的】小児における母子感染以外の HBV 感染の実態を分子疫学的に把握する。【方法】当科でフォロー中の成人および小児 HBV キャリア一82 名のなかで母親が HBs 抗原陰性かつ患児以外に HBV キャリアが存在する 7 家族を対象とした。HBs 抗原陽性の家族から得られた血清を用いて HBV 全遺伝子解析を行い、分子系統樹を用いて感染源の検索を行った。【成績】父親が HBs 抗原陽性例は 4 家族、兄弟のみ HBs 抗原陽性例は 2 家族（両親は HBV マーカー陰性）、祖母 HBs 抗原陽性例は 1 家族であった。 7 家族中 3 家族（2 家族；父親 HBsAg 陽性、 1 家族；祖母 HBsAg 陽性）にて家族から血清が得られ、この 3 家族を対象に HBV 遺伝子解析を行った。Family1 は長女 3 歳が伝染性単核球症罹患時の血液検査にて HBV キャリアが判明。家族内検索にて父親および長男 5 歳が HBsAg 陽性、母親は HBsAb 陽性。Family2 は次男 4 歳が胃腸炎症罹患時の血液検査にて HBV キャリアが判明。家族内検索にて父親、長男 9 歳、長女 2 歳が HBsAg 陽性、母親は HBsAb 陽性。Family 3 は、12 歳女児が黄疸と全身倦怠感を主訴に来院し、B 型劇症肝炎と診断された。祖母が HBV キャリアであり、同居していた。同時期に従弟は B 型急性肝炎と診断された。分子系統樹解析では、 3 家族においていずれも高い相同性を示すとともに、各家族がそれぞれ 1 つのクラスターを形成し、同じ感染源であると考えられた。【考案】アジア諸国の中で HBV 浸淫度が比較的低いと考えられる本邦でも、父子感染など母子感染以外の HBV 感染経路は無視できない。 7 家族中 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。【結語】母子感染など感染リスクが高い集団に対してのみワクチン接種を行う”target strategy”ではこのような水平感染を完全に防止することは不可能であり、本邦で universal vaccination が必要と考えられた。

E-21　治療後もβ-D-グルカン高値が持続するカンジダ血症の一例

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β-D-グルカンは真菌細胞壁の主要成分であり、特にカンジダ感染症では感度の高い検査法として頻用されている。今回我々は、カンジダ血症に対して抗真菌剤の治療を行い、臨床症状、培養を含む検査データから治癒と考えられる状態に至ったにもかかわらず、β-D-グルカン異常高値のみが持続する男児例を経験したので報告する。 症例は生来健康な 4 歳男児。腹痛、下痢、嘔吐のため近医数回受診の後、第 8 病日前医入院。第 12 病日皮下出血斑に気づかれ、アレルギー性紫斑病と診断されプレドニン 2mg/kg/d 開始されたところ翌日には腹痛消失。しかし食事開始すると腹痛・血便が再燃するため食止・再開を繰り返し、PSL 開始 15 日目に当院転院。PSL と第 13 因子製剤で治療継続していたところ、入院 3 日目より発熱。血液培養で *Candida parapsilosis* が検出されたため MCFG にて治療開始。入院 11 日目の血液培養で再度同菌が検出されたためボリコナゾールを併用し、その後解熱したが入院 13 日目の血液培養でも陰性化していなかったため、眼科受診、腹部超音波、腹部 CT、頭部 CT、心臓超音波などで全身検索を行ったが、膿瘍形成や感染性心内膜炎を示唆する所見は得られなかった。抗真菌剤は 2 週間点滴で使用した後 VCZ＋FCZ 内服に変更、再発熱や炎症反応の増悪がみられないことを確認して外来フォローとした。血中 β-D-グルカンは入院時すでに 1610pg/ml と高値であったがその後も増加し、退院前の最高値 3460pg/ml、退院後も発熱などの症状はないが、7400pg/ml まで上昇した。抗真菌剤開始後は腹部症状消失していたがむしろ便秘傾向であったため、緩下剤を開始し、抗真菌剤は合計約 2 ヶ月で中止とした。その後は緩やかに低下傾向であるが、発症から 8 ヶ月経った段階でまだ 884pg/ml と高値が続いている。

別紙様式第2-1

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分		総合機構処理欄
				2008. 11. 20	該当なし		
一般的名称	人血清アルブミン		研究報告の公表状況	古居 保美、五十嵐 正志、蕎麦田 理英子、蕎俣 尋史、星 友二、福田俊洋、松本 千恵子、鈴木 光、柚木 久雄、内田 茂治、三枝 英子、田所 憲治 日本赤十字社NAT研究グループ. 第32回 日本血液事業学会総会; 2008 Oct 2-4; 大阪市.	公表国		
販売名（企業名）	赤十字アルブミン20（日本赤十字社） 赤十字アルブミン25（日本赤十字社）					日本	

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
○NATスクリーニング検査で検出されたHCV-RNA陽性検体の解析 【はじめに】1999年7月のNATスクリーニング検査（以下「NAT」という）導入以降、2008年3月までに111本のHCV-RNA陽性検体が検出され、Genotypeの分類結果について献血者情報等をもとに解析を行い、HCVの感染動向を調査した。 【対象と方法】NATで検出されたHCV-RNA陽性検体のGenotypeについて、Core領域196bpの塩基配列をRT-PCR direct sequence法で決定し、分子系統樹解析により分類した。 【結果】HCV-RNA陽性検体のGenotypeは、1b：30本（27.0%）、2a：52本（46.8%）、2b：29本（26.1%）で、その他のGenotypeは検出されなかった。献血者の性別は男性71人（64.0%）、女性40人（36.0%）で、平成18年度の全献血者男女比（男性64.5%、女性35.5%）と完全に一致した。Genotypeの男女比は1bが15：15、2aは33：19、2bは23：6で、Genotype 2bで男性の割合が高かった。献血者の年齢別では、10代～20代で平成18年度の献血者の年代別構成比よりも高かった。また献血者100万人あたりの陽性者数を求めたところ、1bは中部地方以西で多く、関東地方以北では少なかった。2aは中部地方及び東北地方で若干多いものの、北海道を除き、その他の地域ではあまり差は見られなかった。2bは関東地方で多く、中部地方及び東北地方では検出されていない。 【考察】NATで検出されたHCV-RNA陽性検体はGenotype 2aが最も多く、1bと2bがほぼ同数だった。RNA陽性献血者のGenotypeを分類して感染傾向を調査していくことは、日本の急性肝炎患者の動向を予測するのに有用であると思われるので、引き続き行っていきたい。	赤十字アルブミン20 赤十字アルブミン25 血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
1999年7月からの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がほぼ同数だったとの報告である。 これまで、本剤によるHCV感染の報告はない。本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。また最終製品についてHCV-NAT陰性であることを確認していることから、本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、NATでの陽性となる献血者は新規感染者の可能性があるため、Genotypeを分類して感染傾向を調査していくことは、日本の急性肝炎患者の動向を予測するのに有用であり、今後もGenotypeの調査を継続するとともに、情報の収集に努める。なお、献血時のHCVスクリーニング法としてより感度の高い化学発光酵素免疫測定法（CLEIA）および新NATシステムを導入した。

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HBVの一過性感染におけるeAg/eAb セロコンバージョンとプレコア領域の変異

埼玉県赤十字血液センター

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〈目的〉HBVの慢性持続感染者においては，一般的にプレコア変異，プロモーター変異が生じることによりe抗原の産生が低下し，e抗原期からe抗体期へセロコンバージョンすることが報告されている。HBVの一過性感染でも同様な現象が生じているかどうかを献血者のNAT陽性者を追跡調査した結果から調べたので報告する。〈対象と方法〉1999年から2003年までの間に日赤の血清学的検査陰性でNAT陽性になった349症例の内，e抗原陽性期からe抗体にセロコンバージョンしている追跡可能な症例を対象とした。塩基配列はプレコア領域のPCRを行い，PCR-ScriptAmpCloningKit（STRATAGENE）を用いてクローニングした。得られたクローンはグラスミッドをQIAprepMiniprepKit（QIAGEN）にて抽出しDNAシークエンスを解析した。〈結果と考察〉野生株に一過性感染した献血者のe抗原陽性期の検体から7クローン，e抗体にセロコンバージョンした検体から17クローンを調べたところプレコア変異部位の塩基配列に変異は生じていなかった。一方プレコア変異株の一過性感染では，感染当初はe抗原もe抗体も認められないものの，コア抗体出現に伴いe抗体が認められるようになったが塩基配列の変異は認められなかった。一過性感染では，慢性持続感染の場合と異なり，核酸の変異をほとんど伴わず，野生株のままe抗原からe抗体にセロコンバージョンし，血中HBV-DNA量も定量限界以下に減少することが確かめられた。

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NATスクリーニング検査で検出された HCV-RNA陽性検体の解析

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松本千恵子[1]，鈴木　光[1]，柚木久雄[2]，
内田茂治[3]，三根英子[3]，田所憲治[1]，
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【はじめに】1999年7月のNATスクリーニング検査（以下「NAT」という）導入以降，2008年3月までにHCV-RNA陽性検体111本が検出された。その111本についてGenotype分類を行ってきたので，その結果について献血者情報等を基に解析を行いHCVの感染動向を探ることとした。【対象と方法】NATで検出されたHCV-RNA陽性検体111本を対象とした。GenotypeはCore領域196bpの塩基配列をRT-PCR direct sequence法で決定し，分子系統樹解析により分類した。【結果】HCV-RNA陽性検体111本のGenotypeは，1b：30本（27.0%），2a：52本（46.8%），2b：29本（26.1%）で，その他のGenotypeは検出されなかった。献血者の性別は男性71人（64.0%），女性40人（36.0%）と男性が多かったが，平成18年度の全献血者男女比（男性64.5%，女性35.5%）と完全に一致した。Genotypeの男女比は1bが15：15，2aは33：19，2bは23：6で，Genotype 2bで男性の割合が高かった。献血者の年齢別では，10代～20代で平成18年度の献血者の年代別構成比よりも高かった。また地域別に献血者100万人あたりの陽性者数を求めたところ，1bについては中部地方より西の地方で多く，関東以北では少なかった。2aについては，中部地方で若干多いものの，北海道を除くその他の地域ではあまり差は見られなかった。2bについては関東地方で多く，中部地方及び東北地方では検出されていない。【考察】NATで検出されたHCV-RNA陽性検体はGenotyp2aが最も多く，1bと2bがほぼ同数であった。NATで検出されたHCV検体のGenotypeを分類して感染傾向を調査していくことは，日本の急性肝炎患者の動向を予測するのに有用であると思われるので，引き続き行なっていきたい。

別紙様式第2-1

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分		総合機構処理欄
				2008. 11. 20	該当なし	公表国	
一般的名称	乾燥濃縮人血液凝固第Ⅷ因子		研究報告の公表状況	Ikeda H, Matsubayashi K, Sakata H, Takeda H, Kon E, Sato S, Kato T, Abe I, Satoru H, Tadokoro K. AABB Annual Meeting and TXPO 2008; 2008 Oct 4-7; Montreal.		日本	使用上の注意記載状況・その他参考事項等
販売名（企業名）	クロスエイトM250（日本赤十字社） クロスエイトM500（日本赤十字社） クロスエイトM1000（日本赤十字社）						クロスエイトM250 クロスエイトM500 クロスエイトM1000

研究報告の概要

○北海道の献血者におけるHEV感染症

背景：日本を含む先進工業国でHEVの輸血伝播が複数認められているが，献血者のHEV感染は未解明である。一方，日本のHEV感染は，主に人畜獣共通伝染病の食物介在経路であると考えられており，E型肝炎の散発性症例を引き起こしている。

方法：2005～2007年まで，北海道においてプールNATによりHEV RNAの有無についてスクリーニングを実施した。HEV -NAT RNA陽性（RT-PCR）献血者および抗HEV抗体陽性（ELISA）献血者について遡及及び追跡調査を実施した。HEV遺伝子型はダイレクトシーケンス法により決定した。また，献血者の食事歴についてアンケート調査を実施した。

結果：献血者834,843名のうち，HEV-NAT陽性献血者が100名特定され，男女比72/28，平均年齢41.0±2.5，遺伝子3/4型比92/6であった。74名からは抗HEV抗体は検出されず，20名からIgM抗HEV抗体が検出された。6ヵ月以内の前回献血歴がある39名の前回検体中からは，HEVマーカーは検出されなかった。献血時に肝炎の臨床症状を示す者はなかった。追跡調査を実施できた23名中13名は，ALT値の一過性の上昇（60IU/L超）が見られ，内2名がE型肝炎を発症した（最大ALT値：1,250，3,366 [IU/L]）。HEV RNAは，数ヶ月以内に消失することが確認され，HEVウイルス血症は献血から最長55日間持続した。NAT陽性献血者の76%（59/78）は，献血前に動物内臓を食べていた。

結論：北海道の献血者の約1/8,300はHEV RNA陽性で，多くは無症候性であったがウイルス血症は数ヶ月間持続する。これら献血者は，動物の内臓の摂取による人畜共通性食物媒介感染の可能が高い。

報告企業の意見	今後の対応
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との報告である。HEVは脂質膜のないRNAウイルスである。これまで、本剤によるHEV感染の報告はない。本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、今後もHEV感染の実態に関する情報の収集及び安全対策に努める。日本赤十字社では、厚生労働科学研究「E型肝炎の感染経路・宿主域・遺伝的多様性・感染防止・診断・治療に関する研究班」と共同して、献血者におけるHEV感染の疫学調査を行っている。加えて、北海道における輸血後HEV感染症報告を受け、試験的に北海道では本報告のベースとなった研究的NATを行うなど安全対策を実施している。

血液を原料とすることに由来する感染症伝播等
vCJD等の伝播のリスク

(5)

negative. Self-trigger sites had fewer TPs (1) than primary and neighbor sites (21 and 11 respectively); primary and self-trigger sites yielded more FPs (10 and 4) than the neighbor trigger (2 FPs), $p < 0.0001$. 75% of centers (6 of 8) using primary trigger criteria had ID-yields versus 67% (8 of 12) using neighbor triggers, and 8% (1 of 12) using self triggers. At 57 centers that did not trigger, 17 (30%) had at least 1-PVD identified by MP. FPs occurred more frequently with ID vs MP ($p < 0.0001$); FP rates did not differ between automated (Tigris) and semi-automated (eSAS) testing, $p < 0.2792$. **Conclusions:** These data demonstrate that the recommended minimal AABB trigger criteria of 2-PVDs and a rate of 1:1000 missed viremic donors; therefore it is reasonable to adopt more stringent triggers for the 2008 season, including elimination of the rate criterion and triggering on 1 PVD for regions adjacent to centers which have already triggered. However, self triggering prior to the detection of any PVDs had very limited yield and required a significant proportion of testing capacity.

TABLE 1. WNV Procleix Assay Test Results: June–November 2007

Test Format	Negative		Initial Postives		False Positives		True Positives	
	#	%	#	%	#	%	#	%
MP-NAT	1,143,590	93.88572	103	0.008	5	0.00041	129	0.0106
ID-NAT	74,273	6.097617	100	0.008	35	0.00287	34	0.0028
Total	1,217,863	NA	203		40		163	

Note: MP-NAT true positives include ID-tested donations, positive at 1:16 (MP) dilution.

Disclosure of Conflict of Interest

Joan Dunn Williams, Gene Robertson, Sally Caglioti, Robert Williams, Michael P. Busch, Randall Spizman, Steven Kleinman: Nothing to Disclose

SP156

Effectiveness of Single Unit Testing in Detecting West Nile Virus in Viremic Donations

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Background: A Canadian blood agency has tested all donations for West Nile Virus (WNV) in pools of 6 since July 1, 2003. There are strategies in place to test donations for WNV by Single Unit testing (SUT) following the identification of one positive donation found through Minipool testing (MP) or when human cases within the previous 2 weeks were identified in the population of a health region at a rate of greater than 1 in 1000 in rural areas or greater than 1 in 2500 in urban areas. A study was undertaken to determine the effectiveness of SUT in 2006 and 2007. **Methods:** Plasma was available from 50 donations (4 from 2006 and 46 from 2007) identified as WNV positive by SUT and confirmed by an alternate WNV NAT assay and/or by the presence of WNV IgM and/or IgG antibodies. Master 1 in 6 dilutions of each donation were prepared with 4.5 mL of donor sample plus 22.5 mL of Normal Human Plasma (NHP) as diluent to mimic MP. Each of 2 WNV testing laboratories was sent 3 replicates of each dilution from the 50 donations and 3 replicates of NHP as controls. All replicates were labelled as "blind" samples for each testing site. Testing was performed with the Roche cobas TaqScreen West Nile Virus Test, for use with the cobas s 201 System. **Results:** WNV was consistently detected in MP for 46% of the samples as 23 of 50 donations were MP positive for all 6 replicates. WNV was not consistently detected in MP in 54% of the samples – 12 of 50 donations (24%) were MP negative in 1 to 5 replicates and 15 of 50 donations (30%) were MP negative for all 6 replicates. All NHP controls were MP negative. When IgG and/or IgM WNV antibodies were present, the samples were less likely to be MP positive. The 3 donor samples that were negative by alternate WNV NAT but had detectable WNV IgG and IgM antibodies were negative by MP. **Conclusion:** WNV SUT has proven to be an effective strategy to detect WNV viremic donors through the infectious season. MP testing is still not sensitive enough to detect all potentially infectious donations.

No. MP Replicates Positive	No. Donations	Alternate NAT			WNV IgG and/or IgM Antibodies		
		Pos	Neg	Neg	Pos	Equiv.	NT
All (6)	23	23	0	16	2	0	5
Some (1-5)	12	12	0	2	7	2	1
None (0)	15	12	3	1	13	0	1
Total	50	47	3	19	22	2	7

Equiv. = Equivocal NT = Not Tested

Disclosure of Conflict of Interest

Gordon Hawes, Margaret Fearon, Jamie Brown: Nothing to Disclose
Edna Zuber: Roche Molecular Systems – Board NewGen – No honoraria or financial support
Nicholas Dibdin: Not Specified

SP157

Evaluation of NS1 Antigen Detection of Dengue Virus in Healthy Blood Donors During a Dengue Outbreak in Martinique

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Background: A dengue virus type 2 (DENV-2) outbreak occured in Martinique from Sptember 2007 to January 2008. Among an insular population of 400,000 inhabitants, 17,990 people were infected (5%) according to the dengue vigilance network. Since the first care in blood transfusion remains the viral safety, it was decided by the "Etablissement français du Sang" (EFS) to evaluate the validity of NS1 antigen (Ag) detection in blood donations as screening assay. **Methods:** The presence of NS1 Ag was detected by the Platelia dengue NS1 Ag kit purchased from Bio-Rad Company. The performance of ELISA was evaluated with, as reference test, RT-PCR using serotype-specific primers. Three studies were conducted to evaluate NS1 Ag detection. A first retrospective study included 136 blood samples coming from a clinic serum library and known as RT-PCR positive for dengue virus (DENV-1: 2; DENV-2: 125; DENV-3: 3; DENV-4: 6). All these samples were tested for the presence of NS Ag. A second prospective studies consisted of 110 blood samples from patients consulting, during dengue outbreak, for severe febrile syndrome compatible with dengue infection. On each of the second series NS1 Ag was carried out in comparison with RT-PCR technique. The third study was a prospective screening for NS1 Ag and dengue genomic material on 561 blood samples from healthy blood donors. This last investigation was performed during the epidemical peak of dengue outbreak. **Results:** In the first series, NS1 Ag was found positive in 83/136 (61%) samples positive for dengue virus with RT-PCR. No false positive (NS1 Ag+/RT-PCR-) were observed. In the second prospective study, one half of the samples (55/110) were negative for dengue markers (NS1 Ag and RT-PCR). The other half was positive in RT-PCR for DENV-2. Among these positive samples, 36/55 (65%) reacted with the NS1 Ag assay. In the last prospective investigation in healthy blood donors, one sample was found positive as well for the NS1 Ag as for the DENV-2 RT-PCR (1/561, or 1.8 per thousand). The donor concerned was asymptomatic before and after (1 week) his blood donation. In the mean time, we have performed NS1 Ag detection as screening test for all blood donors during dengue outbreak and we have found 6 sera positive for NS1 Ag among the 6,904 tested donations (1,5 per thousand). All the six donors concerned were asymtomatic. **Conclusions:** In comparison with RT-PCR technique, NS1 Ag assay showed sensitivity around 60-65%. According to these results, dengue NS1 Ag detection did not totally fit the gold standard in transfusion screening. Our first evaluation concerning incidence of dengue virus in healthy blood donors are preliminary results. More specific studies with accurate epidemiological tools will follow.

Disclosure of Conflict of Interest

Michel Rits, Raymond Cesaire: Nothing to Disclose
Najioullah Fatiha, Pascale Richard: Not Specified

SP158

HEV Infection Among Blood Donors in Hokkaido, Japan

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Background: Several cases of transfusion-transmission of HEV have been recognized in industrialized countries including Japan. However, little is known about the situation of the HEV infection among blood donors. On the other hand, zoonotic food-borne route is regarded as a main route of HEV infection in Japan, which causes sporadic cases of hepatitis E. **Methods:** Blood donors were screened for the presence of HEV RNA by pooled NAT from 2005 to 2007 in Hokkaido. Look-back and follow-up studies were carried out for the NAT-positive donors with HEV RNA (real-time RT-PCR) and anti-HEV antibodies (ELISA). For look-back, the samples at previous donations were used. HEV genotype was determined by direct sequencing of PCR products of partial regions within ORF1 and/or ORF2. Questionnaire survey on eating history before the donation was also conducted for the NAT-positive donors. **Results:** Out of 834,843 donors, 100 of HEV NAT-positive donors were detected. Male/female, average age and genotype 3/4 were 72/28, 41.0 ± 12.5 and 92/6, respectively. In 74 HEV positive donors, no anti-HEV was detected and in 20 donors, IgM anti-HEV was detected at the donation. Thirty-nine positive donors had histories of previous donations within 6 months and no HEV marker was detected in the samples of such previous donations. None of donors showed clinical sign of hepatitis at the donation. Out of 23 NAT-positive donors who could be followed up more than twice within a month after the donation, 13 showed elevation of ALT level higher than 60 IU/L. The ALT elevation was transient in 11 donors. However, two of the 13 developed hepatitis E and their peak ALT levels were 1250 and 3366 IU/L, respectively. HEV RNA of all the 23 donors was confirmed to disappear within a few months. HEV viremia persisted up to 55 days at the longest after the HEV-positive donation. In 3 donors, IgG anti-HEV became undetectable after 1 to 1.5 year after donations. Most of NAT-positive donors (59/78, 76%) had histories of eating animal viscera before their donations. **Conclusion:** About 1/8300 of blood donors in Hokkaido were HEV RNA-positive. Most of them were in their early phase of HEV infection at donation and remained asymptomatic, although HEV viremia persists for a few months. They are likely to be infected via zoonotic food-borne route by eating animal viscera.

Disclosure of Conflict of Interest

Hisami Ikeda, Keiji Matsubayashi, Hidekatsu Sakata, Hiromi Takeda, Emi Kon, Shinichiro Sato, Toshiaki Kato, Ikuma Abe, Hino Satoru, Kenji Tadokoro: Nothing to Disclose

SP159

Switching to Single-unit Testing: Importance of an in-house Test for Blood Donor West Nile Virus Testing

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Background: West Nile Virus (WNV) nucleic acid testing (NAT) is routinely done in mini-pool format. Single-donor testing is used for mini-pool resolution, when there are not enough samples to prepare a mini-pool or in situations of high incidence of WNV infection in a given area. Since the summer of 2004, Hema-Quebec has performed single-unit testing on blood donors from areas with high WNV activity. The decision to switch from mini-pool to individual donor testing is based on the identification of a positive donor sample by the testing laboratory. This report describes the contribution of a previously described in a previous AABB meeting (San Diego, 2003) in-house assay to the management of the decision-making process concerning the switch from mini-pools to single-donor testing. **Methods:** Routine screening of blood donations is performed by our testing laboratory in mini-pools of 6 donors using the Cobas TaqScreen WNV NAT assay (Roche Molecular Systems). An in-house confirmatory WNV NAT was designed by our Operational Research unit with specific DNA primers distinct from those used in the Roche Molecular Systems testing kit. In-house kits were produced within a Good Manufacturing Practices environment and their use was approved by Health Canada. Stability and sensitivity were monitored monthly and results were reviewed by quality assurance. WNV-positive samples were sent to the research testing unit for confirmation and test results were returned to the Medical Director within 24 hours. **Results:** During summers of 2004 to 2007, 499,681 blood donors were tested and 10 mini-pools were positive with the WNV assay. After resolution, samples from 2 mini-pools were all negative and 8 samples were found positive. Of these, 7 were tested with the in-house assay. Two samples were confirmed positive while 5 came out negative for WNV. None of the 5 unconfirmed donors have developed antibodies to WNV on follow-up, whereas the two confirmed by our in-house assay were also confirmed by seroconversion with an immunological assay. **Conclusion:** Single-donor testing has a major impact on resources in the blood testing laboratory. Decisions based on false-positive screening test results could lead to substantial costs. The rapid availability of confirmatory results through a close collaboration between Research and Operations contributes to well-informed decisions by Operations management.

Disclosure of Conflict of Interest

Isabel Chateauneuf, Marie-Claire Chevrier, Louis Thibault, Gilles Delage, Cindy Castilloux, Marie-Eve Nolin, Matthieu Guerin, Brigitte Caron, France Bornier, Maryse St-Louis: Nothing to Disclose

SP160

The Role of Platelet Bound Antibodies on Thrombocytopenia in Acute Dengue Virus Infection

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Background: Dengue is an endemic-epidemic mosquito-borne viral disease, caused by the dengue virus (DV) with an increasing incidence in the world-wide distribution. This disease may have unusual complications such as hepatic damage, cardiomyopathy, encephalopathy and severe hemorrhagic manifestations. Even patients with mild symptoms may present thrombocytopenia and the exact mechanism for the low platelet count has not yet been established. The mechanisms proposed are; transient marrow suppression, platelet aggregation to endothelial cells targeted by DV, hemophagocytosis and platelet immune destruction with dengue antibody complexes. The aim of the present study was to identify the prevalence of thrombocytopenia and evaluate a possible correlation to platelet bound antibodies on acutely DV infected (ADI) patients during the 2007 spring outbreak. **Methods:** 47 ADI patients were included (49% female, 51% male; median age: 38.5 years, range: 17-69 y). Platelet counts were performed in an automated counter. Sera were evaluated by flow cytometric assay to investigate the presence of platelet bound IgG or IgM antibodies in patients and in a group of 50 non-transfused group O male blood donors as a control group. A positive result was defined as a fluorescence ≥2 standard deviation (sd) from negative control and inconclusive result as a fluorescence ≥1 sd, <2 sd from negative control. **Results:** Positive IgG or IgM tests were significantly lower in the control group compared to patients (64% x 23.4%, $P = 0.00013$, $x = 14.58$).. The prevalence of thrombocytopenia found among patients was 68.1%. No correlation was found between thrombocytopenia and IgG or IgM tests among patients. Nevertheless, a significantly higher prevalence of positive tests was found in thrombocytopenic patients, when compared to controls (40.6% x 22.0%, $P = 0.002$, $x = 5.65$). The results are summarized in the table below. **Conclusions:** The results of this study confirm that thrombocytopenia is a frequent finding (68%) in ADI patients. Platelet bound antibodies are also frequent in these patients (~45%). These antibodies may have a role on thrombocytopenia as they have higher prevalence in thrombocytopenic ADI (~41%) than in controls (22%), but other mechanisms are probably involved since non-thrombocytopenic patients also have a high prevalence of these antibodies. Study granted by FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo – São Paulo State Research Support Foundation.)

Platelet Bound Antibody	Acute Dengue Patients			Controls
	Plt ≤ 150 × 10^3/L N = 32 (68.1%)	Plt > 150 × 10^3/L N = 15 (31.9%)	Total N = 47	N = 50
IgG/M Negative	9 (28.1%)	2 (13.3%)	11 (23.4%)	32 (64.0%)
IgG/M Inconclusive	10 (31.3%)	5 (33.3%)	15 (31.9%)	6 (16.0%)
IgG/M Positive	13 (40.6%)*	8 (53.4%)*	21 (44.7%)*	11 (22.0%)**

* $P = 0.002$, $x^2 = 5.65$; ** $P = 0.00013$, $x^2 = 14.58$

Disclosure of Conflict of Interest

Rodrigo Angerami, Vagner Castro, Maria L Barjas-Castro: Nothing to Disclose
Fernanda Rossi, Joyce Annichino-Bizzacchi, Brigina Kemp, Manângela Resende, Vania del Guercio, Luiz Silva: Not Specified

TTID 1: Testing Issues (Virology)

SP161

Development of a Parvovirus B19 DNA Assay and Systems Software for Plasma Screening

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Background: Recently the FDA asked manufacturers of derivatives to include "in-process" screening of recovered plasma for high titer Parvovirus

医薬品 研究報告 調査報告書

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研究報告の概要

○病棟におけるE型肝炎ウイルスの患者間感染の分子学的エビデンス
血液疾患病棟で急性白血病の33才の男性が急性肝炎を発症し、患者の血漿及び糞便検体からE型肝炎ウイルス(HEV)遺伝子が検出されHEV感染症と診断された。患者にHEV流行地域への旅行歴、野生動物・ペットとの接触歴及び生肉・貝類の摂食歴はなく、また、複数回の輸血を受けていたが供血者検体の検査結果はHEV RNA陰性であった。
この病棟には、急性E型肝炎を発症し、ほぼ1年間にわたって血液と糞便の両方にHEVを排出した44才のリンパ腫の男性患者がおり、最後の病棟滞在時期がHEVに感染した患者と重なった。
PCRの結果、2人の患者のHEVはいずれもgenotype 3fに属し、シーケンスの同一性は97.8% ～98.6%であった。
2人の患者は地理的に異なった地域に住み、HEVの共通感染源に暴露されていなかったため、2人が同時に病棟に滞在した間に感染が起こったことが示唆される。
病棟での遡及的調査で一般的な衛生予防措置上の重大な違反は確認されなかったが、(1) 免疫抑制患者はウイルスに感染しやすい、(2) 感染患者は長期間にわたり二次感染につながるHEVを排出する、(3) ウイルスは無機物表面で長期間生存する、(4) HEVに対してワクチンは利用できないことから、我々は、免疫抑制患者が治療される病棟でE型肝炎の症例が発生した場合には、一般的な衛生予防措置は強化されなければならないと結論する。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
急性白血病の33才の男性が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たことが示唆されたとの報告である。 免疫抑制状態にある患者では、食物、輸血以外の経路によるHEV伝播の可能性についても、配慮する必要があるものと考える。 HEVは脂質膜のないRNAウイルスである。本剤の製造工程にはコーン分画及び液状加熱の2つのウイルス除去・不活化工程が含まれている。疫学的に見て、血漿分画製剤で最も長い歴史を持つアルブミンでは世界的にHEV感染の報告はないことから、本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、今後もHEV感染の実態に関する情報の収集及び安全対策に努める。なお、日本赤十字社では、北海道における輸血後HEV感染報告を受け、献血者の疫学調査や、北海道で研究的NATを実施している。

MedDRA/J Ver.11.0J

ceftriaxone, and benzylpenicillin were administered empirically. MRI revealed meningeal enhancement around the brainstem, contiguous with a markedly edematous cervical cord and "sugar coating" of the entire cervico-thoraco-lumbar cord (figure 1). A clinical diagnosis of necrotizing varicella myelitis with meningoencephalitis was made. Progressive bulbar palsy and respiratory failure developed. Because of the extremely poor prognosis, the patient was palliated, and she died 60 h after arrival at our institution.

Varicella-zoster virus (VZV) was detected by PCR of the patient's CSF and skin vesicle specimens. Postmortem examination confirmed extensive infarction and necrosis of the entire spinal cord due to necrotizing vasculitis in association with a lymphocytic meningitis.

This fulminant presentation of VZV necrotizing myelitis has been reported infrequently in profoundly immunosuppressed HIV-infected individuals in the pre-ART era [1–4]. To our knowledge, this is the first occurrence in a moderately immunosuppressed individual in the post-ART era. Its occurrence shortly after a change in ART raises the possibility that this is a manifestation of VZV immune restoration disease (IRD).

VZV complications involving the CNS are estimated to occur in 2% of patients with HIV/AIDS, with 4 other recognized variants, including multifocal encephalitis, ventriculitis, focal necrotizing myelitis, and vasculopathy that leads to cerebral infarction [2, 4–6]. Prognosis of VZV necrotizing meningomyelitis is extremely poor, with a median survival of 16 days [7].

The diagnosis of IRD is usually contingent on a clear response to ART with ≥1-log reduction in HIV RNA level [8]. Assessment of HIV RNA level was not performed, but a significant decrease is highly likely, given the initiation of 2 new classes of ART 2 weeks before presentation. The patient's moderate immunosuppression and decrease in CD4+ T cell count after the change of ART regimen does not preclude IRD [9]. Compartmentalization of VZV IRD in the CNS has been suggested and may explain the profound CNS changes in the absence of significant rash or systemic symptoms [10].

Necrotizing myelitis is a devastating complication of VZV. In the context of immunosuppression, necrotizing myelitis may represent a new manifestation of VZV IRD.

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Molecular Evidence of Patient-to-Patient Transmission of Hepatitis E Virus in a Hematology Ward

TO THE EDITOR—A 33-year-old man receiving treatment for acute leukemia in a hematological ward developed acute hepatitis (aspartate aminotransferase level, 1215 IU/L; alanine aminotransferase level, 2960 IU/L). Test results for viral markers (i.e., anti-hepatitis A virus IgM, hepatitis B virus surface antigen and DNA, anti-hepatitis C virus antibodies, and hepatitis C virus RNA) were negative; nonviral causes of liver disease, such as autoimmunity, toxic or iatrogenic hepatitis, and metabolic disorders, were excluded. A diagnosis of hepatitis E virus (HEV) infection was made after the detection of the HEV genome in plasma and stool samples from the patient [1]. Anti-HEV IgG was detected 2 weeks after the onset of the illness and persisted throughout.

The patient had not traveled in areas where HEV was endemic and declared that he had had no contact with wild or domestic animals. He had not eaten raw meat or shellfish. No symptomatologic cases of hepatitis E had been reported in his family or in nurses and medical staff during the same period. The patient had received many transfusions from blood

donors. Because HEV can be transmitted through transfusion [2], all donors' samples were tested and had negative results for HEV RNA.

Medical records from the hematology ward indicated that a 44-year-old man with lymphoma had developed acute hepatitis E 1 year earlier. This patient was hospitalized repeatedly for short periods during that year until his lymphoma was cured. The patient did not recover after the acute phase of hepatitis, and he excreted HEV in both blood and stool for almost a year. His last stay in the ward overlapped with that of the other patient who was infected with HEV.

We therefore looked for a link between the HEV strains from the 2 patients with use of samples that were collected at the time of diagnosis of acute hepatitis E. PCR products amplified from 3 distinct regions of the HEV genome were sequenced. Both strains belonged to HEV genotype 3f. Phylogenetic analyses including HEV sequences from local and GenBank reference strains indicated that the strains from the 2 patients were closely related. The nucleotide identity of the 3 HEV sequences from the 2 patients was 97.8%–98.6%. Both strains also harbored the same insertion in the ORF1 hypervariable region that differed from the reference sequences. Because the 2 patients lived 250 km apart in 2 geographically distinct areas and had not been exposed to a common source of HEV, transmission probably occurred during their overlapping stays in the hospital that occurred 3 weeks prior to the onset of hepatitis E in the patient with acute leukemia.

A retrospective audit of the ward identified no major breaches of universal hygiene precautions. However, a lapse in strict hygiene procedures could be the cause of HEV contamination through enteric transmission, because HEV can persist for weeks on inanimate surfaces [3]. Parenteric iatrogenic transmission has also been suggested [4].

We conclude that universal hygiene precautions must be reinforced when cases of hepatitis E occur in medical wards where immunosuppressed patients are treated. There are several reasons for reinforced precautions: (1) immunosuppressed patients are highly susceptible to viral infections; (2) infected patients excrete HEV for a prolonged time, which results in a high risk of secondary transmission; (3) the virus persists for long periods on inanimate surfaces; and (4) no vaccine is available against HEV, although a phase-2 vaccine trial has had recent success [5].

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Jean-Michel Mansuy,[1] Anne Huynh,[1] Florence Abravanel,[1,2] Christian Recher,[1] Jean Marie Peron,[1] and Jacques Izopet[1,2]

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販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社)					

研究報告の概要

○日本のALT高値献血者のE型肝炎ウイルス陽性率についての全国調査
背景:我々は日本における輸血後E型肝炎感染症例2例を報告したが、日本の献血者のE型肝炎ウイルス(HEV)陽性率は十分明らかになっていない。
試験デザインおよび方法:すべての赤十字血液センターから、ALT高値のため献血不適となった献血者の血液検体を収集し、HEV試験に供した。
結果:北海道のALT高値(500 IU/L超)献血者41名では、8検体(19.5%)にHEV RNAが検出された。日本全土のALT高値(200 IU/L超)献血者1,389名では、HEV RNA、IgM-HEV抗体、IgG-HEV抗体陽性検体数が、それぞれ15(1.1%)、14(1.0%)、45(3.2%)であった。RNA陽性献血者はほとんど男性であり、日本のどの地域にも認められたが、北海道を含む東日本の方が多く、西日本の方が少ない傾向であった。HEV RNA陽性であった23検体のうち、19検体はgenotype 3、4検体はgenotype 4であった。分離株9株のDNA配列は、既知のブタHEV分離株と98.5%以上の相同性を示した。ALT値61～199IU/Lの献血者1,062名では、IgM-HEV抗体およびIgG-HEV抗体陽性検体の割合はそれぞれ0.1および2.7%であったが、これらの検体はHEV RNA陰性であった。
結論:日本各地のALT高値献血者にHEVマーカー(HEV RNAおよび抗HEV抗体)が認められ、いずれのマーカーとも、東日本の方が西日本より高かった。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
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および抗HEV抗体)が認められ、いずれのマーカーとも東日本の方が西日本より高かったとの報告である。 HEVは脂質膜のないRNAウイルスである。本剤の製造工程にはコーン分画及び液状加熱の2つのウイルス除去・不活化工程が含まれている。疫学的に見て、血漿分画製剤で最も長い歴史を持つアルブミンでは世界的にHEV感染の報告はないことから、本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、今後もHEV感染の実態に関する情報の収集及び安全対策に努める。なお、日本赤十字社では、北海道における輸血後HEV感染報告を受け、献血者の疫学調査や、北海道で研究的NATを実施している。

A nationwide survey for hepatitis E virus prevalence in Japanese blood donors with elevated alanine aminotransferase

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BACKGROUND: Although we reported two cases of transfusion-transmitted hepatitis E in Japan, the prevalence of hepatitis E virus (HEV) in Japanese blood donors is not very clear.

STUDY DESIGN AND METHODS: Blood samples of donors who were deferred from donation because of elevated alanine aminotransferase (ALT) levels were collected from all Japanese Red Cross Blood Centers and subjected to HEV tests.

RESULTS: Among the 41 donors with elevated ALT levels higher than 500 IU per L in Hokkaido, HEV RNA was detected in 8 (19.5%) samples. In 1389 donor samples with ALT levels of higher than 200 IU per L in nationwide Japan, the numbers of positive HEV RNA, immunoglobulin M (IgM) anti-HEV, and immunoglobulin G (IgG) anti-HEV samples were 15 (1.1%), 14 (1.0%), and 45 (3.2%), respectively. Although RNA-positive donors were predominantly male and found in any geographic area of Japan, they tended to be higher in number in eastern Japan including Hokkaido and lower in number in western Japan. Of the 23 HEV-positive samples, 19 were Genotype 3 and 4 were Genotype 4. DNA sequences of the 9 isolates showed more than 98.5 percent homology with the known swine HEV isolates. In 1062 donor samples with ALT levels of 61 to 199 IU per L, the percentages of IgM and IgG anti-HEV–positive samples were 0.1 and 2.7 percent, respectively, although there was no HEV RNA–positive sample.

CONCLUSION: HEV markers (HEV RNA and anti-HEV) were detected in donors with elevated ALT levels who were widely distributed over Japan. The prevalence and incidence were higher in eastern Japan than in western Japan.

Although hepatitis E virus (HEV) is an emerging pathogen of enterically transmitted viral hepatitis in endemic areas, its infection is now recognized as a form of zoonosis in which swine, wild boar, and deer act as reservoirs for human infection in Japan.[1-8] HEV subgenomic sequencing studies have revealed a close relationship between the strains infecting humans and those infecting pigs. Accumulating evidence suggests that eating undercooked meat and viscera of pig and other animals is associated with a high risk of acquiring HEV infection. The HEV-infected individuals show transient viremia, which suggests the potential risk of a blood-borne route of HEV infection.[9-12] We previously reported two cases of transfusion-transmitted acute hepatitis E in Hokkaido, Japan.[9,12] In both cases, sequence analyses showed that the isolates of both donors and patients appeared to be identical. Moreover, HEV RNA has been reported to be present among some blood donors with elevated alanine aminotransferase (ALT) levels in Japan.[9,13,14] Although HEV was previously considered to be endemic only in developing countries, approximately 13 percent of the non-A, non-B, and non-C acute hepatitis cases were caused by HEV in Japan, a developed country.[15] However, no report has been available on a nationwide survey for HEV prevalence in Japan.

ABBREVIATIONS: B19 = human parvovirus B19; EBV = Epstein-Barr virus; HAV = hepatitis A virus; HEV = hepatitis E virus; JRC = Japanese Red Cross; RT = room temperature.

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Here we report the results of two studies. First, we studied the presence of HEV in plasma samples collected from blood donors showing extremely high ALT levels in Hokkaido, Japan. Subsequently, we expanded the area of investigation to nationwide and studied HEV prevalence in Japanese blood donor samples with elevated ALT levels obtained from all Japan.

MATERIALS AND METHODS

Blood donor samples with elevated ALT levels in Hokkaido

For the preliminary study, we studied the blood donors with elevated ALT levels of 500 IU per L and greater in Hokkaido. There were 1,049,566 blood donations in Hokkaido from April 2000 through March 2003. Of these, 23,827 (2.3%) were disqualified because of an elevated ALT level of 61 IU per L or greater, which was cutoff value in the Japanese Red Cross (JRC). Of these, 41 had an ALT level of 500 IU per L or greater (Table 1). The samples from these 41 donors enrolled in this study were stored below –20°C until testing. The tests for qualitative HEV RNA and/or for antibodies were performed as described below.

Blood donor samples with elevated ALT levels in nationwide Japan

All donor samples (n = 1389) with ALT levels higher than 200 (mean ± standard deviation [SD], 314 ± 249) IU per L were collected from all JRC Blood Centers over Japan between April 2003 and March 2004. In addition, 1062 donor samples with ALT levels of 61 to 199 IU per L were collected randomly from 3 blood centers (Hokkaido, Hiroshima and Fukuoka). The 47 blood centers were divided into eastern Japan (three blocks: Hokkaido, Miyagi, and Tokyo) and western Japan (four blocks: Aichi, Osaka, Okayama, and Fukuoka; Fig. 1). Hiroshima and Fukuoka blood centers belong to western Japan. The samples were subjected to real-time reverse transcription–polymerase chain reaction (RT-PCR) testing for the presence of HEV RNA and enzyme-linked immunosorbent assay (ELISA) for antibody tests against HEV as described below. The samples were kept frozen below –20°C until testing.

Real-time RT-PCR for HEV RNA detection and sequence analyses

Total nucleic acids were extracted from 200 µL of plasma sample using a virus spin kit (QIAamp MinElute, Qiagen K.K., Tokyo, Japan) according to the manufacturer's instructions. The 20-µL eluate was subjected to one-step real-time RT-PCR and quantitative assay for HEV RNA as described in our previous study.[12] The amplification products were then sequenced directly on both strands and were analyzed as described previously.[16] The amplification products of ORF2 (412 nucleotides) from HEV RNA–positive samples were sequenced and compared with those of reported swine HEV isolates from pigs or pig livers by using GenBank Basic Local Alignment Search Tool (BLAST) homology search at the National Center for Biotechnology Information server (http://www.ncbi.nlm.nih.gov).

The nucleotide sequence data reported in this article will appear in DDBJ/EMBL/GenBank nucleotide sequence databases with the Accession Numbers AB434132 for HRC-HE1, AB434133 for HRC-HE2, AB434134 for HRC-HE3, AB434135 for HRC-HE4, AB434136 for HRC-HE5, AB434137 for HRC-HE6, AB434138 for HRC-HE7, AB434139 for HRC-HE8, AB434140 for HRC-HE9, AB434141 for HRC-HE10, AB434142 for HRC-HE11, AB434143 for HRC-HE12, AB434144 for JRC-HE1, AB434145 for JRC-HE2, AB434146 for JRC-HE3, AB434147 for JRC-HE4, AB434148 for JRC-HE5, AB434149 for JRC-HE6, AB434150 for JRC-HE7, AB434151 for JRC-HE8, AB434152 for JRC-HE9, AB434153 for JRC-HE10, and AB434154 for JRC-HE11.

TABLE 1. ALT-disqualified donors from April 2000 through March 2003 in Hokkaido, Japan (total number of donors, 1,049,566)

	Number of donors with each ALT level (IU/L)						
Donors	61-99	100-199	200-299	300-399	400-499	500-	Total
Male	16,809	3,714	226	35	11	29	20,824
Percent*	88.1	85.8	78.7	60.3	52.4	70.7	87.4
Percent†	1.60	0.35	0.02	0.00	0.00	0.00	1.98
Female	2,281	616	61	23	10	12	3,003
Percent*	11.9	14.2	21.3	39.7	47.6	29.3	12.6
Percent†	0.22	0.06	0.01	0.00	0.00	0.00	0.29
Total	19,090	4,330	287	58	21	41	23,827
Percent†	1.82	0.41	0.03	0.01	0.00	0.00	2.27
Percent‡	80.1	18.2	1.2	0.2	0.1	0.2	100.0

* Rate relative to the donors with each ALT level, showing the ratio of sex difference.
† Rate relative to the total donors (1,049,566).
‡ Rate relative to the ALT-disqualified donors (23,827).

ELISA for HEV antibodies

Purified HEV Genotype 1 virus-like particles derived from recombinant baculovirus-infected insect cells were used as antigens for detection of antibodies to HEV.[17,18] HEV RNA–positive samples from 41 donors enrolled in the preliminary study were assayed by commercial HEV antibody ELISA kit (Cosmic Corp., Ltd., Tokyo, Japan) which basically consisted of the recombinant ORF2 protein as the antigen according to the manufacturer's protocol. In the subsequent study of all samples (n = 1389 and 1062) from all areas of

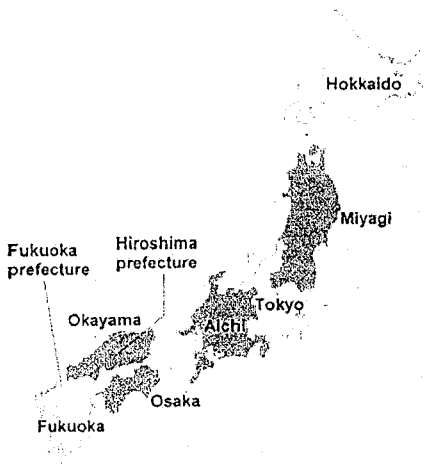

Fig. 1. Map of Japan showing the locations of seven geographic blocks. The 47 blood centers were divided into eastern Japan (three blocks: Hokkaido, Miyagi [six prefectures], and Tokyo [nine prefectures]) and western Japan (four blocks: Aichi [eight prefectures], Osaka [six prefectures], Okayama [nine prefectures] including Hiroshima prefecture, and Fukuoka [eight prefectures] including Fukuoka prefecture).

Japan, ELISA was performed as follows. Wells of microplates (Number 2592, 96-well Stripwell, flat bottom, Corning Life Sciences, Corning, NY) were coated with 50 μL of the recombinant ORF2 protein (3 μg/mL in phosphate-buffered saline [PBS]), and the plates were incubated at room temperature (RT) for 2 hours followed by incubation with 100 μL of blocking buffer containing 40 percent (vol/vol) calf serum (Gibco-BRL, Tokyo, Japan) at RT for 1 hour. The blocking buffer was discarded, and each well was washed five times with 450 μL of washing buffer (0.05% Tween 20 in PBS). To test for anti-HEV immunoglobulin G (IgG), 50 μL of each sample was added to each well at a dilution of 1:100 in saline containing 40 percent calf serum. The microplates were incubated at RT for 1 hour and then washed five times with washing buffer. Fifty microliters of horseradish peroxidase–conjugated goat anti-human IgG (IGB22; Institute of Immunology Co., Ltd., Tokyo, Japan; 1:2000) or immunoglobulin M (IgM; IGM49, Institute of Immunology Co., Ltd.; 1:500) in PBS containing 25 percent (vol/vol) fetal calf serum (PAA Laboratories GmbH, Pasching, Austria) was added to each well and incubated at RT for 1 hour. The wells were washed five times with washing buffer. Fifty microliters of tetramethylbenzidine soluble reagent (Dako Co., Ltd., Carpinteria, CA) as a substrate was added to each well. The plate was incubated at RT for 10 minutes in the dark, and then 50 μL of 1 N sulfuric acid (Kanto Chemical Co., Inc., Tokyo, Japan) as tetramethylbenzidine stop buffer was added to each well. The optical density (OD) of each sample was read at 450 nm. Test samples with OD values equal to or greater than the cutoff value were considered positive for the presence of anti-HEV IgG or anti-HEV IgM in this ELISA. ODs of 0.18 [mean (0.019) + 7 × SD (0.024)] for anti-HEV IgG, and that of 0.19 [mean (0.022) + 6 × SD (0.028)] for anti-HEV IgM were used as the cutoff values. Reactive samples were tested by another HEV antibody ELISA kit (Cosmic) described previously. Samples were determined as positive if they were reactive by both ELISA methods.

Statistical analysis

A two-sided Fisher's exact test was used to compare the percentages of subjects with each HEV marker in the two geographic groups (eastern Japan vs. western Japan) or two age groups (10s-30s vs. 40s-60s).

RESULTS

Prevalence of HEV RNA in donors with elevated ALT levels in Hokkaido

In the primary study, more than 98 percent of those disqualified donors had an ALT level of less than 200 IU per L and more than 87 percent were male (Table 1). The number of donors with elevated ALT levels higher than 500 IU per L was 41 (0.2%). Among the 41 donors, HEV RNAs were detected in 8 (19.5%). Of these, 6 samples were described in our previous study.[9]

Prevalence of HEV RNA in donors with elevated ALT in Japan

Thereafter, we studied a nationwide survey for HEV prevalence in Japanese blood donor samples with elevated ALT levels including levels of less than 500 IU per L, obtained from all Japan. Of 5,621,096 blood donations in 47 blood centers from April 2003 through March 2004, a total of 114,583 (2.0%) were disqualified because of elevated ALT levels of higher than 61 IU per L. Of these, 1389 donors (men vs. women, 5.5 vs. 1; age, 32 ± 11 years [mean ± SD]) showed elevated ALT level of higher than 200 IU per L. A total of 1062 donors with an ALT level of 61 to 199 IU per L were randomly collected from three blood centers as described.

The results are summarized in Table 2 and Fig. 2. Of 1389 donor samples with elevated ALT levels higher than 200 IU per L, 15 (1.1%) were HEV RNA–positive. Although the HEV-positive donor samples were found in any block of Japan, they tended to be more frequent in eastern Japan

TABLE 2. Prevalence of HEV RNA, IgM anti-HEV, and IgG anti-HEV among elevated ALT donors from April 2003 through March 2004 in Japan (total number of donors, 5,621,096)

	ALT levels (61-199 IU/L)						ALT levels (200- IU/L)					
Geographic blocks	Number of donors*	Number RNA-positive (%)		Number IgM-positive (%)		Number IgG-positive (%)	Number of donors†	Number RNA-positive (%)		Number IgM-positive (%)		Number IgG-positive (%)
Hokkaido	364	0	(0.0)	1	(0.3)	21 (5.8)	87	4	(4.6)	3	(3.4)	6 (6.9)
Miyagi	NA	NA	NA	NA	NA	NA	143	3	(2.1)	3	(2.1)	3 (2.1)
Tokyo	NA	NA	NA	NA	NA	NA	335	4	(1.2)	3	(0.9)	19 (5.7)
Aichi	NA	NA	NA	NA	NA	NA	223	1	(0.4)	2	(0.9)	6 (2.7)
Osaka	NA	NA	NA	NA	NA	NA	234	1	(0.4)	1	(0.4)	3 (1.3)
Okayama	345	0	(0.0)	0	(0.0)	7 (2.0)	188	1	(0.5)	1	(0.5)	1 (0.5)
Fukuoka	353	0	(0.0)	0	(0.0)	1 (0.3)	179	1	(0.6)	1	(0.6)	7 (3.9)
Total	1062	0	(0.0)	1	(0.1)	29 (2.7)	1389	15	(1.1)	14	(1.0)	45 (3.2)
(95% CI)				(0.0-0.5)		(1.8-3.9)		(0.6-1.8)		(0.6-1.7)		(2.4-4.3)

* Random sampling of donors with elevated ALT (61-199 IU/L) from three prefectures (Hokkaido, Hiroshima, and Fukuoka).
† All donor samples with elevated ALT levels of higher than 200 IU per L during this period.
CI = confidence interval; NA = not available.

(Hokkaido, Miyagi, and Tokyo; p = 0.015). No HEV RNA–positive sample was detected in 1062 donors with elevated ALT levels of 61 to 199 IU per L. The results indicate that HEV RNA–positive donors with elevated ALT levels higher than 200 IU per L were widely distributed over Japan and the prevalence was the highest in Hokkaido.

Antibodies against HEV in donors with elevated ALT levels in Japan

Of 1389 donor samples with elevated ALT levels higher than 200 IU per L, 14 samples (1.0%) were positive for the presence of IgM antibodies to HEV. Donors with IgM anti-HEV were also frequently found in eastern Japan (p = 0.099) and associated with positive HEV RNA (Table 2). Of 1062 donor samples with elevated ALT levels of 61 to 199 IU per L, only 1 sample was positive for the presence of IgM anti-HEV.

Of 1389 donor samples with elevated ALT levels higher than 200 IU per L, 45 samples (3.2%) were positive for the presence of IgG anti-HEV. Again, donors with IgG anti-HEV were more frequent in eastern Japan (p = 0.003) and not associated with HEV RNA–positive donors (Table 2). The frequency of IgG anti-HEV–positive donors appeared to be age-dependent, that is, from 0 percent of donors in their 10s to 12.5 percent of donors in their 60s (10s-30s vs. 40s-60s; p < 0.0001; Fig. 2). Of 1062 donor samples with elevated ALT levels of 61 to 199 IU per L, 29 samples (2.7%) were positive for the presence of IgG anti-HEV (Table 2). Again, the IgG anti-HEV–positive donors were more frequent in eastern Japan (p < 0.0001) and it appeared to be age-dependent (10s-30s vs. 40s-60s; p = 0.001, data not shown).

Analysis for HEV RNA–positive donors

We verified in detail the HEV RNA–positive samples obtained from two studies. Results of analyses for 8 (ALT ≥ 500 IU/L from Hokkaido) and 15 (ALT ≥ 200 IU/L from Japan) HEV RNA–positive donors are summarized in Table 3. The ensuing investigation revealed that all had no history of recent travel in HEV-endemic areas and remained asymptomatic despite of their elevated ALT levels. The concentration of HEV RNA varied from 1.9 to 7.5 log copies per mL. Of the 23 samples, 3 were seronegative, 2 were IgM anti-HEV–positive, 17 were IgM/IgG anti-HEV–positive, and 1 were IgG anti-HEV–positive samples. Twenty-three HEV RNA–positive samples were segregated into Genotype 3 (n = 19) and Genotype 4 (n = 4). These constituted 21 males and 2 females ages 25 to 62 years. Some of the 23 HEV RNA–positive donors were repeat donors. The results of the tests with samples from their other donations revealed that HEV RNA was detected in the previous donation in Donor 12 (HRC-HE12). The sample was negative for the presence of both IgM and IgG

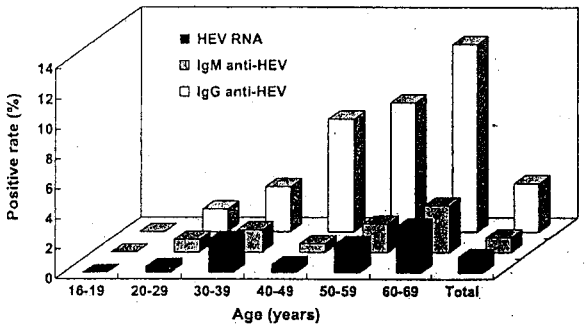

Fig. 2. Age-specific prevalence rates of HEV RNA (■), IgM anti-HEV (▨), and IgG anti-HEV (□) in Japanese donors with elevated ALT levels of 200 IU per L and greater from April 2003 through March 2004. The total number of tested donors was 1389.

anti-HEV with normal ALT. The donated blood (whole blood) was not used for transfusion, because of the low volume of red cells. The plasma was in quarantine. Except for Donor 12, neither HEV RNA nor anti-HEV was detected in other donations.

When the 412-nucleotide ORF2 partial sequences of the HEV-positive 23 isolates were compared with those of reported HEV isolates from pigs or pig livers of Japan, all had a high nucleotide sequence identity of higher than 92.2 percent. More specifically, HRC-HE8 and JRC-HE5 had the highest nucleotide sequence identity, of 99.8 percent, with swJ11-4 and swJ19-1, respectively. Also, JRC-HE1, HRC-HE12, and HRC-HE3 had 99.3, 99.3, and 98.8 percent identities with swJ18-3, swJ13-1, and swJL145, respectively (Table 3).

DISCUSSION

The aim of this study was to investigate the prevalence of HEV among elevated ALT blood donors in Japan. The results of the primary study suggest that HEV was a major causative agent among blood donors with ALT levels higher than 500 IU per L in Hokkaido, since we demonstrated that HEV RNA was detected in 8 of 41 (19.5%) of the high ALT donor samples. Subsequently, a nationwide survey for HEV prevalence in blood donor samples with elevated ALT from all JRC revealed that 1.1 percent (n = 15) of donor samples with elevated ALT levels higher than 200 IU per L were positive for the presence of HEV RNA. No HEV RNA–positive samples were detected in donor samples with elevated ALT levels of 61 to 199 IU per L. Although the 15 HEV RNA–positive donors were widely distributed over Japan, they were frequently found in eastern Japan, especially in Hokkaido (4/15), Miyagi (3/15), and Tokyo (4/15).

It should be noted that in Hokkaido, 8 of the 41 donors with ALT levels of 500 IU per L or greater were positive for the presence of HEV, which is known to be transmitted by transfusion. Thus, as a result of performing HEV tests as the following study among 124 blood donors with ALT levels of 200 to 499 IU per L in Hokkaido, 1 donor (0.8%) was HEV RNA–positive (data not shown). Based on these results, in the subsequent study we expanded the area of investigation to nationwide and studied HEV prevalence in Japanese blood donor samples with elevated ALT including levels of less than 500 IU per L, obtained from all Japan. As for the geographical distribution of hepatitis E in Japan, it was reported that there was a higher prevalence of HEV-infected donors in the eastern part of Japan (Hokkaido, Miyagi, and Tokyo blocks).[15] We cannot clearly explain the reason why blood donors with HEV markers were more frequent in eastern than western Japan. Further studies with a larger number of donors including normal ALT levels will be necessary to draw a definitive conclusion.

Twenty-three HEV RNA–positive samples were divided into Genotype 3 (n = 19) and Genotype 4 (n = 4). Because it is commonly assumed that blood donors are healthy adults, most of those HEV-positive donors appeared to be asymptomatic. Since the isolates of acute hepatitis E patient samples were predominantly Genotype 4 in Japan,[19] the genotypes may play an important role in clinical progression of HEV infection. HEV-positive donors with ALT levels higher than 500 IU per L appeared to be asymptomatic and their ALT elevation was transient (unpublished observation).

In this study, the routes of HEV transmission of infected donors are not clear. The HEV RNA–positive donors had no history of recent travel abroad in areas where HEV is hyperendemic. Yazaki and his colleagues[4] reported that of the 363 packages of raw pig liver sold in grocery stores as food in Hokkaido, 7 (1.9%) packages had detectable HEV RNA. In this study, some isolates from the HEV RNA–positive donor samples showed close sequence homology with the isolates from pigs in Japan, suggesting that HEV transmission may be associated with the consumption of undercooked or inadequately cooked pig meat. Emerson and colleagues[20] reported that some HEV would most likely survive the internal temperatures of rare-cooked meat. When the 412-nucleotide ORF2 partial sequences of the 23 HEV RNA–positive donor isolates were compared with those of reported HEV isolates from pigs or pig livers of Japan, at least 9 isolates (39%) showed close sequence homology (98.5%-99.8%) with the

TABLE 3. Profile of HEV RNA–positive donors

Donor*	Geographic blocks	Date of donation	Age (years)	Sex	ALT (IU/L)	HEV RNA (log copies/mL)	Anti-HEV IgM	Anti-HEV IgG	HEV genotype	Strain	HEV strain with the highest homology among the known swine isolates [Accession No.] (%)†
1	Hokkaido	Dec. 2000	29	M	767	5.6	+	+	4	HRC-HE1	swJL145‡ [AB105902] (98.5)§
2	Hokkaido	Mar. 2001	30	M	506	5.0	+	+	3	HRC-HE2	swJHR1-1 [AB194528] (93.9)
3	Hokkaido	Apr. 2001	40	M	1,470	6.9	+	+	4	HRC-HE3	swJL145‡ [AB105902] (98.8)§
4	Hokkaido	Jul. 2001	47	M	713	5.1	+	+	3	HRC-HE4	swJTT1-1 [AB194526] (93.4)
5	Hokkaido	Oct. 2001	62	M	2,080	6.3	+	+	3	HRC-HE9	swJL234‡ [AB105903] (98.5)§
6	Hokkaido	Oct. 2001	39	M	641	5.1	+	+	3	HRC-HE5	swJL234‡ [AB105903] (98.5)§
7	Hokkaido	Nov. 2001	48	M	740	3.6	+	+	4	HRC-HE6	swJL145‡ [AB105902] (98.5)§
8	Hokkaido	Feb. 2003	39	F	578	6.2	−	+	3	HRC-HE7	swJL234‡ [AB105903] (96.1)
9	Hokkaido	Jul. 2003	35	M	575	5.0	+	+	3	HRC-HE8	swJ11-4‡ [AB094243] (99.8)§
10	Hokkaido	Oct. 2003	38	M	244	3.4	−	−	3	HRC-HE10	swJHK5-1‡ [AB194486] (95.4)
11	Hokkaido	Nov. 2003	52	M	576	3.9	+	+	3	HRC-HE11	swJL234‡ [AB105903] (96.1)
12	Hokkaido	Jan. 2004	38	M	793	5.9	+	+	4	HRC-HE12	swJ13-1‡ [AB094254] (99.3)§
13	Miyagi	Dec. 2003	39	M	470	5.4	+	+	3	JRC-HE4	swJ24-1 [AB094306] (92.5)
14	Miyagi	May 2003	25	M	222	4.2	+	+	3	JRC-HE6	swJL234‡ [AB105903] (95.1)
15	Miyagi	Jan. 2004	34	M	273	3.8	+	+	3	JRC-HE7	swJ2-1‡ [AB094207] (92.7)
16	Tokyo	Mar. 2004	41	F	216	1.9	+	+	3	JRC-HE9	swJAK6-2 [AB194512] (93.7)
17	Tokyo	Jun. 2003	34	M	211	3.1	+	+	3	JRC-HE5	swJ19-1 [AB094279] (99.8)§
18	Tokyo	Nov. 2003	34	M	447	6.8	−	−	3	JRC-HE1	swJ18-3 [AB094277] (99.3)§
19	Tokyo	Feb. 2004	36	M	328	5.2	+	−	3	JRC-HE10	swJC1990 [AB096756] (92.7)
20	Aichi	Feb. 2004	62	M	281	3.9	+	+	3	JRC-HE11	swJS21-1 [AB194524] (92.2)
21	Osaka	Mar. 2004	37	M	793	5.9	−	+	3	JRC-HE8	swJHR1-1 [AB194528] (95.9)
22	Okayama	May 2003	29	M	554	5.3	+	+	3	JRC-HE2	swJIW4-1 [AB194496] (92.7)
23	Fukuoka	Aug. 2003	57	M	398	7.5	+	−	3	JRC-HE3	swJHR1-1 [AB194528] (93.4)

* HEV RNA–positive donors; samples from Donors 1 through 8 were obtained from the primary study (ALT ≥ 500 IU/L from Hokkaido) and Donors 9 through 23 from the secondary study (ALT ≥ 200 IU/L from all Japan).
† Nucleotide sequences were compared to the GenBank databases utilizing the BLAST program available at http://www.ncbi.nlm.nih.gov as of March 2008.
‡ Isolates from Hokkaido.
§ Identities of 412-nucleotide ORF2 sequences over 98.5 percent are indicated.
+ = positive; − = negative; M = male; F = female.

isolates from pigs or liver of pigs.[2,4] It should be noted that among 12 HEV RNA–positive donors from Hokkaido, 10 isolates (83%) showed high nucleotide homology (>95%) of 412-nucleotide sequences with the isolates from pigs or pig livers from Hokkaido. The results are consistent with the possibility that at least some of the HEV RNA–positive donors were infected through the zoonotic food-borne route. Similarly, Feagins and colleagues[21] recently reported that of the 127 packages of commercial pig livers purchased from local grocery stores in the United States, 14 (11.0%) tested positive for the presence of HEV RNA. The widespread distribution of HEV is being clarified in developed countries other than Japan.[22,23]

In this study, IgM anti-HEV–positive as well as HEV RNA–positive samples were also frequently found in eastern Japan. IgM anti-HEV is known as a marker of the early seroconversion period. ALT elevation is observed in the early/middle stage of the infection; that is, ALT elevation follows viremia and accompanies/precedes seroconversion.[24] Most (12/15) of the HEV RNA–positive donor samples were positive for the presence of IgM anti-HEV. Of the 15 IgM anti-HEV–positive samples, 14 showed elevated ALT levels higher than 200 IU per L.

Although there were no HEV RNA–positive samples and only one IgM anti-HEV–positive sample detected in donors with elevated ALT levels of 61 to 199 IU per L, 2.7 percent of them were positive for the presence of IgG anti-HEV, which was comparable to the positive rate (3.2%) of IgG anti-HEV–positive donors with elevated ALT levels higher than 200 IU per L. In contrast to IgM anti-HEV–positive donors, IgG anti-HEV–positive donors were not associated with positive HEV RNA. There are several reports from Japan that IgG anti-HEV–positive samples are not rare (1.9%-14.1%) in blood donors with normal ALT levels who are mostly HEV RNA–negative.[13,25,26] In the present report we observed that the number of IgG anti-HEV–positive samples increased with advancing age in both groups, that is, one with an ALT level higher than 200 IU per L and the other with ALT levels of 61 to 199 IU per L. The IgG anti-HEV appears to be present for a prolonged period after infection. Ijaz and his colleagues[27] reported HEV-infected patients with non–travel-associated disease were more likely to be older and tended to be male in England. They estimated that male sex is a risk factor for acquiring the non–travel-associated disease. Most (14/15) of our HEV RNA–positive donors were also male. Because high-ALT-level donors were male-dominant, it will be necessary to investigate whether HEV RNA–positive donors were also male-dominant in ALT-normal donors. We also observed in this report that the number of IgG anti-HEV–positive donors increased with advancing age. This suggests that high prevalence of IgG anti-HEV in older Japanese persons is the consequence of their increased exposure to HEV with time. Among donors with ALT levels of higher than 200 IU per L, positive rates of IgG anti-HEV and HEV RNA were dissociated in Fukuoka (IgG anti-HEV vs. HEV RNA, 3.9% vs. 0.6%) and Tokyo (5.7% vs. 1.2%), in contrast to those (6.9% vs. 4.6%) in Hokkaido. These observations suggest that HEV infection was once prevalent in Fukuoka and Tokyo, while it is now prevalent in Hokkaido. It will be essential to investigate HEV prevalence among blood donors with normal ALT levels in each area of Japan to clarify these points.

As to the donors with ALT levels higher than 500 IU per L, our preliminary study indicated that, besides HEV, other viruses (hepatitis A virus [HAV], Epstein-Barr virus [EBV], cytomegalovirus [CMV], and human parvovirus B19 [B19] were detectable in some of the 41 donors (data not shown). Among hepatitis-associated viruses, screening tests including nucleic acid testing (NAT) for HCV and HBV have been implemented in Japan. Although ALT testing may not be very effective in the early stage of infection or as a surrogate test for HBV or HCV infection, it may be an effective method for eliminating the other hepatitis viruses in transfusion blood, especially HEV, HAV, EBV, CMV, and B19, which could be eliminated from blood for transfusion by ALT testing. Although the distinct populations collected during different periods, HEV RNA was detected in 8 of 41 (19.5%), 1 of 124 (0.8%), and 0 of 364 (0.0%) among donors with high ALT levels of 500 or greater, 200 to 499, and 61 to 199 IU per L in Hokkaido, respectively. Therefore, it is assumed that HEV RNA–positive rate may be lower among the ALT-normal donors (ALT < 61 IU/L) and that elimination of blood with high ALT levels may be effective in reducing the risk of infection caused by HEV. HEV NAT screening has been implemented as a trial in Hokkaido, the highest HEV-prevalent area in Japan.

Further, elimination of blood donors with ALT levels of 500 IU per L or greater would be an effective tool to reduce the infection risks of not only HEV but also HAV, EBV, CMV, and B19. Although ALT testing appears effective in decreasing the risk for infection of HEV, there are some problems. First, ALT testing resulted in the loss of much of the donor blood, which might have been appropriate for transfusion. Approximately 2 percent of donated blood is disqualified owing to an elevated ALT level of greater than 60 IU per L in Japan. Ninety-eight percent of these donors had an ALT level of less than 200 IU per L. Furthermore, studies in the United States and Europe have confirmed that values of ALT in normal males are considerably higher than those in normal females so that a single cutoff value for ALT rejects a higher proportion of men than women.[28,29] Second, hepatitis viruses including HEV RNA were detected in ALT-normal donors. It has been reported that HEV RNA–positive samples were detected in volunteer donors with ALT levels of 61 IU per L.[13] In the near future, it is necessary to compare the virus-positive rates both in normal and in high-ALT donors and to reevaluate a cutoff value of ALT after considering the balance of the benefits and costs.

Besides ALT testing, IgM anti-HEV screening may be effective to eliminate asymptomatic HEV RNA–positive donors in the middle stage of infection. Most of the HEV-positive samples with high ALT levels were also positive for the presence of IgM anti-HEV, although neither ALT test nor IgM anti-HEV will be effective to eliminate HEV-positive donors in the window period. Since the zoonotic food-borne route appears to be a major cause of HEV infection in Japan,[1-8] it is most important to halt the potential spread of HEV by disseminating information on the risk of eating viscera or vaccination of animals as reservoirs.

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別紙様式第2-1

No. 2

医薬品 研究報告 調査報告書

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研究報告の概要

○米国の供血者におけるヘルペスウイルス8(HHV 8)ゲノム

背景:カポジ肉腫の原因となるヘルペスウイルス8(HHV 8)について、これまで供血者のウイルスゲノム陽性率は系統的に調査されたことがなかった。

方法:ランダムに選択された米国供血者から分離したCD19+Bのリンパ球DNA抽出物からHHV8ゲノムを検出するため、高感度定量RT-PCR法を用いた。血液採取から24時間以内にCD19+Bリンパ球を選択し、HHV8のPCR反応のDNAインプットを決定するため、GAPDH遺伝子の細胞標的を用いて、DNAの細胞相当量を定量した。

結果:950名の供血者から検体を入手し、684名から1 × 10^6 B細胞相当以上の精製DNAが得られた。RT-PCRにてGAPDH細胞標的を増幅させ、それぞれの供血者の細胞DNA量を測定した。HHV8 RT-PCR反応には、3 × 10^5 B細胞(全血1 mL中のB細胞の総量に当たる)に相当する細胞DNAを加えた。検出限界8コピーのRT-PCRで、3〜6 × 10^5 CD 19+ Bリンパ球相当のDNAからHHV8ゲノムは検出されなかった(95% CI : 0〜3/684)。

結論:PCR反応の検出限界が8コピーであるRT-PCRにおいてHHV8ゲノムが検出されなかったことから、健康な供血者中のHHV8ゲノム陽性率は極めて低い。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
米国の供血者のヘルペスウイルス8(HHV 8)ゲノム陽性率について、高感度定量RT-PCR法によりDNAの細胞相当量を定量した結果、684名の供血者からはHHV8ゲノムは検出されなかったとの報告である。 HHV-8は脂質膜を持つ大型DNAウイルスである。これまで、本剤によるHHV-8感染の報告はない。本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、今後も情報収集に努める。

⑧

MedDRA/J Ver.11.0J

Groups for Comparison	Crude Prev (% Positive)	Adjusted Odds Ratio* (95% CI)
Southeast vs. Northeast US	49.0 vs. 28.2	2.25 (2.2, 2.3)
Age group ≥70 years vs. <20-29 years	60.6 vs. 27.9	5.20 (5.0, 5.4)
Female vs. male	35.9 vs. 28.9	1.52 (1.5, 1.5)
US vs. Non-US born	31.0 vs. 62.7	0.40 (0.4, 0.4)
Asian vs. white	65.3 vs. 30.0	3.20 (3.0, 3.4)
Black vs. white	60.0 vs. 30.0	2.99 (2.9, 3.1)
Hispanic vs. white	50.3 vs. 30.0	2.27 (2.2, 2.4)
Transfused vs. non-transfused	40.3 vs. 31.7	1.13 (1.1, 1.2)
Body mass index (BMI, kg/M²) <18.5 vs. ≥35	27.5 vs. 34.7	0.8 (0.8, 0.9)

* Adjusted for region, gender, age, race/ethnicity, country of birth, body mass index (BMI), transfusion, collection procedure, and first-time vs. repeat status.

Disclosure of Conflict of Interest

Ram Kakaiya, Darrell Triulzi, John D. Roback, Junyong Fang, Yongling Tu, Steven Kleinman, Michael P. Busch, Jorge A. Rios, Christopher Hillyer, Simone Glynn, George Schreiber, for the Retrovirus Epidemiology Donor Study-II: Nothing to Disclose
Jerome L. Gottschall: Not Specified

SP197

Control Charts for Monitoring Viral Incidence Rates: An Illustration

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Background: Monitoring of new and repeat donor incidence rates is a means to ensure control of transfusion related infectious disease transmission risks. In the Netherlands systematic evaluation of annual incidence rates is performed since the 1980s. Analysis of infection data allows identification of trends in incidence rates and of years with excessively deviating incidence rates. Analysis results can potentially pinpoint to areas for improvement of blood supply safety. **Methods:** HIV infection data from the years 1995 through 2006 were analyzed using a Shewhart Control Chart which is commonly applied in industrial statistics. The likelihood of the observed number of incidents in a particular year is calculated on basis of the mean incidence rate over the whole observation period and the population size in that particular year. The observed number of incidents is presumed to follow a Poisson distribution. **Results:** The results show that in the year 2002 there was an unusual increase in the HIV incidence rate. The likelihood of the observed 8 infections (or more) in that year on basis of the average HIV incidence rate (0.0000057) is less than 0.7% (1 in 138). **Conclusion:** Given the low exceedance probability it is unlikely that the observed 8 infections in 2002 were a chance finding. This conclusion holds even if the result is corrected for multiple testing (as there are 12 years of observation). Therefore other causes for the incidence rate increase in this particular year should be considered. Control Charts can be easily applied to monitor and control viral incidence rates. The graphical presentation of the Control Chart (not give here) provides an intuitive and easily interpretable result.

Disclosure of Conflict of Interest

Mart P. Janssen, Cees L. van der Poel: Nothing to Disclose

SP198

Cost-Utility of a Publicly Funded Hepatitis B Vaccination Program for Blood Donors in British Columbia, Canada

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Background: The current strategy for preventing transfusion-transmitted hepatitis B virus (TT-HBV) infection in Canada and the United States relies on donor behavioral risk and laboratory screening. The objective of this study, undertaken in British Columbia (BC) Canada in 2007, was to assess the cost-utility and benefits to transfusion safety, of offering a publicly funded HB vaccination program for previously unvaccinated blood donors. **Methods:** A "health care payer" perspective, using deterministic estimates, was taken. Fixed costs (e.g. space) and savings from prevented infections were not included. Direct and indirect program costs associated with vaccinating eligible donors through the existing regional, mixed, public health/physician vaccine delivery model in BC, were included in the analysis, along with relevant blood donor and recipient data, obtained from Canadian Blood Services (CBS) and the BC Ministry of Health. Ninety percent of donors under 25 years were estimated to have had prior HB vaccination. Sensitivity analyses were conducted around estimates for prevalence of prior HB vaccination among donors >25 years (10-30%) and HB vaccine uptake (80-100%). **Results:** As of May 2007 there were 52,758 active donors in BC and CBS attracts approximately 8000 new donors per year in the province. Assuming 100% vaccine uptake among eligible donors, total program cost over the first program year ranged between $CDN 2.55 M and $CDN 3.04 M. Program cost would drop to $CDN 0.38 M in the following year. Up to 2.46 TT-HBV infections might be averted in the first 2 program years, with a corresponding range of cost-utility based on scenarios of 30% and 10% prevalence of prior HB vaccination among donors >25 years, of $CDN 6.92-$8.09 M per Quality Adjusted Life Year (QALY) gained. An estimated one TT-HBV related death would be averted over 40-80 years. **Conclusions:** Although costing about $2.90 M in the first year (assuming 100% uptake), program cost would drop by 87% to about $0.38 M in the following year and likely continue to decrease in ensuing years, as the proportion of new donors previously HB vaccinated increases, as a result of existing public health HB immunization programs. The estimated cost-utility of the program in its first 2 years, approximately $7.77 M per QALY, would also improve over the longer term. Although not within the usual cost-utility range of many healthcare interventions, it is comparable to that of other safety measures implemented by many blood suppliers over the past decade, such as donor nucleic acid testing for HIV and hepatitis C virus. Conceptually, this program could expand the current means of enhancing blood safety, which focus on donor risk behavior screening and testing, to include donor primary disease prevention, that better integrates blood safety into a comprehensive public health disease-prevention strategy.

Disclosure of Conflict of Interest

Mark Bigham, Jane Buxton, Shannon Waters: Nothing to Disclose

SP199

Detection of Hepatitis C Virus in Brazilian Blood Donors – Age Group Study

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Background: Hepatitis C virus (HCV) is a public health problem worldwide; it is estimated that about 170 millions people are infected and 2.4 millions only in Brazil. Blood transfusion is one way of HCV transmission that fortunately has relative decreased after introduction of ELISA and genomic tests. The 3rd generation ELISA test (ELISA1) targeted to antibodies against HCV capsid and 4th generation ELISA test (ELISA2) directed to antibodies against the capsid and the core proteins allied to HCV genomic test provide most powerfull instruments of safe HCV detection. **Methods:** One year screening of 98,581 blood bank samples of healthy donors at COLSAN/UNIFESP using immunological and molecular HCV tests. It was studied 584 (0.59%) positive ELISA1 donors samples (ELISA Hepanostika HCV ultra – BioMerrieux); all these samples were submitted to ELISA2 (ELISA Ortho HCV – Ortho) and to genomic HCV amplification by Reverse Transcriptase Nested-Polimerase-Chain-Reaction (RT-NPCR). The blood donors were distributed in five age groups, to study the rate for HCV detection tests. **Results:** It was detected 333 samples (0.34%) positive to both ELISA tests and the presence of HCV genome in 208 samples (0.21%). The age groups rates were: 18-29 years – 0.41%/ELISA1 and 0.13%/RT-NPCR; 30-39 years – 0.62%/ELISA1 and 0.19%/RT-NPCR; 40-49 years – 0.75%/ELISA1 and 0.32%/RT-NPCR; 50-59 years – 0.96%/ELISA1 and 0.42%/RT-NPCR; 60-65 years – 1%/ELISA1 and 0.27%/RT-NPCR. **Conclusions:** Immunological and molecular tests comparison demonstrated that 65% HCV positive ELISA1 test do not correspond to positive viral genome detection in brazilian blood donors at COLSAN/UNIFESP. Despite been characterized as healthy donors 0.2% of the blood donators in our Institution have positive genomic HCV test, remarkably groups 40-49 and 50-59 years.

Disclosure of Conflict of Interest

Fabricio Carvalho, Jose Augusto Barreto, Madalena Pares, Italiana Rodart, Cleidenice Silva, Mittermeyer Reis: Nothing to Disclose

SP200

Herpesvirus 8 (HHV 8) Genomes in US Blood Donors

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Background: HHV-8 is a gamma-herpesvirus that causes Kaposi's sarcoma. The prevalence of viral genomes in blood donors has not been systemically studied. **Methods:** We employed a sensitive and quantitative real-time PCR

assay to detect HHV 8 genomes from DNA extracted from purified CD19+ B lymphocytes from randomly selected US whole blood donors. Blood specimens were stored at 4C overnight prior to processing. CD19+ B lymphocytes were selected within 24 hours of specimen collection. Cellular target for the GAPDH gene was used to quantify cell-equivalent DNA in order to determine the DNA input into the HHV 8 PCR reaction. Real-time HHV 8 PCR was run in duplicate for each donor specimen along with an HHV 8 genomic copy standard. Five-fold dilution series of a calibrated HHV8 DNA provided 200, 40, 8 and 1.6 copies for a standard curve. Two sets of standard DNA were run with each plate, the 8 copy HHV 8 genome standard was always detected; the 1.6 copy control was detected at greater than 50% of the time. **Results:** Specimens were obtained from 950 blood donors and purified DNA from greater than 1×10^6 B cell-equivalents was obtained from 684 donors. DNA of lesser amount was obtained from168 donors. The remaining 98 specimens did not produce sufficient DNA for HHV 8 PCR. The quantity of cellular DNA from each donor was measured with a real-time PCR target amplifying cellular GAPDH target. Cellular DNA equivalent to 3×10^6 B cells (which approximates total B cells from 1 ml whole blood) was used as input material for each real-time HHV8 PCR reaction. No HHV 8 DNA was detected from any of the blood donor specimens. For the 684 donors from whom sufficient DNA were obtained, HHV 8 genomes were not detected in the DNA equivalent of 3 to 6×10^5 CD19+ B lymphocytes with real time PCR which has a detection limit of 8 copies per PCR reaction (95% CI: 0-3/684). Negative results from the 168 donors were potentially confounded by insufficient input DNA into the PCR reactions. **Conclusions:** HHV8 genomes were not detected from 684 blood donors using DNA equivalent of 3 to 6×10^5 CD19+ B lymphocytes with a real-time PCR, which has a detection limit of 8 copies per PCR reaction. Therefore, the prevalence of detectable HHV8 genomes in healthy blood donors is very low.

Disclosure of Conflict of Interest

Lirong Qu, Darrell Triulzi: Nothing to Disclose

SP201

Identification of a Parvovirus B19 Genotype 3 Isolate in the United States

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Background: Parvovirus B19 (B19V) is a human pathogen frequently detected in plasma donations through the detection of nucleic acids. Three B19V genotypes have been defined based on isolates having greater than 10% divergence in overall DNA sequence. B19V genotype 3 is a rarely occurring genotype that has been detected primarily in Ghana with sporadic reports in Brazil and France. B19V genotype 3 has not been previously reported in North America. **Methods:** A multi-probe fluorogenic PCR assay has been developed to ensure broad specificity for the detection of B19V. A detection probe specific for genotype 1 contains the DNA sequence of the B19V Au prototype strain and a second probe contains a DNA consensus sequence derived from the A6 (genotype 2) prototype strain and the V9 and D91.1 (genotype 3) isolates. The assay was used to evaluate over 400,000 clinical samples. Determinations of the B19V virus titer and antibody concentration were performed on samples of interest. **Results:** This evaluation identified a series of 8 plasma donations spanning 28 days from a single donor in the United States. DNA sequence analysis of nucleic acids isolated from the index donation indicates significant homology with B19V genotype 3. The B19V titer of this series of donations showed virus titers that peaked at greater than 10^{11} International Units (IU)/mL. The virus titer decreased significantly over the next several donations coinciding with an increase in IgM levels. The IgG levels also increased but lagged approximately 7 days after the IgM levels. **Conclusions:** Recent reports surrounding the incidence of the B19V genotype 3 infection among blood and Source Plasma donors indicate that the prevalence of this genotype is quite low. Our data corroborate these reports since testing over 400,000 clinical samples yielded only one donor that tested positive for genotype 3. Analysis of the viral load through the course of infection for this donor suggests an infection cycle similar to that associated with B19V genotype 1 infection. The significance of detecting this rare B19V genotype 3 and its importance to public health is unclear.

Disclosure of Conflict of Interest

Michael Gray, Lori Rinckel, Todd Gierman, Douglas Lee: Nothing to Disclose

SP202

Methoxypoly (Ethylene Glycol) Modification of Viruses or Host Cells: A Broad Spectrum Antiviral Prophylactic

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Background: Nosocomial viral infections (both transfusion and non-transfusion associated) pose a risk to patients. Previously, we have demonstrated that covalent grafting of methoxypoly (ethylene glycol) (mPEG; pegylation) to the surface of RBC and WBC prevented cell-cell interaction, allorecognition, and cell activation. Thus, as a novel means of viral inactivation, we evaluated the efficacy of mPEG-modification of respiratory syncytial virus (RSV) or its host cells as a model system. **Methods:** Four mPEG linker chemistries (cyanuric chloride mPEG (CmPEG), benzotriazole carbonate mPEG (BTCmPEG), succinimidyl propionate mPEG (SPAmPEG) and succinimidyl carbonate mPEG (SCmPEG)) were tested. These mPEGs were assessed via syncytia formation and immunostaining using two polymer sizes (2 and 5 kDa) and at concentrations ranging from 0-15 mM mPEG. For direct viral modification, ~120 syncytia forming units of RSV were modified with mPEG, overlaid on Vero cells, and examinnd over 5 days. For host cell modification, Vero cells were similarly modified with mPEG, challenged with unmodified-RSV and followed for 5 days. **Results:** For all linker chemistries examined direct modification of RSV significantly reduced the number of syncytia. For example, modification with 15 mM, 5 kDa SCmPEG significantly reduced the number of syncytia from 12612 to 145 ($p < 0.001$) per well (1.9 cm). Furthermore, at the same concentration, modification with 2 kDa SCmPEG showed complete inhibition of viral infection. For host cell modification, 5 kDa CmPEG and 2 kDa SCmPEG grafting also inhibited infection, resulting in a 33 and 45% reduction in the number of syncytia, respectively ($p < 0.001$). Immunostaining over 96 hours further demonstrated the efficacy of pegylating either the virus or host cells. Pegylation of RSV with 15 mM SCmPEG (2 kDa) resulted in a >95% reduction in RSV infection at 24 hours ($p < 0.001$). **Conclusions:** Our findings demonstrate that mPEG modification of RSV or its host cell can effectively limit or prevent viral invasion. Application of this technology to blood products could prove to be a valuable method for inactivating known and unknown blood-borne viruses. Furthermore, additional studies demonstrate that pegylation of viruses, or their host cells provide, a broad spectrum anti-viral prophylaxis effective against both enveloped and non-enveloped viruses.

Disclosure of Conflict of Interest

Troy Sutton, Mark Scott: Nothing to Disclose

SP203

Prevalence of Transfusion Transmitted Infections in Brazilian Blood Donors as Determined by a Dual EIA Strategy

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Background: Representative data on prevalence of infection markers among Brazilian blood donors are scarce due to the lack of common informational systems infrastructure and because confirmatory assays are not routinely performed on reactive samples at the time of screening. Here we describe infectious marker prevalence results obtained in Brazil during the first year of the study. **Methods:** Donation data including supplemental testing results were collected and compiled from 3 Brazilian blood centers located in states of São Paulo, Minas Gerais and Pernambuco for 2007. Donation samples that tested EIA repeat reactive were tested with alternative EIA assays to confirm infection. Prevalence of transfusion transmissible infections (TTI) were calculated using the number of donors reactive on the confirmatory EIA at their index donation divided by the total number of donors screened for that disease in 2007. **Results:** There were 307,085 blood donations collected from 245,445 donors at these three blood centers. Thirty-five percent were first time (FT) donors (n = 85,954). HIV prevalence was 2x higher in FT compared to repeat donors. Whereas for the other markers prevalence was 10x or more higher in FT donors. Stratified prevalence in FT donors is reported in the lower portion of the table. Strong differences were noted by demographic characteristics for all agents. For example HIV prevalence in FT donors in Pernambuco is over 2x that of Sao Paulo. Patterns of the epidemic for each agent were dramatically different

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研究報告の概要

○欧州のHIV/AIDS調査:2007年最新データ
ヒト免疫不全ウイルス(HIV)感染症はヨーロッパの公衆衛生にとって重要な問題であり、複数の国でHIV感染増加のエビデンスが示されている。本稿は、HIVおよび後天性免疫不全症候群(AIDS)の調査データの概要を提供し、ヨーロッパにおいて症例報告された人口100万人当たりの新規HIV感染率が、2000年以降にほぼ2倍となったことを示す。
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。欧州連合(EU)および欧州自由貿易連合(EFTA)諸国において、HIV感染の主要感染経路は男性間の性行為であり、次いで異性間接触である。WHO欧州地域東部では、現在も静注薬物使用が主な感染経路であるが、中部では異性接触が主要な感染経路である。2007年のAIDS診断症例の報告件数は、東部を除く全域で減少した。
HIV/AIDS調査データは、HIV流行の傾向をモニターし、公衆衛生の対応を評価するために不可欠である。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
ヨーロッパにおいて症例報告された人口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との報告である。 これまで、本剤によるHIV感染の報告はない。また本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。さらに最終製品についてHIV-NAT陰性であることを確認している事から本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、今後も情報の収集に努める。なお、日本赤十字社ではHIV抗体検査に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)を導入したことに加え、20プールNATについてもHIV-2及びHIVグループOの検出が可能な新NATシステムを導入し、陽性血液を排除している。また、輸血感染症対策として、男性と性的接触を持った男性は1年間献血不適としている。

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Rapid communications

HIV/AIDS SURVEILLANCE IN EUROPE: UPDATE 2007

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Human immunodeficiency virus (HIV) infection remains of major public health importance in Europe, with evidence of increasing transmission of HIV in several countries. This article provides an overview of HIV and acquired immunodeficiency syndrome (AIDS) surveillance data, and indicates that since 2000 the rate of newly reported cases of HIV per million population has almost doubled in Europe. In 2007, a total of 48,892 cases of HIV infection were reported from 49 of 53 countries in the Region, with the highest rates in Estonia, Ukraine, Portugal and the Republic of Moldova. In the European Union (EU) and European Free Trade Association (EFTA) countries, the predominant mode of transmission for HIV infection is sex between men followed by heterosexual contact. Injecting drug use is still the main mode of transmission in the eastern part of the WHO European region, while in the central part heterosexual contact is the predominant mode of transmission. In 2007, the reported number of AIDS cases diagnosed decreased in the Region overall, except in the eastern part. HIV/AIDS surveillance data are vital to monitor the trends of the HIV epidemic and evaluate public health responses.

Introduction

Since January 2008, the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization Regional Office for Europe have been jointly carrying out the HIV/AIDS surveillance in Europe [1]. This article presents the main findings for the whole WHO European Region, the three geographical regions of the WHO European Region (West, Centre and East)* and the European Union (EU) and European Free Trade Association (EFTA)** countries.

TABLE 1
Characteristics of newly diagnosed cases of HIV infection reported in the WHO European Region and by geographical area, 2007

	WHO European Region*	West*	Centre*	East*
Number of HIV cases	48892	24202	1897	22793
Rate per million population	76.4	77.0	10.1	164.8
Percentage of cases:				
Age 15-29 years	33%	26%	41%	40%
Female	33%	31%	24%	36%
Transmission mode**				
Heterosexual***	35%	29%	53%	42%
Men who have sex with men	20%	40%	30%	0.4%
Injecting drug users	32%	8%	13%	57%

* Missing data: Austria, Italy, Monaco, Russian Federation.
** Transmission group unknown is excluded from the percentages.
*** Excludes persons originating from countries with generalised epidemics (4555 in total; 4540 in West).

HIV case reports in WHO European Region

In 2007, 48,892 newly diagnosed HIV cases (76 per million population) were reported from 49 of the 53 countries in the WHO European Region (no data from Austria, Italy, Monaco and the Russian Federation). In the three parts of the WHO European Region, the rate of newly reported cases of HIV per million population was highest in the East (Table 1), whereas among individual countries, the highest rates were reported in: Estonia (472 per million), Ukraine (285 per million), Portugal (217 per million) and the Republic of Moldova (204 per million). Between

TABLE 2
Characteristics of newly diagnosed cases of HIV infection reported in the EU/EFTA countries*, 2007

	EU/EFTA countries*
Number of HIV cases	25279
Rate per million population	64.1
Percentage of cases:	
Age 15-29 years	28%
Female	31%
Transmission mode**	
Men who have sex with men	29%
Heterosexual***	35%
Injecting drug users	9%

* Missing data: Italy, Austria.
** Transmission group unknown is excluded in the percentages.
*** Excludes persons originating from countries with generalised epidemics (4422 in total).

2000 and 2007, the annual rate of newly reported cases of HIV per million population has increased from 39 to 75 per million (90% increase) among the 44 countries that have consistently reported.

HIV case reports in the EU/EFTA

In 28 of the 30 EU/EFTA countries, 26,279 cases of HIV infection (64 per million) were reported in 2007 (Table 2), with the highest rates reported in Estonia (472 per million), Portugal (217 per million) and Latvia (149 per million). The predominant mode of transmission is sexual contact between men (39%), followed by heterosexual contact (29%), when persons originating from countries with generalised epidemics are excluded. Injecting drug use accounted for 9% of newly reported infections. Among the countries that have consistently reported, the rate has increased from 44 per million in 2000 to 58 per million in 2007. Rates of reported HIV infection have doubled in Bulgaria, Czech Republic, Hungary, the Netherlands, Slovakia, Slovenia, Sweden and the United Kingdom.

The number of HIV reports among men who have sex with men (MSM) has increased by 39% between 2003 and 2007 (Figure 1). The number of heterosexually acquired cases has remained fairly stable at around 6,000 cases (although higher numbers were reported in 2004-2006). Further, the number of cases originating from countries with generalised epidemics amongst heterosexually acquired cases varied between 5,000 in 2005 and 4,400 in 2007. The number of HIV reports among injecting drug users (IDUs) has declined by 30% between 2003 and 2007.

HIV case reports by geographical area

The HIV epidemics across the three geographical areas show remarkable differences (Figure 2).

The data suggest that the HIV epidemic in the western part of the WHO European Region is characterised by a continuing increase in sexual transmission of HIV infection. The distribution of transmission modes largely mirrors that described for the EU/EFTA countries. In 2007, 24,202 new cases of HIV infec¬tion (77/million) were reported from 20 countries (Table 1).

The HIV epidemic in the central part of the WHO European Region remains at low and stable levels (1,897 cases; 10 per million), although there is evidence of increasing sexual (both heterosexual and homosexual) transmission in many countries (Table 1). Heterosexual transmission accounted for 53% of all reported cases, followed by 30% cases reported among MSM and 13% cases among IDUs, data on transmission mode were missing for 33% of cases.

In the eastern part of the WHO European Region, in 2007, 14 countries reported 22,793 new HIV cases (165 per million), of which 58% were from Ukraine. The predominant mode of trans¬mission in this region is through IDUs, accounting for 57% of the reported cases. Between 2000 and 2007, the rate of newly reported HIV infections has in¬creased from 54 per million to 160 per million. However, the numbers in this region are greatly underestimated as no data were reported from the Russian Federation.

AIDS diagnoses

In 2007, 5,244 AIDS cases were reported as being diagnosed in 48 of the 53 countries (9 per million) in the WHO European Region (no data from Italy, Kazakhstan, Monaco, Russian Federation and Ukraine). Due to incomplete reporting and no adjustment for reporting delays the total number of AIDS cases is underestimated.

Trends in AIDS diagnoses per million population (Figure 3) have continued to decrease in the WHO European Region overall, from 16 per million in 2000 to 9 per million in 2007, mainly due to decrease in western and central regions probably due to a combination of reporting delay and the effect of highly active antiretroviral therapy (HAART) [2]. However, during the same period, the rate increased in 21 (mainly eastern) countries, with the largest increases in Belarus and the Republic of Moldova.

Discussion and conclusion

HIV infection remains of major public health importance in Europe with a continued increase in the number of HIV cases reported [1,3]. In contrast, the number of AIDS cases diagnosed (not adjusted for reporting delays) has continued to decline, except in the eastern part of the WHO European Region. The data suggest evidence of increased transmission of HIV in many countries. However, the predominant transmission group varies by country and geographical area and the data illustrate the wide diversity in the epidemiology of HIV in Europe.

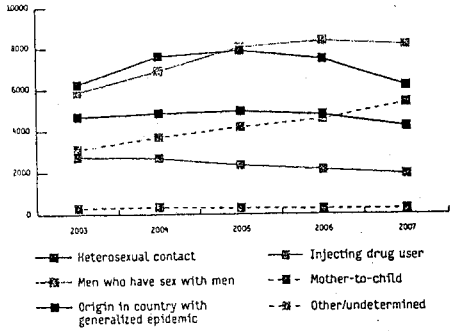
In 2007, in the EU/EFTA countries, also reflecting the western part of the WHO European Region, the highest proportion of HIV cases was reported among MSM. National prevention programmes aimed at reducing HIV transmission within Europe should have a strong focus on MSM [4]. Migrant populations should also be targeted in national prevention programmes and access to treatment and care services should be ensured. Although there seems to be a decline in the number of new diagnoses among IDUs, this is still the predominant transmission group in the Baltic States. In the central part of the WHO European Region, levels of HIV remain low and stable, al¬though there is evidence of increasing sexual transmission in many countries. In the eastern part, the number of HIV cases has increased substantially, mainly driven by an increase in cases acquired through IDU but also by an increase in heterosexually-acquired cases. Interventions to control HIV among IDUs should be the cornerstone of HIV prevention strategies in the eastern part but measures should also be strengthened to prevent heterosexual transmission, especially targeted at those with high-risk partners.

In interpreting the presented data, it should be taken into account that data are incomplete due to non-reporting from a few large countries. Therefore the findings and conclusions are limited to the surveillance data reported by these 49 countries. Had all data from all countries been available, the total number of reported HIV infections could have doubled to almost 100,000 cases in 2007.

Surveillance of HIV/AIDS is essential to monitor the epidemic and evaluate the public health response to control the transmission of infections. Countries in Europe need to ensure that surveillance data is of high quality by implementing case-based reporting systems for HIV and AIDS cases and ensuring its completeness, especially regarding the probable mode of transmission. Achieving full coverage of reporting from all countries in Europe is of utmost importance.

FIGURE 1

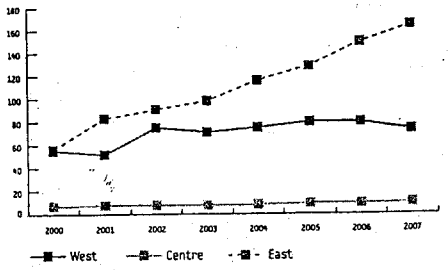
Number of reported HIV infections by transmission mode, origin and year of notification, EU/EFTA, 2003–2007



Data were not available for: Austria, Estonia (except for IDU), Italy, and Malta.

FIGURE 2

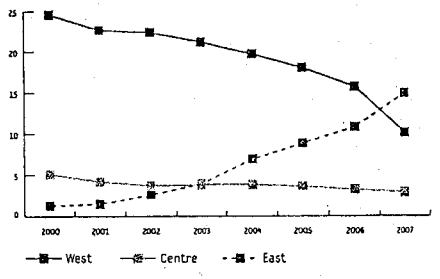
HIV cases per million population in geographic areas of the WHO European Region (West, Centre, East) by year of notification, 2000-2007



Data not included from: West: Andorra, Austria, France, Italy, Malta, Monaco, Spain; Centre: Serbia; East: Russian Federation.

FIGURE 3

Number of diagnosed AIDS cases per million population in the geographic areas of WHO European Region (West, Centre, East) by year of diagnosis, 2000-2007



Data not included from: West: Andorra, Italy, Monaco; East: Kazakhstan, Russian Federation, Ukraine

*The WHO European Region comprises:

The West, 23 countries: Andorra, Austria (EU), Belgium (EU), Denmark (EU), Finland (EU), France (EU), Germany (EU), Greece (EU), Iceland (EFTA), Ireland (EU), Israel, Italy (EU), Luxembourg (EU), Malta (EU), Monaco, the Netherlands (EU), Norway (EFTA), Portugal (EU), San Marino, Spain (EU), Sweden (EU), Switzerland (EFTA), United Kingdom (EU).

The Centre, 15 countries: Albania, Bosnia and Herzegovina, Bulgaria (EU), Croatia, Cyprus (EU), Czech Republic (EU), Hungary (EU), the Former Yugoslav Republic of Macedonia, Montenegro, Poland (EU), Romania (EU), Serbia, Slovakia (EU), Slovenia (EU), Turkey.

The East, 15 countries: Armenia, Azerbaijan, Belarus, Estonia (EU), Georgia, Kazakhstan, Kyrgyzstan, Latvia (EU), Lithuania (EU), Republic of Moldova, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan.

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医薬品 研究報告 調査報告書

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研究報告の概要

○米国における供血者の *Trypanosoma Cruzi* 抗体スクリーニング：米国赤十字の1年間の経験

背景：*Trypanosoma Cruzi* (*T. cruzi*)により発症するシャーガス病は、ラテンアメリカ諸国の大半で流行しており、米国では2007年から供血者に対するスクリーニングを開始した。

方法：*T. cruzi* ELISA(Ortho社)を用いたスクリーニングで繰り返し陽性(RR)となった検体および最初の検査で10% negative gray zoneとなった検体について、RIPA(Quest社)を用いて再検査した。また、陽性供血者に対してリスク質問票に回答するよう依頼した。

結果：2007年1月29日～2008年1月28日までのARC供血者のRR率は0.009%(586/6,549,933; 1:11,117)であった。586例中129例(22%)が確定陽性で、うち2例は10% negative gray zoneであった。最も陽性率が高い地域はフロリダ南部で、RIPA(+)供血者が68名特定された(1:3,600)。RIPA(+)の供血者(75名)はRIPA(−)の供血者(169名)と比較して、既知のリスク因子を有する可能性が12～225倍高かった。米国内で生まれたRIPA(+)供血者18名はリスク因子が特定されなかったが、残りのRIPA(+)供血者は12の流行国とリンクされた。RIPA(+)供血者56名由来の輸血済268製剤から155名の受血者が追跡され、65名の受血者(血小板受血者7名を含む)から採取された68件の追跡検体の検査結果からは、輸血感染の可能性は示されなかった。

結論：供血者の有病率は1/30,000で、感染供血者のほとんどに明確なリスク因子があった。感染供血者では寄生虫血症が示される場合があったが、検査を実施した65名の受血者のうち、明白な感染症例はなかった。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見

米国赤十字で2007年から開始された供血者に対する *T. cruzi* スクリーニングの結果、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との報告である。

今後の対応

日本赤十字社は、輸血感染症対策として献血時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、シャーガス病の既往がある場合には献血不適としている。日本在住の中南米出身献血者については、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して検討する予定である。今後も引き続き情報の収集に努める。

reported only a single episode of MSM activity; by contrast, 42% reported exposure that lasted 2 years or more. Of 1,652 whose date of last exposure was recorded, 64.6% had MSM contact within the last 1-year period, and 84% within the prior 5 years. Those donors reporting a single MSM exposure were 2-1/2 times more likely to have reported their last exposure more than 5 years ago compared to donors reporting multiple incidents (32% vs. 13%). One in seven blood donors with a single MSM exposure reported that the exposure was within the last 3 months. **Conclusions:** The epidemiology of HIV in the United States shows a strong association between MSM activity and risk for HIV infection, justifying the exclusion from blood donation of men with ongoing MSM exposures. Harmonizing the deferral period for MSM exposure to that of other TTVI risks (1-year) or to that of other tissue donations (5 years) is likely to lead to only modest increases in the proportion of MSM-deferred donors who regain eligibility; the deferral period for MSM exposure to that of other TTVI risks (1-year) or to that of other tissue donations (5 years) is likely to lead to only modest increases in the proportion of MSM-deferred donors who regain eligibility; barring significant changes in the presenting donor population. From our population, only a small minority appear to present a risk profile epidemiologically distinct from those MSM deferrals with ongoing or recent exposures.

Disclosure of Conflict of Interest

Bryan Spencer, Jorge A. Rios, Richard Cable: Nothing to Disclose

P4-020A

Selection, Expansion and Functional Restoration of NS3-Specific CD4 T Cells from HCV-Infected Patients

Marta Bes[1](jestebe@vhebron.net), Silvia Sauleda[1], Lluis Puig[1], Josep Quer[2], Maria Cubero[2], Juan Esteban[1]. [1]Banc de Sang i Teixits, Barcelona, Spain; [2]Banc de Sang i Teixits de Catalunya, Barcelona, Spain; Barcelona, Spain.

Introduction: Tolerance of T cells to non-structural antigens of HCV virus may explain persistent infection. We hypothesize that this state can be reversed ex vivo in absence of the anergy-inducing antigens and in presence of homeostatic cytokines. **Aims:** To isolate HCV-specific CD4 T cells from chronic patients according to antigen-induced surface expression of CD154 and determine the degree of functional restoration after ex vivo expansion in absence of antigenic stimulus. **Patients and methods:** Lymphocytes from peripheral blood were obtained from 5 patients with persistent infection and 5 patients with spontaneous resolved infection. After stimulation with NS3-helicase recombinant protein, the CD4+/CD154+ lymphocytes were selected and expanded in complete medium supplemented with IL-7/IL-15 during 3 weeks. Cellular phenotype was determined by flow cytometry (CD4/CD45RO/CCR7/CD28/CL). HCV-specific cellular immune response was measured by IFN-gamma spot forming units (SFU-ELISPOT assay) and soluble cytokine production of IFN-gamma, IL-4 and IL-10 (CBA). Proliferation was determinate by CFSE. **Results:** In the group of chronic patients the mean yield of sorted CD4+/CD154+ was 0.076% while in the recovered patients was 0.81% of sorted CD4+ cells. After 21 days of culture, sorted patients had expanded 3 logarithms and, after ex vivo expansion, 96-98% of cells had effected memory phenotype. In patients with persistent infection, mean IFN-gamma production for expanded NS3-helicase specific cells was 785 SFU/10E5 CD4+, that is, 42 times higher than basal production (19 SFU/10E5 CD4+) by only three-fold increase in patients with resolved infection (752 vs. 252 IFN-gamma SFU/10E5 CD4+). CBA assay confirmed production of IFN-gamma (943.6 pg/ml for NS3-specific T cells vs. 7.65 pg/ml for basal CD4+) in individuals with persistent infection, and mean production of IL-10 and IL-4 for specific T cells was 327.7 pg/ml and 92.8 pg/ml, respectively and higher than basal CD4+ production (4.3 and 6.75 pg/ml). Proliferation capacity was not different between CD4+ specific and basal CD4 T cells. The expanded cells did not respond or proliferate when cultured with HCV core protein and therefore specificity of selection and expansion to NS3-helicase protein was confirmed. **Conclusions:** We were able to select NS3-specific T CD4 cells in patients with persistent infection and to expand them ex vivo with homeostatic interleukins. In absence of the anergy-inducing antigens, the capacity to produce IFN-gamma is restored thus confirming the presence of anergic T cells in chronic patients. This finding also raises the possibility of designing strategies for adoptive immunotherapy in non responders to standard antiviral therapy or difficult to treat subjects, such as liver transplant patients.

Disclosure of Conflict of Interest

Marta Bes, Silvia Sauleda: Nothing to Disclose
Lluis Puig, Josep Quer, Juan Esteban, Maria Cubero: Not Specified

P5-020A

Trypanosoma Cruzi Antibody Screening In US Blood Donors: One Year Experience at the American Red Cross

S L Stramer[1] (Dodd@usa.redcross.org), G Foster[2], R Townsend[3], D Krysztof[4], E Notari[4], J Trouern-Trend[4], J Brodsky[4], B Lenes[4], M Nguyen[4], M Proctor[4], A Bet[4], D Leiby[4], C Rouault[4], R Dodd[4]. [1]American Red Cross Biomedical Services, Gaithersburg, MD; [2]American Red Cross – Scientific Support Office, MD; [3]American Red Cross, Rockville, MD; [4]American Red Cross Blood Services, Holland Lab, Rockville, MD; [4]Quality Analytics, Inc, Glenview, IL; [4]Community Blood Centers of South Florida, Lauderhill, FL.

Background: *T. cruzi*, the blood-borne parasite that causes Chagas disease, is endemic in most of Latin America. The majority of infected individuals acquire infection outside the US; some autochthonous cases have been reported. Blood donor screening for most of the US was initiated during 2007 (75-80% of the US blood supply); we report the ARC experience. **Methods:** All donations collected on or after 1/29/07 were screened using the Ortho *T. cruzi* ELISA. All repeat reactive (RR) and initially reactive samples repeating with one or both retests in a 10% negative gray zone were tested by RIPA (Quest); in addition, all reactive donors were invited to participate in follow up (f/u) testing and the completion of a donor risk questionnaire. F/u samples from RIPA (+) donors at index were retested simultaneously by ELISA, RIPA (in-house), PCR (in-house) and Immunoblot (IHC). In-house) whereas f/u samples from RIPA (−) donors were tested by ELISA and the other tests only if ELISA RR. Recipients of prior components from RIPA (+) donors were traced and consenting recipients tested. **Results:** Prevalence by donor/donation for ARC donors is shown in the table for 1/29/07-1/28/08. The RR rate (586/6,549,933) was 0.009% or 1:11,177; 129/586 (22%) confirmed (+) of which 2 were in the 10% gray zone. An additional 68 RIPA (+) donor from South Florida were identified by the ARC; this was the highest prevalence area of the US (1:3600). An ELISA S/CO of 3.8 or greater had a 95% likelihood of being RIPA (+). RIPA (+) donors (75) as compared to RIPA (−) donors (169), who provided risk info, were 12-225 times more likely to have a known risk factor; nevertheless, 18 (24%) RIPA (+) donors born in the US had no identified risk factors. ELISA/RIPA false (+) must be considered as a possibility for some of these potential autochthonous cases. The remaining RIPA (+) donors were linked to 12 endemic countries. 268 transfused components from 56 RIPA (+) donors were traced to 155 recipients; 68 f/u samples were collected from 65 recipients including only 7 who received platelets. Of the 68 samples tested, 7 had isolated reactive test results: none ELISA RR but either RIPA or PCR (+) plus 1 ELISA/RIPA (+) recipient born in an endemic country. No recipient could be demonstrated to have been infected by transfusion. In contrast, PCR and IHC found that 3-15% of RIPA (+) donors may have circulating parasites. **Conclusions:** Donor prevalence is 1:30,000; most infected donors have established risk factors however 24% did not. Although parasitemia could be demonstrated in infected donors, there were no unequivocal cases of infection among the 65 recipients tested.

Donation Type	No. Screened	No. RIPA Pos	Prevalence
Total donors	3,872,957	129	1:30,023
Allogeneic	3,542,989	125	1:28,344
Autologous	41,618	3	1:13,873
Pheresis	288,250	1	1:288,350
Total donations	6,549,933	129	1:50,775
Allogeneic	5,789,336	125	1:46,356
Autologous	59,520	3	1:19,840
Pheresis	691,077	1	1:691,077

Disclosure of Conflict of Interest

Susan L. Stramer, Gregory Foster, Rebecca Townsend, David Krysztof, Edward Notari, Jonathan Trouern-Trend, Jaye Brodsky, Bruce Lenes, Megan Nguyen, Melanie Proctor, Anne Bet, Charles Rouault, Roger Dodd: Nothing to Disclose
David Leiby: Ortho Clinical Diagnostics – Consulting or Board of Director Fees

別紙様式第２－１

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日 2009年2月2日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称	別紙のとおり		研究報告の公表状況	ProMED-mail, 20090129.0400	公表国 スウェーデン	
販売名(企業名)	別紙のとおり					

研究報告の概要

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（バレコウイルス属、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。

使用上の注意記載状況・その他参考事項等

記載なし

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

MedDRA/J ver.11.1

別紙

一般的名称	①人血清アルブミン、②人血清アルブミン、③人血清アルブミン*、④人免役グロブリン、⑤乾燥ペプシン処理人免疫グロブリン、⑥乾燥スルホ化人免疫グロブリン、⑦乾燥スルホ化人免疫グロブリン*、⑧乾燥濃縮人活性化プロテインC、⑨乾燥濃縮人血液凝固第Ⅷ因子、⑩乾燥濃縮人血液凝固第Ⅸ因子、⑪乾燥抗破傷風人免疫グロブリン、⑫抗 HBs 人免疫グロブリン、⑬トロンビン、⑭フィブリノゲン加第ⅩⅢ因子、⑮乾燥濃縮人アンチトロンビンⅢ、⑯ヒスタミン加人免疫グロブリン製剤、⑰人血清アルブミン*、⑱人血清アルブミン*、⑲乾燥ペプシン処理人免役グロブリン*、⑳乾燥人血液凝固第Ⅸ因子複合体*、㉑乾燥濃縮人アンチトロンビンⅢ
販売名(企業名)	①献血アルブミン20“化血研”、②献血アルブミン25“化血研”、③人血清アルブミン“化血研”*、④“化血研”ガンマーグロブリン、⑤献血静注グロブリン“化血研”、⑥献血ベニロンーⅠ、⑦ベニロン*、⑧注射用アナクトC2,500単位、⑨コンファクトF、⑩ノバクトM、⑪テタノセーラ、⑫ヘパトセーラ、⑬トロンビン“化血研”、⑭ボルヒール、⑮アンスロビンP、⑯ヒスタグロビン、⑰アルブミン20%化血研*、⑱アルブミン5%化血研*、⑲静注グロブリン*、⑳ノバクトF*、㉑アンスロビンP1500注射用
報告企業の意見	ユンガンウイルスが属するバレコウイルス属は、9つあるピコルナウイルス科の属の1つで、他にヒトバ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。ヒトバ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

ProMED-mail

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

LJUNGAN VIRUS, INTRAUTERINE FETAL DEATH - SWEDEN
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A ProMED-mail post
<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.

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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

別紙様式第2-1

No. 15

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 2. 18	該当なし	
一般的名称	乾燥濃縮人血液凝固第Ⅷ因子		研究報告の公表状況	ProMED 20090218.0669, 2009 Feb 18. 情報源:AllAfrica, This Day report, 2009 Feb 16.	公表国 ナイジェリア	
販売名(企業名)	クロスエイトM250(日本赤十字社) クロスエイトM500(日本赤十字社) クロスエイトM1000(日本赤十字社)					

研究報告の概要

○ナイジェリア:ラッサ熱ー専門家が拡大に対する懸念を表明
Irrua の専門病院院長は、最近のラッサ熱の広範囲の感染拡大を懸念しており、2008年1月から12月にかけて、229人の感染疑い患者が報告され、30人が死亡していることを明らかにした。
2009年2月14～15日のNational Lassa Fever Stakeholders Forum〈全国ラッサ熱関係者フォーラム〉において、2008年12月～2009年1月に感染の疑いのある患者および感染確定患者が、それぞれ60%、80%急増したことが報告された。
しかし、Irruaの専門病院は、ドイツ・ハンブルグのBehard-Notch熱帯疾患協会、米国ハーバード大学の協力を得て、ラッサ熱に対する対策が実施されていることも明らかにした。

使用上の注意記載状況・その他参考事項等

クロスエイトM250
クロスエイトM500
クロスエイトM1000

血液を原料とすることに由来する感染症伝播等
vCJD等の伝播のリスク

報告企業の意見	今後の対応
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月に感染の疑いのある患者および感染確定患者は、それぞれ60%、80%急増したとの報告である。 ラッサウイルスはアレナウイルス群に属する、脂質膜を持つ比較的大型のRNAウイルスである。これまで、本剤によるラッサウイルス感染の報告はない。本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、念のため今後も情報収集に努める。なお、日本赤十字社では帰国(入国)後4週間は献血不適とし、輸入感染症の防止に努めている。

(12)

MedDRA/J Ver.11.0J

Nigeria: Lassa Fever - Specialist Expresses Concern Over Spread

Adibe Emenyonu

16 February 2

lin — The Chief Medical Director of Irrua Specialist Hospital, Prof George Akpede, has expressed concern over wide spread of Lassa fever in recent times, disclosing that out of 229 suspected cases reported between January a December 2008, 30 people died.

Prof Akpede, who spoke at National Lassa Fever Stakeholders Forum at Ekpoma, weekend noted that there had b a marked rise in the number of suspected and confirmed cases between December 2008 and January 2009 representing about 60 percent and 80 percent increases respectively.

, however, disclosed that some drastic measures were under way as the Irrua Specialist Teaching Hospital had entered into partnerships with Behard-Notch Institutue of Tropical Medicine, Hamburg, Germany and Harvard University, USA for collaboartion in lassa fever research and control efforts.

Part of the collaboration according to him had resulted in the donation of diagnostic facilities for the confirmation the disease in the hospital without samples being nedded to be sent out of the country any longer.

In his contribution, member representing Esan Central/Esan West/Igueben Federal Constituency in the House of Representatives, Mr. Patrick Ikhariale, also expressed concern over the spread of the lassa fever epidemic nation-w and called for urgent control measures at the national level.

Ikhariale assured that he would draw the attention of the National Assembly to the menace posed by the disease to millions of Nigerians.

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Subject PRO/AH/EDR> Lassa fever - Nigeria

LASSA FEVER - NIGERIA
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Date: Mon 16 Feb 2009
Source: AllAfrica, This Day report [edited]
<http://allafrica.com/stories/200902160188.html>

Nigeria: Lassa fever -- specialist expresses concern over spread
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The chief medical director of Irrua Specialist Hospital, Prof George Akpede, has expressed concern over the wide spread of Lassa fever in recent times, disclosing that out of 229 suspected cases reported between January and December 2008, 30 people died.

Prof Akpede, who spoke at National Lassa Fever Stakeholders Forum at Ekpoma [at the] weekend [14-15 Feb 2009] noted that there had been a marked rise in the number of suspected and confirmed cases between December 2008 and January 2009 representing about 60 percent and 80 percent increases respectively. He, however, disclosed that some drastic measures were under way as the Irrua Specialist Teaching Hospital had entered into partnerships with Behard-Notch Institute of Tropical Medicine, Hamburg, Germany, and Harvard University, USA for collaboration in Lassa fever research and control efforts. Part of the collaboration, according to him, had resulted in the donation of diagnostic facilities for the confirmation of the disease in the hospital without samples having to be sent out of the country any longer.

In his contribution, [the] member representing Esan Central/Esan West/Igueben Federal Constituency in the House of Representatives, Mr. Patrick Ikhariale, also expressed concern over the spread of the Lassa fever epidemic nation-wide and called for urgent control measures at the national level. Ikhariale assured that he would draw the attention of the National Assembly to the menace posed by the disease to millions of Nigerians.

[Byline: Adibe Emenyonu]

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Communicated by:
ProMED-mail Rapporteur A-Lan Banks

[Lassa fever is a zoonotic disease, whereby humans become infected from contact with infected animals. The animal reservoirs of Lassa virus are rodents of the genus _Mastomys_, the "multimammate rat." Lassa virus-infected animals do not become ill, but they can shed the virus in their urine and faeces. (A photograph of a multimammate rat can be accessed at
<http://i127.photobucket.com/albums/p145/hawthornrats/other%20pets/multis/I

In humans Lassa viral haemorrhagic fever is an acute illness of 1-4 weeks duration that occurs in West Africa. The virus is a single-stranded RNA virus belonging to the virus family _Arenaviridae_. Lassa fever is known to be endemic in Guinea (Conakry), Liberia, Sierra Leone, and parts of Nigeria, but probably exists in other West African countries as well.

About 80 percent of human infections are asymptomatic; the remaining cases have severe multi-system disease, where the virus affects several organs in the body, such as the liver, spleen, and kidneys. The incubation period of Lassa fever ranges from 6-21 days. It has been estimated that about 300 000 to 500 000 cases of Lassa fever and 5000 deaths occur yearly across West Africa. The overall case-fatality rate is 1 percent, and up to 15 percent among hospitalized patients.

The disease is especially severe late in pregnancy, with maternal death and/or fetal loss occurring in greater than 80 percent of cases during the 3rd trimester.

Humans usually become infected with Lassa virus from exposure to excreta of infected _Mastomys_. Lassa virus may also be spread between humans through direct contact with the blood, urine, faeces, or other bodily secretions of a person with Lassa fever. There is no epidemiological evidence supporting airborne spread between humans. Person-to-person transmission occurs in both community and health care settings, where the virus may be spread by contaminated medical equipment, such as re-used needles.

The current increase in cases of Lassa fever in some parts of Nigeria may by a consequence of increased abundance of the vector or some other factor resulting in increased contact between humans and rodents promoting the spread of the disease in the human population. - Mo

The HealthMap/ProMED-mail interactive map of Nigeria is available at <http://healthmap.org/promed/en?v=9.6,6.1,6>. - CopyEd.MJ]

[see also:
Lassa fever - UK ex Nigeria (03): fatal 20090130.0414
Lassa fever - UK ex Nigeria (02) 20090124.0308
Lassa fever - UK ex Nigeria 20090123.0296
2008

Lassa fever - Nigeria (02) 20080611.1847
Lassa fever - Nigeria: (Ebonyi) 20080323.1100
2007

Lassa fever - Nigeria 20071205.3925
Lassa Fever - South Africa ex Nigeria 20070222.0657
2005

Lassa fever - Nigeria (Edo) 20050303.0654
2004

Lassa fever - Nigeria (Edo) 20040214.0487
Lassa fever - Nigeria: RFI 20040213.0482
2001

Lassa fever, suspected - Nigeria (Edo) (02) 20010319.0552
Lassa fever, suspected - Nigeria (Edo): RFI 20010315.0524
2000

Lassa fever - Germany ex Nigeria (03) 20000424.0609
Lassa fever - Germany ex Nigeria (02) 20000405.0497
Lassa fever - Germany ex Nigeria 20000404.0495]
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(13)

別紙様式第２－１

医薬品　研究報告　調査報告書

番号：3

識別番号・報告回数			報告日	第一報入手日 平成 21 年 4 月 6 日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	ﾃｸﾈﾁｳﾑ人血清ｱﾙﾌﾞﾐﾝ (99mTc)		研究報告の公表状況	Promed 20090402.1272	公表国 ブラジル	
販売名（企業名）	テクネアルブミンキット （富士フイルムＲＩファーマ株式会社）					使用上の注意記載状況・その他参考事項等
研究報告の概要	要約：サンパウロでの黄熱の母子感染に関する初めての報告： サンパウロ奥地において、2009 年 2 月末より黄熱が流行しているが、その中で母子感染が確認された。黄熱における母子感染の報告は前例のないことである。息子への感染は血清学的検査で確認されている。 報告者は、「今後は我々は黄熱症例の妊婦により注意をはらう必要がある」と説明している。 住民の 90%以上への大量のワクチン接種により、黄熱のリスクは減少しており、現在の一番の懸念事項は、奥地で流行している黄熱が都市部へ移動し拡大することである。					特になし
報告企業の意見			今後の対応			
編集者によれば、黄熱が属するフラビウイルス属では、胎盤経由の感染伝播の可能性が元々言われていること、また、今回の流行で最も懸念されているのは、現在の奥地での発生が、都市部へ拡大することであって、この母子の垂直感染により、現地規制当局でも特に措置等を講じるということではないということである。また、子への感染は血清学的検査で確認されていることであるので、詳細は不明であるものの、重大な感染症の新規感染経路に関する報告と判断する。			ヒト血液を原料とする血漿分画製剤とは直接関連のない報告であり、現時点では特に措置等は必要ないと判断する。			

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Archive Number 20090402.1272
Published Date 02-APR-2009
Subject PRO/AH/EDR> Yellow fever - South America (20): Brazil (SP)

YELLOW FEVER - SOUTH AMERICA (20): BRAZIL (SAO PAULO)
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Date: Tue 31 Mar 2009
Source: Terra [in Portuguese, trans & summ. Mod. TY, edited]
<http://noticias.terra.com.br/brasil/interna/0,,OI3672572-EI306,00.html>

Public health physicians of Universidade Estadual Paulista (UNESP) who are fighting the epidemic of yellow fever [YF] in the interior of Sao Paulo [state] were surprised on Tuesday [31 Mar 2009] to see the transmission of disease from a mother to her child. The discovery is unprecedented. "This type of transmission scared us because it has never been reported before in the medical literature," said Tania Ruiz, Coordinator of the Center for Epidemiological Surveillance of the Hospital of Unesp in Botucatu (Sao Paulo).

According to the Coordinator, the serological tests proved that a baby, son of a [YF] infected mother, was born with the disease. The serological tests are results of studies by researchers from UNESP and other institutions of the country According to Tania, the immediate importance of discovery is in the procedures adopted in epidemics the disease. "From now on, we need to take more care with pregnant [YF cases]," she explained.

The epidemic of yellow fever in Sao Paulo began on 27 February [2009]. This Tuesday [31 Mar 2009], 2 more cases were reported. The total documented confirmed deaths from the disease reached 8 in the cities of Piraju, Sarutaia and Itatinga in the southern part of the state. So far, 15 total reported [YF cases] were confirmed.

Mass vaccination is still being done in health posts and even supermarkets. According to Tania, over 90 percent of residents of these municipalities are immunized, which reduces the risks [of YF infection]. However, most health concern is to prevent the disease, currently considered to be a sylvan [jungle transmission cycle], that might move into an urban area.

So far, all cases are related to victims who were in rural areas. According to public health officials, the expansion of the disease into urban areas would be "a disaster."

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[This is not surprising, nor is it a reason for alarm. The yellow fever virus is a flavivirus; other flaviviruses, such as dengue virus, can have transplacental transmission.

The poor infant, now an orphan, is not a public health threat for urbanization of yellow fever, should it happen, it would certainly not be by means of a case (rare) of vertical transmission. - Mod.LJS]

[A map of Brazil showing the location of Sao Paulo state can be accessed at
<http://www.lib.utexas.edu/maps/americas/brazil.jpg>.
A HealthMap/ProMED-mail interactive map of Brazil can be accessed at
<http://healthmap.org/promed/en?q=3451133&v=-10.8,-53.1,4>.
- Mod.TY]

[see also:
Yellow fever - South America (19): Brazil (SP) 20090326.1180
Yellow fever - South America (18): Brazil (SP) 20090323.1140
Yellow fever - South America (17): Brazil (RS), monkey 20090223.0748
Yellow fever - South America (16): 20090219.0700
Yellow fever - South America (15): Brazil (RS) 20090211.0618
Yellow fever - South America (14): Brazil (MG ex RS) 20090201.0456
Yellow fever - South America (12): Brazil (RS) 20090128.0389
Yellow fever - South America (08): Brazil (RS) monkey, susp. 20090122.0279
Yellow fever - South America (07): Brazil (RS), susp. 20090120.0251
Yellow fever - South America (06): Brazil (RS), susp 20090118.0211
Yellow fever - South America (02): Brazil (RS), susp., corr. 20090109.0091
Yellow fever - South America (02): Brazil (RS), susp. 20090108.0079
2008

Yellow fever - South America (26): Brazil (SP), Peru 20080608.1823
Yellow fever - South America (19): Paraguay 20080326.1136
Yellow fever - South America (18): Brazil (PR) 20080319.1061]
.....jw/ty/ejp/mpp

番号：1

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1月19日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	ﾃｸﾈﾁｳﾑ人血清ｱﾙﾌﾞﾐﾝ（^{99m}Tc）	研究報告の公表状況	CDC/MMWR 58(01)4-7/2009.1.16	公表国 米国	
販売名（企業名）	テクネアルブミンキット（富士フイルムＲＩファーマ株式会社）				
研究報告の概要	要約：ラクロス(La Crosse)脳炎ウイルスの先天性感染の可能性―ウエストヴァージニア,2006-2007： 米国ウエストヴァージニアで、妊婦における初めてのラクロス脳炎ウイルス（LACV）感染症例に関する報告があり、その後分娩時の臍帯血清からLACV特異的IgM抗体が検出されたことから、子の先天性LACV感染の可能性が示唆された。子は出生時及び出生後６ヶ月間はとくに異常は認められておらず、LACVの兆候も示していない。さらに母親が子の血清等の検体の採取を拒絶していることから、血清中のLACV特異的IgM抗体の有無等は確認できていないため、子の先天性LACV感染は可能性であり、確定されたものではない。ウエストヴァージニアは、蚊媒介性のLACVが多発する地域であるため、それらの地域の妊婦は蚊を避けるようアドバイスすべきと提言している。				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			
子のLACV先天性感染については、確定したものではなく可能性の報告ではあるが、重大な感染症の新規感染経路（可能性）に関する報告であるため、感染症定期報告の対象と判断する。		ヒト血液を原料とする血漿分画製剤とは直接関連のない報告であり、現時点では特に措置等は必要ないと判断する。			

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(14)

The findings in this report are subject to at least three limitations. First, identification of hospitalizations for pneumonia and nonpneumonia ARI was based on ICD-9-CM codes and might be subject to misclassification, despite internal quality control and validation for consistency within the Nationwide Inpatient Sample. Second, establishing the etiology of pneumonia is difficult. Nationwide Inpatient Sample data are deidentified before public release and chart reviews cannot be performed to confirm recorded diagnoses. Because most pneumococcal pneumonias are classified as pneumonias without further characterization, this report provides an estimate of the effect of PCV7 on all-cause pneumonia without regard to pneumococcal serotypes. Furthermore, serotyping is not part of routine diagnostic work-ups, and this information would not be recorded in medical charts. However, the decrease in nonpneumonia ARI hospitalizations among children aged <2 years suggests that the decreases in pneumonia hospitalizations were unlikely to result from a shift in coding of pneumonia to nonpneumonia ARI codes. Finally, factors other than shifts in coding could affect hospitalization rates. Reduced clinician concerns for severe pneumococcal disease among immunized children, for example, might lead to outpatient treatment rather than hospitalization. However, other data indicate that ambulatory-care visits for pneumonia among children aged <2 years also have decreased since introduction of PCV7 (5). In addition, the proportion of all hospitalizations that were attributable to pneumonia or nonpneumonia ARI decreased significantly, suggesting that the declines were unlikely to result from a secular reduction in overall hospitalization rate.

Despite the substantial morbidity associated with childhood pneumonia, no pneumonia-specific prospective population-based surveillance system exists for monitoring trends in the incidence of pneumonia hospitalizations or pneumonia-related ambulatory-care visits in the United States. Monitoring childhood pneumonia is important for the evaluation of effects of current and future pneumococcal immunization programs. Increases in pneumococcal disease caused by serotypes not included in PCV7 could result in some increase in pneumonia, even though observed increases in non-PCV7 serotype IPD have been modest thus far (9). In addition, extended-valency pneumococcal conjugate vaccines are expected to be licensed by late 2009 to early 2010 and might further reduce pneumonia rates. Finally, vaccination of children against influenza, as recommended by the Advisory Committee on Immunization Practices, is increasing and also might reduce pneumonia hospitalization rates (10).

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Possible Congenital Infection with La Crosse Encephalitis Virus — West Virginia, 2006–2007

La Crosse encephalitis virus (LACV) is a mosquitoborne bunyavirus of the California encephalitis serogroup (1). During 2003–2007, West Virginia had the greatest number of cases (95) and highest incidence of LACV disease (5.1 cases per 100,000 population) of any state.* The majority of persons infected with LACV either have no symptoms or a mild febrile illness; a limited number experience encephalitis (2). Although only 1%–4% of those infected with LACV develop any symptoms, children aged <16 years are at highest risk for severe neurologic disease and possible long-term sequelae (2,3). The effects of LACV infection during pregnancy and the potential for intrauterine transmission and adverse birth or developmental outcomes are unknown. This report describes the first known case of LACV infection in a pregnant woman, with evidence of possible congenital infection with LACV in her infant, based on the presence of immunoglobulin M (IgM)

*Confirmed and probable California serogroup viral (mainly La Crosse) encephalitis cases, human, United States, 1964–2007, by state. Available at http://www.cdc.gov/ncidod/dvbid/arbor/pdf/cal_lac.pdf.

antibodies in umbilical cord serum at delivery. The infant was born healthy with normal neurologic and cognitive functions and no LACV symptoms. Further investigation is needed to confirm the potential for intrauterine LACV transmission and to identify immediate and long-term health risks posed to infants. Because of the potential for congenital infection, pregnant women in areas where LACV is endemic should be advised to avoid mosquitoes; health-care providers should monitor for LACV infection and sequelae among infants born to women infected with LACV during pregnancy.

In August 2006, a previously healthy woman aged 43 years in week 21 of her pregnancy was admitted to a West Virginia hospital after experiencing severe headaches, photophobia, stiff neck, fever, weakness, confusion, and a red papular rash. The patient had reported a 3-month history of severe headaches, which were diagnosed initially as migraines and treated with morphine for pain. Two previous pregnancies had proceeded without complication, and each resulted in delivery of a healthy infant. The patient's medical history included anxiety, depression, and hypothyroidism, for which she received ongoing thyroid hormone replacement therapy.

After hospital admission, analysis of cerebrospinal fluid revealed an elevated white blood cell count (556 cells/mm^3 [94% lymphocytes, 5% monocytes, and 1% polymorphonuclear neutrophilic leukocytes]), elevated protein (66 mg/dL), and normal glucose (55 mg/dL). A diagnostic panel for viral encephalitis was performed, and the patient's serum was determined positive for the presence of LACV-specific IgM and immunoglobulin G (IgG) antibodies by immunofluorescence assay and for IgM by capture enzyme-linked immunosorbent assay (ELISA) (Table). The patient's serum was negative for IgM and IgG antibodies to the other three diseases in the diagnostic panel: eastern equine encephalitis, western equine encephalitis, and St. Louis encephalitis. A diagnosis of La Crosse encephalitis was made, and supportive therapy was initiated. During hospitalization, the patient experienced a low-grade fever and exhibited panleukocytosis (absolute neutrophil count: 12,800/μL), which persisted after discharge despite resolution of clinical signs.

After reporting the case to the West Virginia Department of Health and Human Resources, active follow-up of the patient and her fetus was initiated in collaboration with the patient's primary-care providers and CDC. With her consent, the patient's medical and prenatal histories were reviewed. Because guidelines for evaluating pregnant women infected with LACV do not exist, interim guidelines for West Nile virus were used to direct maternal and infant follow-up (*4*). Specifically, collection of blood and tissue products at time of delivery was arranged with the patient's obstetrician. Umbilical cord serum and maternal serum were tested for LACV-specific antibodies by ELISA and serum-dilution plaque-reduction neutralization test (PRNT). Sera also were tested for neutralizing antibodies to the closely related Jamestown Canyon virus by PRNT to rule out potential cross-reactivity. Umbilical cord and placental tissue were tested for LACV RNA by reverse transcription–polymerase chain reaction (RT-PCR). Data were collected regarding the infant's health at delivery and through routine well-child visits during the first 6 months of life.

The patient had a normal, spontaneous, vaginal delivery of a healthy girl at approximately 40 weeks gestation. The child had normal birth weight (2,970 g), length (52 cm), and head circumference (33 cm). Apgar scores at 1 minute and 5 minutes postpartum were within normal limits (8 and 9, respectively). LACV-specific IgM antibodies were detected in umbilical cord serum, although no evidence of LACV RNA was detected in umbilical cord tissue or placental tissue by RT-PCR (Table).

The mother declined collection of additional specimens of infant serum for confirmation of congenital LACV infection. Maternal serum collected at 11 weeks postpartum was positive for LACV IgG antibodies but negative for IgM. Except for intermittent nasal congestion associated with upper respiratory infections, the infant remained healthy and exhibited appropriate growth and development through the first 6 months of life. No neurologic abnormalities or decreased cognitive functions were observed.

Reported by: *A Hinckley, PhD, Div of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases; A Hall, DVM, EIS Officer, CDC.*

Editorial Note: This report summarizes the first case of symptomatic LACV infection identified during pregnancy. Congenital LACV infection of the fetus was suggested through identification of IgM antibodies in umbilical cord serum, although the newborn was asymptomatic and development was normal. Although unlikely to cross the placental barrier, LACV IgM antibodies detected in cord serum might have been attributable to transplacental leakage induced by uterine contractions that disrupt placental barriers during labor, which has been documented for anti-*Toxoplasma* IgM antibodies (*5*). Because specificity of standard laboratory techniques used to detect LACV IgM antibodies in cord serum or newborn serum is unknown, a follow-up evaluation of infant serum is necessary to confirm congenital infection. However, in this case, the mother declined collection of any additional specimens from her infant.

Certain infectious diseases have more severe clinical presentations in pregnant women (*6*). Symptomatic LACV infection is rare among adults; therefore, effects of pregnancy on the risk for or severity of illness are unknown. Because LACV-specific IgM can be present for as long as 9 months after infection (*1*), LACV might not have been responsible for the symptoms reported during this woman's pregnancy. However, the woman resided in an area where LACV is known to be endemic; during 2006, 16 (24%) of 67 LACV cases in the United States reported to CDC occurred in West Virginia, including three other cases from the same county as this patient.† Although antimicrobial treatment of pregnant women often is controversial because of limited information regarding efficacy and risk to the developing infant (*7*), certain in vitro evidence indicates that the antiviral agent ribavirin might be useful for treating LACV infection in nonpregnant patients (*2*). However, supportive treatment continues as the standard of care for managing all LACV patients (*2*).

Congenital infection with other arboviral diseases has been reviewed and documented previously (*8*). Although no human congenital infection with a bunyavirus of the California serogroup has been reported, congenital infection with other bunyaviruses of the Bunyamwera serogroup has been associated with macrocephaly. In addition, animal studies have determined that infection with LACV during pregnancy can cause teratogenic effects in domestic rabbits, Mongolian gerbils, and sheep (*9,10*).

Pregnant women in areas where LACV is endemic should take precautions to reduce risk for infection by avoiding mosquitoes, wearing protective clothing, and applying a mosquito repellent to skin and clothing. Additionally, health-care providers serving areas where LACV is endemic should consider LACV in the differential diagnosis of viral encephalitis. As a nationally notifiable disease, all probable and confirmed cases of LACV should be reported to the appropriate state and local public health authorities. When LACV infection is suspected in a pregnant woman or infant, appropriate serologic and virologic testing by a public health reference laboratory is recommended. Testing breast milk for the presence of LACV also might be reasonable to evaluate the potential for maternal-infant transmission and to determine the suitability for continued breastfeeding. Additional investigations are needed to confirm the potential for congenital infection with LACV and to identify immediate and long-term health risks LACV poses to infants.

TABLE. Summary of laboratory test results during investigation and follow-up of possible congenital infection with La Crosse encephalitis virus (LACV) — West Virginia, 2006–2007

Collection date	Specimen	Test	Result
August 20, 2006	Maternal serum	LACV IgM* capture ELISA†	Positive
	Maternal serum	LACV IgM IFA§	Positive
	Maternal serum	LACV IgG¶ IFA	Positive
	Maternal serum	LACV neutralizing antibodies PRNT**	Positive
	Maternal serum	JCV†† neutralizing antibodies PRNT	Negative
January 5, 2007	Placental tissue	LACV RNA RT-PCR§§	Negative
	Umbilical cord tissue	LACV RNA RT-PCR	Negative
	Umbilical cord serum	LACV IgM capture ELISA	Positive
	Umbilical cord serum	LACV IgG capture ELISA	Equivocal
	Umbilical cord serum	LACV neutralizing antibodies PRNT	Positive
	Umbilical cord serum	JCV neutralizing antibodies PRNT	Negative
March 23, 2007	Maternal serum	LACV IgM capture ELISA	Negative
	Maternal serum	LACV IgG capture ELISA	Positive

* Immunoglobulin M.
† Enzyme-linked immunosorbent assay.
§ Immunofluorescence assay.
¶ Immunoglobulin G.
** Plaque-reduction neutralization test.
†† Jamestown Canyon virus.
§§ Reverse transcription–polymerase chain reaction.

† La Crosse encephalitis, human: cumulative 2006 data. Available at http://diseasemaps.usgs.gov/2006/lac_us_human.html.

Acknowledgments

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Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis

Guidelines for the use of nucleic acid amplification (NAA) tests for the diagnosis of tuberculosis (TB) were published in 1996 (*1*) and updated in 2000 (*2*). Since then, NAA testing has become a routine procedure in many settings because NAA tests can reliably detect *Mycobacterium tuberculosis* bacteria in specimens 1 or more weeks earlier than culture (*3*). Earlier laboratory confirmation of TB can lead to earlier treatment initiation, improved patient outcomes, increased opportunities to interrupt transmission, and more effective public health interventions (*4,5*). Because of the increasing use of NAA tests and the potential impact on patient care and public health, in June 2008, CDC and the Association of Public Health Laboratories (APHL) convened a panel of clinicians, laboratorians, and TB control officials to assess existing guidelines (*1,2*) and make recommendations for using NAA tests for laboratory confirmation of TB. On the basis of the panel's report and consultations with the Advisory Council for the Elimination of TB (ACET),* CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations. These guidelines update the previously published guidelines (*1,2*).

Background

Conventional tests for laboratory confirmation of TB include acid-fast bacilli (AFB) smear microscopy, which can produce results in 24 hours, and culture, which requires 2–6 weeks to produce results (*5,6*). Although rapid and inexpensive, AFB smear microscopy is limited by its poor sensitivity (45%–80% with culture-confirmed pulmonary TB cases) and its poor positive predictive value (50%–80%) for TB in settings in which nontuberculous mycobacteria are commonly isolated (*3,6,7*).

NAA tests can provide results within 24–48 hours. The Amplified *Mycobacterium tuberculosis* Direct Test (MTD, Gen-Probe, San Diego, California) was approved by the Food and Drug Administration (FDA) in 1995 for use with AFB smear-positive respiratory specimens, and in a supplement application, an enhanced MTD test was approved in 1999 for use with AFB smear-negative respiratory specimens from patients suspected to have TB. In addition, the Amplicor *Mycobacterium tuberculosis* Test (Amplicor, Roche Diagnostics, Basel, Switzerland) was approved by FDA in 1996 for use with AFB smear-positive respiratory specimens from patients suspected to have TB. NAA tests for TB that have not been FDA-approved also have been used clinically (e.g., NAA tests based on analyte specific reagents, often called "home-brew" or "in-house" tests) (*8,9*).

Compared with AFB smear microscopy, the added value of NAA testing lies in its 1) greater positive predictive value (>95%) with AFB smear-positive specimens in settings in which nontuberculous mycobacteria are common and 2) ability to confirm rapidly the presence of *M. tuberculosis* in 50%–80% of AFB smear-negative, culture-positive specimens (*3,7–9*). Compared with culture, NAA tests can detect the presence of *M. tuberculosis* bacteria in a specimen weeks earlier than culture for 80%–90% of patients suspected to have pulmonary TB whose TB is ultimately confirmed by culture (*3,8,9*). These advantages can impact patient care and TB control efforts, such as by avoiding unnecessary contact investigations or respiratory isolation for patients whose AFB smear-positive specimens do not contain *M. tuberculosis*.

Despite being commercially available for more than a decade (*1*), NAA tests for TB have not been widely used in the United States largely because of 1) an uncertainty as to whether NAA test results influence case-management decisions or TB control activities; 2) a lack of information on the overall cost-effectiveness of NAA testing for TB; and 3) a lack of demand from clinicians and public health authorities. However, recent

* Additional information regarding ACET is available at http://www.cdc.gov/maso/facm/facmacet.htm.

別紙様式第 2-1
番号 1

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1月13日	新医薬品等の区分	厚生労働省処理欄
一般的名称	①献血アルブミン-WI ②献血アルブミン(5%)-WI ③ノイアート ④ノイアート静注用 1500 単位 ⑤ハプトグロビン注-ヨシトミ ⑥コンコエイト-HT	研究報告の公表状況	OIE/2008/12/23	公表国 フィリピン	
販売名(企業名)	①②人血清アルブミン ③④乾燥濃縮人アンチトロンビンIII ⑤人ハプトグロビン ⑥乾燥濃縮人血液凝固第Ⅷ因子				使用上の注意記載状況・その他参考事項等
研究報告の概要	ブタにおけるEbola-Reston ウイルスの初めての検出： フィリピンにおいて，ブタからEbola-Reston ウイルスが検出されたことを受けて，フィリピン政府が国連FAO，OIEおよびWHOに専門家の派遣を要請したことが発表された。 2007年および2008年にNueva EcijaおよびBulacanの農場においてブタの死亡が増加したことから調査が開始され，2008年5月，6月および9月に病気のブタのサンプルが研究所に送付され，10月に豚繁殖・呼吸器障害症候群（PRRS）およびEbola-Reston ウイルス感染が確認された。 ブタにおいてEbola-Reston ウイルスが検出されたのは世界的に初めてである。フィリピンのサルにおいては1989–1990年，1992年および1996年にアウトブレイクしたことが確認されている。 フィリピン保健当局は，感染したブタと接触したと思われる人における初期検査はEbola-Reston ウイルス感染陰性であったと報告した。 フィリピンの農務省動物産業局（BAI）は感染した家畜はすべて破棄され，埋められるか焼却され，施設は消毒されたこと，また，感染地域は厳しい検疫と管理体制の下にあることをOIEに報告した。				使用状の注意にヘパリン由来の感染症に関連する記載なし。
	報告企業の意見		今後の対応		
	フィロウイルス科エボラウイルス属には，エボラ・アイボリーコーストウイルス，エボラ・ザイールウイルス，エボラ・スーダンウイルス，エボラ・レストンウイルスの4種がある。エボラレストンウイルスは，長径 800～1,500nm，短径 80～100nm のエンベロープを有する RNA ウイルスであり，人にも感染するが重病や死に至る危険性はないと言われている。ヘパリンからのエボラウイルス感染に関する報告は，入手していない。 万一，ブタ原料にエボラ・レストンウイルスが混入したとしても，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，ヘパリンの製造工程中の過酸化水素処理，加熱処理工程で十分に不活化・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。		

(19)

- The OIE
- The Veterinary Services
- Press releases/Editorials
  - Editorials
  - Press releases
- International meetings
- World animal health situation
- Official country disease status
- Animal diseases data
- OIE Expertise
- Certification of diagnostic assays
- Health standards
- Online Bookshop
- Jobs/Internships/Services
- Links

First detection of Ebola-Reston virus in pigs

FAO/OIE/WHO offer assistance to the Philippines

MANILA 23 December 2008 – Following the detection of the Ebola-Reston virus in pigs in the Philippines, the UN Food and Agriculture Organization (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO) announced today that the government of the Philippines has requested the three agencies send an expert mission to work with human and animal health experts in the Philippines to further investigate the situation.

An increase in pig mortality on swine farms in the provinces of Nueva Ecija and Bulacan in 2007 and 2008 prompted the Government of the Philippines to initiate laboratory investigations. Samples taken from ill pigs in May, June and September 2008 were sent to international reference laboratories which confirmed in late October that the pigs were infected with a highly virulent strain of Porcine reproductive and respiratory syndrome (PRRS) as well as the Ebola-Reston virus.

Although co-infection in pigs is not unusual, this is the first time globally that an Ebola-Reston virus has been isolated in swine. It is not, however, the first time that the Ebola-Reston virus has been found in the Philippines : it was found in monkeys from the Philippines in outbreak s that occurred in 1989-1990, 1992, and 1996.

The E bola virus belongs to the Filoviridae family (filovirus) and is comprised of five distinct species: Zaïre , Sudan , Côte d'Ivoire, Bundibugyo and Reston . Zaïre , Sudan and Bundibugyo species have been associated with large Ebola hemorrhagic fever (EHF) outbreak s in Africa with high case fatality ratio (25–90%) while Côte d'Ivoire and Reston have not. Reston species can infect humans but no serious illness or death in humans have been reported to date.

Since being informed of this event in late November, FAO, OIE and WHO have been making every effort to gain a better understanding of the situation and are working closely with the Philippines Government and local animal and human health experts.

The Department of Health of the Philippines has reported that initial laboratory tests on animal handlers and slaughterhouse workers who were thought to have come into contact with infected pigs were negative for Ebola Reston infection, and that additional testing is ongoing. The Bureau of Animal Industry (BAI) of the Philippines Department of Agriculture has notified the OIE that all infected animals were destroyed and buried or burned, the infected premises and establishments have been disinfected and the affected areas are under strict quarantine and movement control. Vaccination of swine against PRRS is ongoing in the Province of Bucalan. PRRS is not transmissible to humans.

The planned joint FAO/OIE/WHO team will work with country counterparts to address, through field and laboratory investigation, important questions as to the source of the virus, its transmission, its virulence and its natural habitat, in order to provide appropriate guidance for animal and human health protection.

Until these questions can be answered, the FAO and WHO stressed the importance of carrying out basic good hygiene practices and food handling measures.

Ebola viruses are normally transmitted via contact with the blood or other bodily fluids of an infected animal or person. In all situations, even in the absence of identified risks, meat handling and preparation should be done in a clean environment (table top, utensils, knives) and meat handlers should follow good personal hygiene practices (e.g. clean hands, clean protective clothing). In general, hands should be r egularly washed while handling raw meat.

Pork from healthy pigs is safe to eat as long as either the fresh meat is cooked properly (i.e. 70°C in all part of the food, so that there is no pink meat and the juices run clear), or, in the case of uncooked processed pork, national safety standards have been met during production, processing and distribution.

Meat from sick pigs or pigs found dead should not be eaten and should not enter the food chain or be given to other animals. Ill animals should be reported to the competent authorities and proper hygiene precautions and protection should be taken when destroying and disposing of sick or dead pigs. The Philippines Department of Agriculture has advised the Philippine public to buy its meat only from National Meat Inspection Services certified sources.

As a general rule, proper hygiene and precautionary measures (wearing gloves, goggles and protective clothing) should also be exercised when slaughtering or butchering pigs. This applies both to industrial and home-slaughtering of pigs. Children and those not involved in the process of slaughtering should be kept away.

December 2008

[top]

Maria Zampaglione

Updated : 23-Déc-2008

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		回	報告日 年　月　日	第一報入手日 2009 年 2 月 17 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	Ebola-Reston in pigs and humans in the Philippines. www.who.int/csr/don/2009_02_03/en/print.html	公表国 スイス	
販売名（企業名）						

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
2009 年 1 月，フィリピン政府はエボラレストンウイルス株（ERV）罹患ブタからヒトへの最初の伝播が認められた可能性が高いことを公表した。罹患ブタとの直接接触があったと考えられた 5 名は抗 ERV 抗体に対して陽性結果を示しているもののいずれも良好な健康状態にあると考えられ，臨床徴候を呈した者はいなかった。しかしながら，感染した 5 名は健康成人であり，当該ウイルスが高齢者，免疫が低下した者，妊婦，小児或いは基礎疾患のある者などの他の集団に及ぼし得る影響については不明である。フィリピン政府はこれら 5 名に関連する接触者の追跡などの ERV によるヒトおよび動物の健康リスクを制限する方策を実施中である。	BYL-2009-0369 The Lancet Infectious Disease 9; 148, 2009

報告企業の意見	今後の対応
米国ではアジアを起源とする ERV の感染が，動物において報告されており，そのため弊社の組換え製品の培養培地に用いる血漿分画製剤を製造するための血漿ドナーが，感染動物と接触していた可能性があるという理論上のリスクがある。しかしながら，こうした状況に至る可能性は極めて低く，また，エボラウイルスはエンベロープウイルスであるため，製造工程におけるウイルス除去・不活化工程が有効である。	現時点で新たな安全対策上の措置を講じる必要はないと考える。 今後，米国における ERV 感染のアウトブレイクが発生した場合には，動物からヒトへの感染の情報収集に努める。

World Health Organization

Ebola Reston in pigs and humans in the Philippines

3 February 2009 -- On 23 January 2009, the Government of the Philippines announced that a person thought to have come in contact with sick pigs had tested positive for Ebola Reston Virus (ERV) antibodies (IgG). On 30 January 2009 the Government announced that a further four individuals had been found positive for ERV antibodies: two farm workers in Bulacan and one farm worker in Pangasinan - the two farms currently under quarantine in northern Luzon because of ERV infection was found in pigs - and one butcher from a slaughterhouse in Pangasinan. The person announced on 23 January to have tested positive for ERV antibodies is reported to be a backyard pig farmer from Valenzuela City - a neighbourhood within Metro Manila.

The Philippine Department of Health has said that the people who tested positive appear to be in good health and have not suffered from any significant illnesses in the past 12 months. The investigation team reported that it was possible that all 5 individuals had been exposed to the virus as a result of direct contact with sick pigs. The use of personal protective equipment (PPE) is not common practice among these animal handlers.

From these observations and previous studies of ERV, the virus has shown it can be transmitted to humans, without resulting in illness. However, the evidence available relates only to healthy adults and it would be premature to conclude the health effects of the virus on all population groups. The threat to human health is likely to be low for healthy adults but is unknown for all other population groups, such as immuno-compromised persons, persons with underlying medical conditions, pregnant women and children.

The Philippine Government is conducting contact tracing in relation to the five individuals who tested positive for antibodies. In addition, testing is ongoing for other persons who could have come into contact with sick pigs on the two quarantined farms in the provinces of Bulacan and Pangasinan where pigs co-infected with the Porcine Respiratory and Reproductive Syndrome (PRRS) and ERV were reported in 2008. The two farms remain under quarantine and the Philippine Government is maintaining its voluntary hold of exports of live pigs and fresh and frozen pork meat.

The Philippine Government has announced a combined Department of Health and Department of Agriculture strategy to limit the animal and human health risks of the Ebola Reston Virus and emphasized that local governments, the pig farming industry and the public will play a critical role in the strategy.

Along with its international partners, the WHO will continue to support the Philippine Government in its efforts to gain a better understanding of the Ebola Reston virus, its effects on humans, and the measures that need to be taken to reduce any risks to human health.

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. 2. 18	該当なし	
一般的名称	乾燥濃縮人血液凝固第Ⅷ因子		研究報告の公表状況	Hamaguchi T, Noguchi-Shinohara M, Nozaki I, Nakamura Y, Sato T, Kitamoto T, Mizusawa H, Yamada M. Emerg Infect Dis. 2009 Feb;15(2):265-71.	公表国 日本	
販売名(企業名)	クロスエイトM250(日本赤十字社) クロスエイトM500(日本赤十字社) クロスエイトM1000(日本赤十字社)					

研究報告の概要

○医学的処置と孤発性クロイツフェルト・ヤコブ病のリスク(日本、1999～2008年)
孤発性クロイツフェルト・ヤコブ病(sCJD)と医学的処置との関連性を解明するため、日本において1999～2008年の期間にCJDサーベイランス委員会により登録された患者の医学的処置(すべての外科治療、脳神経外科手術、眼科手術および輸血)について分析した。
sCJD患者753名および対照210名の年齢層別化症例対照調査および同一病院で神経外科的処置または眼科処置を受けた患者についての調査を行った。比較的小規模な対照群であったが、sCJD発症前に施行された当該医学的処置によりプリオン病が感染したという証拠は見つからなかった。sCJD発症後にsCJD患者の4.5%が手術を受けた(脳外科手術0.8%、眼科手術1.9%を含む)。プリオン病伝播に対する特別な予防措置はとられなかったが、幸いにも、これらの手術に起因するプリオン病患者は特定されなかった。
我々の所見は、外科的処置または輸血はsCJDの発生にほとんど影響を及ぼさないことを示している。

使用上の注意記載状況・その他参考事項等

クロスエイトM250
クロスエイトM500
クロスエイトM1000

血液を原料とすることに由来する感染症伝播等
vCJD等の伝播のリスク

報告企業の意見

日本において1999～2008年の期間にCJDサーベイランス委員会により登録された患者の医学的処置と孤発性クロイツフェルト・ヤコブ病(sCJD)との関連性について分析した結果、外科的処置または輸血はsCJDの発生にほとんど影響を及ぼさないことを示しているとの報告である。

今後の対応

本報告を含めて、これまでの疫学研究等では、血液製剤を介して古典的CJD(弧発性、遺伝性および医原性CJD)が伝播するという証拠はない。またCJDの病原因子とされる異常プリオンが本製剤の製造工程で効果的に除去されるとの成績もあるが、第Ⅷ因子製剤を介しvCJDに感染する可能性が示唆された報告もあることから、今後も引き続き情報の収集に努める。なお、日本赤十字社は、CJD、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)、CJDの既往歴(本人、血縁者)、hGH製剤投与の有無を確認し、該当するドナーを無期限に献血延期としている。

(17)

Medical Procedures and Risk for Sporadic Creutzfeldt-Jakob Disease, Japan, 1999–2008

Tsuyoshi Hamaguchi, Moeko Noguchi-Shinohara, Ichiro Nozaki, Yosikazu Nakamura, Takeshi Sato, Tetsuyuki Kitamoto, Hidehiro Mizusawa, and Masahito Yamada

To elucidate the association between medical procedures and sporadic Creutzfeldt-Jakob disease (sCJD), we analyzed medical procedures (any surgical procedure, neurosurgery, ophthalmic surgery, and blood transfusion) for patients registered by the CJD Surveillance Committee in Japan during 1999–2008. We conducted an age-stratified case–control study with 753 sCJD patients and 210 controls and a study of patients who underwent neurosurgical or ophthalmic surgical procedures at the same hospital. Although the control group was relatively small, no evidence was found that prion disease was transmitted through the investigated medical procedures before onset of sCJD. After onset of sCJD, 4.5% of the sCJD patients underwent operations, including neurosurgical for 0.8% and ophthalmic for 1.9%; no special precautions against transmission of prion diseases were taken. Fortunately we have not identified patients with prion disease attributed to these operations. Our findings indicate that surgical procedures or blood transfusion had little effect on the incidence of sCJD.

Prion disease is characterized by spongiform change and abnormal prion protein deposition in the brain and is transmissible under certain situations. Human prion disease is divided into 3 categories: genetic prion diseases with mutations of the prion protein (PrP) gene; prion diseases acquired by transmission of the prion through exposure to contaminated materials, including iatrogenic transmission; and sporadic Creutzfeldt-Jakob disease (sCJD) with no PrP mutation or evidence of exposure to prion. To date, >400 patients with iatrogenic CJD, who received prions through contaminated neurosurgical instruments, intracerebral electroencephalographic electrodes, human pituitary hormone, corneal transplants, or dura mater grafts, have been reported (*1*). Furthermore, some case–control studies reported that medical procedures were possible risk factors for sCJD (*2–6*). However, other studies did not demonstrate any significant association between medical procedures and sCJD (*7–10*).

After a results of a case–control study that found an association between CJD and medical procedures was reported from Japan in 1982 (*2*), 132 patients with dura mater graft–associated CJD (dCJD) have been found in Japan (*11,12*); however, no recent studies have investigated medical procedures as a risk for acquiring sCJD. In Japan, 66 (8.6%) of 766 patients with prion diseases had iatrogenic cases that were all dCJD (*12*), and the outbreak of iatrogenic CJD required a new study about the association between sCJD and medical procedures in Japan. Here we analyzed the role of medical procedures in cases of sCJD by using relevant data from CJD surveillance in Japan.

Methods

Patients

We investigated 1,339 patients with suspected prion diseases who had been registered by the CJD Surveillance Committee in Japan from April 1999 through February 2008. The surveillance system was initiated in April 1999, and each patient was prospectively assessed with a surveillance protocol that assembled information about life

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history; previous medical history, including the history of surgical treatment and blood transfusion; clinical history; laboratory data; and results of molecular genetic and pathologic examinations. Information on patients with suspected prion diseases were obtained through 1) the application for registration with the Japanese Intractable Diseases Information Center (www.nanbyou.or.jp/english/nan_kenkyu_45.htm) by each patient's family, 2) the law on infectious diseases, or 3) request for genetic or cerebrospinal fluid analyses sent to members of the CJD Surveillance Committee by the physicians. In Japan, 123 diseases have been defined as intractable disease, and for 45 of them, including prion diseases, patients receive additional economic support for medical costs. Furthermore, medical doctors must report patients suspected of having prion disease to the local public health department within 7 days after the diagnosis, according to the law on infectious diseases (which has been enforced since April 1999 in Japan to monitor some specific infectious diseases). After written consent approved by the Institutional Ethics Committee was obtained from each patient's family, members of the CJD Surveillance Committee directly examined the patient and collected data from the clinical records. For each patient with a history of surgery, we collected information about the underlying disease from the patient's family, including the date and hospital in which the operation was performed. For each patient with a history of blood transfusion, we collected information about the date of blood transfusion. Most information was collected by interviewing the patient's family members.

On the basis of discussions by the CJD Surveillance Committee, we confirmed or denied the diagnosis of prion disease in each case. In patients with a confirmed diagnosis of prion disease, we classified prion diseases into 4 categories: sCJD, acquired prion disease, genetic prion disease, and unclassified prion disease. sCJD was diagnosed according to the revised classical criteria established by Masters et al. (*13*): definite CJD (neuropathologically confirmed spongiform encephalopathy or abnormal prion protein deposition in the brain); and probable CJD (neuropathologically unconfirmed cases showing progressive dementia, periodic sharp-wave complexes on electroencephalogram, and at least 2 of the following features: myoclonus, pyramidal signs/extrapyramidal signs, cerebellar signs or visual symptoms, and akinetic mutism). Acquired prion diseases included iatrogenic CJD, in which the criteria for sCJD were applied for a diagnosis with a history of iatrogenic exposure, and variant CJD, in which the diagnosis was based on the World Health Organization (WHO) 2001 criteria (*14*). Regarding the accuracy of the diagnosis of genetic prion diseases, pathologically verified cases were defined as "definite," and cases demonstrating mutations in the PrP gene and neuropsychiatric manifestations compatible with prion diseases were defined as "probable." We selected patients with definite or probable sCJD for analysis.

Patients who did not receive a diagnosis of prion diseases were classified into 3 categories: prion diseases definitely denied; prion diseases probably denied; and diagnosis unclear. "Prion diseases definitely denied" indicated patients whose conditions were definitively diagnosed as diseases other than prion diseases, and "prion diseases probably denied" indicated patients for whom the diagnosis of prion diseases was clearly unlikely due to the improving or nonprogressive disease course or for other reasons, although a definitive diagnosis of another disease was not established. Because patients with "prion diseases definitely denied" or "prion disease probably denied" had no or little possibility of prion disease, we selected these cases as the controls in our case–control study.

Surgical Procedures and Blood Transfusions before Onset of sCJD

To estimate the risk for sCJD through past surgery or blood transfusion, we performed a case–control study. Operations were divided into the following categories: neurosurgery, ophthalmic surgery, and surgery other than neurosurgery or ophthalmic surgery (other surgery), because neurosurgery or ophthalmic surgery for those with prion diseases are categorized in the guidelines of the CJD Incident Panel in the United Kingdom as high- or medium-risk procedures for transmission of infective PrP (*15*). In these guidelines, procedures involving the olfactory epithelium are also categorized as medium risk (*15*). However, the number of persons who underwent the operation possibly involving the olfactory epithelium is too small to be estimated by statistical analysis (2 sCJD patients and 2 controls underwent surgery for sinusitis), and we categorized these operations as other surgery. Neurosurgery included operations on the brain, cerebral blood vessels, and spinal cord. Ophthalmic surgery included all operations involving the eyeball and optic nerve. Other surgery included all surgical procedures other than neurosurgery and ophthalmic surgery. Furthermore, the committee performed a detailed investigation of sCJD patients who underwent neurosurgery or ophthalmic surgery at a hospital where other patients with any type of prion disease had ever undergone neurosurgery or ophthalmic surgery.

Surgical Procedures after Onset of sCJD

We analyzed sCJD patients who underwent surgical procedures after the onset of sCJD because such procedures might cause secondary transmission of the disease through contaminated instruments. In particular, for neurosurgery and ophthalmic surgery, we investigated the reason for the operation, interval between the operation and onset of sCJD symptoms, age at onset of sCJD, and symptoms at onset of sCJD.

Statistical Analyses

Between the sCJD and control groups, age at onset was compared by Student *t* test, and medical procedures before the onset of diseases were compared by Fisher exact test. The case–control study of surgical procedures and blood transfusions before the onset of diseases was estimated by logistic-regression analysis. Because age at onset was different among sCJD patients (mean ± SD, 67.7 ± 9.5 years) and controls (59.3 ± 16.6 years) ($p<0.0001$), we divided the sCJD patients and controls into 3 categories according to age at disease onset; 31–50 years, 51–70 years, and ≥71 years. We performed a single regression analysis for any operation, neurosurgical procedure, ophthalmic surgical procedure, other operation, and blood transfusion in each age group. The strength of association between sCJD and putative risk factors was assessed by the odds ratios and 95% confidence intervals. Significance was defined as $p<0.05$. Statistical analyses were performed by using StatView J-7.5 (Abacus Concepts, Berkeley, CA, USA).

Results

A total of 990 patients received a diagnosis of definite or probable prion disease. Summary of the characteristics of patients with prion diseases is shown in Table 1, in which 760 patients with sCJD are included. There were 221 patients with "prion disease definitely denied" and "prion disease probably denied." Seven sCJD patients and 11 control patients were excluded from the case–control study because information on medical history was not sufficient for analysis. Diagnoses of the 210 control patients is shown in Table 2.

Medical Procedures before Onset of sCJD

Frequencies of medical procedures before the onset of sCJD in sCJD patients and in controls are compared in Table 3. For both the sCJD and control groups, ≈50% had a history of surgery, and ≈10% had received a blood transfusion. No significant differences were found between them in frequency of any surgery, neurosurgery, ophthalmic surgery, other surgery, or blood transfusion (Table 3). In the logistic-regression analysis, no significant risk was associated with any medical procedures investigated in this study (Table 4).

Five sCJD patients had a history of neurosurgery or ophthalmic surgery at hospitals where neurosurgery or ophthalmic surgery had been performed on patients in whom prion disease later developed (Table 5); intervals between operations at the same hospitals were >3 years (Table 5).

Table 1. Characteristics of patients with definite or probable prion disease, Japan, 1999–2008*

Type of prion disease	No. (%) patients
Sporadic CJD	760 (76.8)
Genetic prion diseases	167 (16.9)
Acquired prion diseases†	62 (6.3)
Unclassified CJD	1 (0.1)
Total	990

*CJD, Creutzfeldt-Jakob disease.
†Acquired prion diseases included 61 cases of dura mater CJD and 1 case of variant CJD.

Surgical Procedures after Onset of sCJD

Except for 2 patients suspected of having prion disease, who had undergone brain biopsy with disposable instruments, 34 (4.5%) of 760 sCJD patients underwent some type of surgical procedure before the diagnosis of prion disease, including neurosurgery in 6 (0.8%), ophthalmic surgery in 14 (1.8%), and other surgery in 16 (2.1%). The 6 case-patients who underwent neurosurgery had these operations within 3 months after sCJD onset: procedures performed for subdural hematoma (n = 3), aneurysm (n = 2), and menigioma (n = 1) (Table 6). All 14 case-patients who underwent ophthalmic surgery underwent operations for cataracts, and 7 of these patients had had visual disturbance as an initial symptom of sCJD (Table 7). Among 5 patients for whom information on the effects of ophthalmic surgery could be obtained, 2 had some improvement of visual symptoms after surgery, but the other 3 patients had no improvement. Although both cataracts and sCJD could contribute to the visual symptoms, sCJD would contribute to visual symptoms in patients who had no effects of ophthalmic surgery. We have obtained information about instrument cleaning and sterilization procedures for 3 of 5 patients who underwent neurosurgery and for 5 of 14 patients who underwent ophthalmic surgery after the onset

Table 2. Diagnoses for 210 controls in case–control study of sCJD, Japan, 1999–2008*

Disease	No. diagnoses
Encephalitis	27
Alzheimer disease	21
Frontotemporal dementia	15
Metabolic encephalopathy	15
Cerebrovascular disorders	12
Spinocerebellar degeneration	12
Corticobasal degeneration	9
Epilepsy	7
Psychiatric disorders	7
Hypoxic encephalopathy	7
Hashimoto encephalopathy	6
Dementia with Lewy bodies	6
Paraneoplastic syndrome	5
Mitochondrial encephalopathy	4
Malignant lymphoma	3
Other disorders	54

*sCJD, sporadic Creutzfeldt-Jakob disease.

Table 3. Medical procedures before disease onset, case–control study of sCJD, Japan, 1999–2008*

Medical procedures	sCJD case-patients, no. (%), n = 753	Controls, no. (%), n = 210
Surgery	372 (49.4)	104 (49.5)
Neurologic	25 (3.3)	13 (6.2)
Ophthalmic	42 (5.6)	11 (5.2)
Other	337 (44.8)	89 (42.4)
Blood transfusion	78 (10.4)	20 (9.5)

*sCJD, sporadic Creutzfeldt-Jakob disease. p values were not significant.

of sCJD. All surgeons reused some of the surgical instruments, but according to the WHO guidelines (*16*), the sterilization methods of the instruments were not appropriate for eliminating infectious PrP, including the use of ethylene oxide gas or incomplete autoclaving.

Discussion

In this case–control study, we found no evidence of increased sCJD risk associated with patient's history of surgical procedures or blood transfusions. In the previous case–control study and in our study, receipt of a blood transfusion was not shown to be a significant risk for CJD (*2–10*). However, whether surgical procedures contribute to the risk for sCJD has been controversial. Our results, in which any operation was not a significant risk for sCJD, were consistent with results of 2 previous large case–control studies (*8,9*) and a reanalysis of results of 3 case–control studies (*10*). Even in the studies with positive results, some different results were provided when the surgical procedures were categorized by affected organ. One previous case–control study indicated significant risk for sCJD after neurosurgical procedures (*3*), but no significant risk was shown in other studies (*5,6,8–10*). Ophthalmic surgery was reported as causing significant risk for sCJD in a case–control study in Australia (*4*) but not in other studies (*5,6–10*).

In a recent study in the United Kingdom (*6*), the increased risk associated with having undergone surgical procedures was restricted to the category "other surgery," which included such procedures as sutures to skin, and the association largely disappeared when the whole of the other-surgery category was excluded. These different results may show little possibility for transmission of infectious PrP through surgical procedures, although we cannot exclude the possibility that such transmission occurs occasionally because iatrogenic CJD exists.

The conflicting results in case–control studies, including ours, may be explained by differences in the area, race, period in which studies were performed, number of patients, and methods as discussed below. Our study, which attempted to determine when medical procedures were associated with an increased risk for sCJD, had the largest number of sCJD patients in case–control studies to date. The relatively small number of controls is a potential limitation. In case–control studies, methods of obtaining data from controls should be the same as those from patients. In our study, patients in the groups "prion diseases definitely denied" or "prion diseases probably denied" in our CJD surveillance, who had no or little possibility of having prion disease, were used as the controls. Therefore, data from controls could be collected at the same level of precision as those from the sCJD cases. Because the ages of the sCJD patients and controls were significantly different, age-stratified analysis was required in our study. A recent study reported that some methodologic differences might partially explain conflicting data regarding the association between surgical procedures and CJD (*17*). The report suggested that the use of controls from the community would be preferable to using those from the hospital because community-based controls are often more representative and would result in a more valid comparison (*17*). Furthermore, using proxy informants for controls may be advisable for the purpose of comparability with case-patients, although this practice does not necessarily offset biases in data ascertainment (*17*). In our case–control study, we used proxy informants for controls who were recruited from hospitals under the same condition as the sCJD case-patients.

Table 4. Medical procedures and risk for sCJD, by age at disease onset, Japan, 1999–2008*

Age range, y	Data category	Total no. patients	Any surgery	Neurosurgery	Ophthalmic surgery	Other surgery	Blood transfusion
31–50	sCJD	32	50.0%	6.3%	6.3%	40.6%	3.1%
	Control	37	45.9%	10.8%	2.7%	37.8%	5.4%
	OR		1.66	0.38	2.15	0.78	0.64
	95% CI		0.04–74.09	0.02–6.64	0.05–101.51	0.02 – 33.39	0.05–9.09
	p value		0.79	0.50	0.70	0.90	0.74
51–70	sCJD	414	43.7%	1.7%	2.2%	41.8%	9.4%
	Control	97	46.4%	5.2%	3.1%	40.2%	11.3%
	OR		0.18	0.69	2.71	5.57	0.84
	95% CI		0.02–1.73	0.13–3.62	0.24–30.38	0.62–50.05	0.40–1.77
	p value		0.14	0.66	0.42	0.13	0.64
≥71	sCJD	317	57.0%	5.2%	10.1%	49.2%	12.4%
	Control	60	65.0%	6.7%	10.0%	56.7%	11.7%
	OR		0.81	0.76	1.15	0.83	1.27
	95% CI		0.15–4.37	0.15–3.80	0.38–3.48	0.17–4.02	0.52–3.10
	p value		0.80	0.74	0.81	0.82	0.60

*sCJD, sporadic Creutzfeldt-Jakob disease; OR, odds ratio; CI, confidence interval.

Regarding the 5 sCJD patients with a history of neurosurgical or ophthalmic surgical procedures at hospitals where other patients with prion disease had previously undergone such procedures, we consider that the possibility of transmission through these procedures was extremely limited because the intervals between procedures and the acquisition of sCJD had been >3 years for all patients. According to the Incident Panel in the United Kingdom, most instruments that have gone through 10 cycles of use and decontamination are unlikely to pose a substantial risk (*15*). We assume that all instruments had gone through >10 cycles of use during the 3-year interval, and almost no infectivity remained on the instruments. In Japan, a large number of dCJD patients have been recognized with no other types of iatrogenic CJD (*11,12*); this study confirmed that no surgically transmitted cases occurred among patients with sCJD.

It is noteworthy that 4.5% of the sCJD patients underwent some types of surgical procedures after the disease onset, including neurosurgical (0.8%) and ophthalmic procedures (1.8%). Through surgical instruments, neurosurgical operations may transmit high infectivity from the brain tissues of sCJD patients, and ophthalmic operations may transmit moderate infectivity of the eye tissues in cases of cataracts (*15*). In this study, all these neurosurgical and ophthalmic procedures were performed without suspicion of prion diseases or special precautions to reduce the risk for secondary transmission of prion infection through the instruments. These findings suggest that delayed diagnosis of sCJD would be linked to increased risk for secondary transmission of prion diseases through surgical instruments. In neurosurgical procedures, the symptoms of sCJD were misdiagnosed as those of other neurologic diseases, and operations were performed near the time of disease onset. In terms of ophthalmic surgery, all patients underwent operations for cataracts, and 7 (50%) of 14 patients had visual disturbances as an initial symptom of sCJD. These data are similar to those in a report from the United Kingdom (*18*). Visual disturbances might prompt ophthalmic surgery. More seriously, 3 patients underwent operations ≥8 months after sCJD onset. In this study, all surgeons who provided information reused the surgical instruments with incomplete sterilization, and the potential for infection was the same as in our previous study of ophthalmic surgery (*19*).

Neurosurgeons and ophthalmologists should become better informed about prion diseases and the necessity of using disposable instruments whenever possible. Further-

Table 5. Characteristics of 5 sCJD patients who underwent neurosurgery or ophthalmic surgery at hospitals where other patients with prion diseases had previously undergone neurosurgery or ophthalmic surgery, Japan, 1999–2008*

Patient	Type of CJD	Onset of CJD	Date of surgery	Reason for surgery
1	sCJD	2003 Aug	1991 Aug	Subarachinoid hemorrhage
	dCJD	2001 May	1976	Spinal cord tumor
			1986 Aug	Spinal cord tumor
2	sCJD	2002 Feb	1994 Sep	Subdural hematoma
			1997 Sep	Cataract
	dCJD	1998 Jan	1987 Jan	Meningioma
3	sCJD	2001 Jan	1989 Apr	Subarachinoid hemorrhage
	dCJD	1995 Jul	1980 Jul	Aneurysm
4	sCJD	2001 Jul	1999	Spinal cord lesion (details unknown)
	dCJD	2001 Aug	1978 Sep	Astrocytoma
5	sCJD	2002 May	2002 Apr	Cataract
	sCJD	2002 May	1997 Aug	Cataract
			1999 Jan	Cataract

*CJD, Creutzfeldt-Jakob disease; sCJD, sporadic CJD; dCJD, Creutzfeldt-Jakob disease associated with cadaveric dura mater graft.

Table 6. Data for sCJD patients who underwent neurosurgery after onset of sCJD symptoms, Japan, 1999–2008*

Patient no.	Reason for surgery	Interval between onset of sCJD symptoms and surgery, mo	Age at onset of sCJD, y	Symptom at onset of sCJD
1	Subdural hematoma	0	71	Dementia
2	Subdural hematoma	0	77	Apathy
3	Subdural hematoma	1	57	Dementia
4	Meningioma	1	74	Vertigo
5	Aneurysm	2	46	Dementia
6	Aneurysm	3	67	Vertigo

*sCJD, sporadic Creutzfeldt-Jakob disease.

Table 7. Data for sCJD patients who had ophthalmic surgery for cataracts after onset of sCJD symptoms, Japan, 1999–2006*

Patient no.	Interval between onset of sCJD symptoms and surgery, mo	Age at onset of sCJD, y	Symptom at onset of sCJD
1	0	60	Gait disturbance
2	0	61	Dementia
3	0	63	Visual impairment
4	0	71	Visual impairment
5	0	74	Visual impairment
6	0	74	Visual impairment
7	1	66	Dementia
8	1	74	Depression
9	1	85	Visual impairment
10	2	79	Tremor
11	4	81	Visual impairment
12	8	77	Anxiety
13	10	57	Dementia
14	14	64	Visual impairment

*sCJD, sporadic Creutzfeldt-Jakob disease.

more, a more sensitive method for early diagnosis of sCJD is needed because clinical diagnosis is sometimes difficult, particularly in atypical sCJD cases, such as MM2, MV2, VV1, or VV2 types (*20–23*), according to 6 phenotypes of sCJD divided by codon 129 polymorphisms of PrP (methionine/valine) and type of infectious PrP by Western blotting (*24*). Even neurologists may misdiagnose the initial stage of the atypical sCJD cases as being another neurodegenrative disease such as Alzheimer disease and progressive supranuclear palsy (*20*). Moreover, patients who have undergone surgical procedures with possibly contaminated instruments need to undergo a risk assessment with long-term follow-up after careful ethical consideration. Since June 2004, we have identified and monitored all patients who underwent neurosurgical procedures with possibly contaminated instruments, CJD has developed in none of those patients.

In conclusion, we did not demonstrate any evidence of increased risk for sCJD associated with a history of surgery or blood transfusion in the Japanese surveillance system. However, the fact that some patients had surgeries, including neurosurgery, even after the onset of sCJD indicates that we cannot deny any possibility of transmission of prion diseases by medical procedures. Neurosurgeons, ophthalmologists, and other surgeons need to focus more attention on prion diseases to reduce the iatrogenic risk, as well as realize that prolonged, careful surveillance of prion diseases is necessary.

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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 2009年2月9日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称	別紙のとおり		研究報告の公表状況	CDC／Travelers' Health (Updated: February 04, 2009)	公表国 ジンバブエ	
販売名(企業名)	別紙のとおり					

研究報告の概要	使用上の注意記載状況・その他参考事項等
問題点：ジンバブエにおけるコレラのアウトブレイクで61,304人の感染疑い例、3,181人の死亡例が報告されている。 ジンバブエの保健当局からコレラのアウトブレイクについて報告されている。国連人道問題調整事務所によると、2008年8月26日から2009年1月31日までにジンバブエ国内で61,304人の感染疑い例、3,181人の死亡例が報告されている。被害が大きい地域は、首都のHarare (14,126人感染、592人死亡)、Mashonaland WestManicaland South (7,081人感染、458人死亡) である。コレラの発生例は、ジンバブエの全ての州から報告されている。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例が報告されている。	記載なし

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

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、⑫ヘパトセーラ、⑬トロンビン“化血研”、⑭ボルヒール、⑮アンスロビンP、⑯ヒスタグロビン、⑰アルブミン20%化血研*、⑱アルブミン5%化血研*、⑲静注グロブリン*、⑳ノバクトF*、㉑アンスロビンP1500注射用
報告企業の意見	コレラは代表的な経口感染症の1つで、コレラ菌で汚染された水や食物を摂取することによって感染する。コレラ菌は、菌体表面のO抗原（リポ多糖体）の違いによって、現在205種類（11種類は未発表）に分類されている。このうち、コレラを起こすのはO1およびO139血清型のみである。わが国におけるコレラは、最近はほとんどが輸入感染症として発見される。すなわち熱帯・亜熱帯のコレラ流行地域への旅行者の現地での感染例である。国内での感染例の報告もあるが、輸入魚介類などの汚染が原因であろうと推定されていて、二次感染例と思われる例はほとんど無い。(http://idsc.nih.go.jp/idwr/kansen/k00-g15/k00_01/k00_01.html) 仮に、本剤の原材料であるヒト血液にコレラ菌が混入していたとしても、弊所で製造している全ての血漿分画製剤の製造工程には、約0.2μmの「無菌ろ過工程」および、コレラ菌よりも小さいウイルスの除去を目的とした平均孔径19nm以下の「ウイルス除去膜ろ過工程」が導入されているので、これらの工程により除去されるものと考えられる。更に、これまでに本剤によるコレラ菌感染の報告例は無い。 以上の点から、本剤はコレラ菌感染に対して一定の安全性を確保していると考えるが、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。

*現在製造を行っていない

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Centers for Disease Control and Prevention Travelers' Health
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Outbreak Notice

Cholera in Zimbabwe and Neighboring Countries

This information is current as of today, February 11, 2009 at 23:51

Updated: February 04, 2009

An outbreak of cholera has been reported by health officials in Zimbabwe. According to the United Nations Office of the Coordination of Humanitarian Affairs, from August 26 through January 31, 2009, 61,304 suspected cases and 3,181 deaths have been reported in the country. The worst-affected areas are the capital city of Harare (14,126 cases and 592 deaths), Mashonaland West (14,259 cases and 685 deaths), Manicaland South (7,081 cases and 458 deaths). Cases of cholera have been reported in all of Zimbabwe's provinces. Cases have also been confirmed in the neighboring countries of Botswana, Mozambique, South Africa, and Zambia. Additional sources have reported cases in Angola, Burundi, Democratic Republic of Congo, Kenya, Malawi, Namibia, Nigeria, Guinea-Bissau and Togo.

Cholera is a potentially fatal bacterial infection that causes severe diarrhea and dehydration. The disease is spread through untreated sewage and contaminated drinking water. There is no cholera vaccine available in the United States.

Advice for People Traveling to Zimbabwe

Most travelers are not at high risk for getting cholera, but travelers should be aware of the outbreak and make sure they are taking steps to prevent getting sick. Although no cholera vaccine is available in the United States, U.S. travelers can greatly reduce their risk for cholera by following CDC's safe food and water advice:

- Before departing for Zimbabwe, talk to your doctor about getting a prescription for an antibiotic to treat traveler's diarrhea.
- Drink water that you have boiled for at least one minute or treated with chlorine or iodine. Other safe beverages include tea and coffee made with boiled or treated water, as well as drinks that have been bottled and sealed (such as bottled water, carbonated drinks, and sports drinks).
- Do not put ice in drinks, unless the ice is made from boiled or treated water.
- Eat only foods that have been thoroughly cooked and are still hot, or fruit that you have peeled yourself.
- Do not eat undercooked or raw fish or shellfish, including ceviche.
- Make sure all vegetables are cooked. Do not eat salads or other raw vegetables.
- Do not eat foods and drink beverages from street vendors.
- Do not bring perishable seafood back to the United States.

A simple rule of thumb for safe food and water is "*Boil it, cook it, peel it, or forget it.*"
If you are traveling in Zimbabwe or neighboring countries and have severe watery diarrhea seek medical care right away. It is important to remember to drink fluids and use oral rehydration solution (ORS) to prevent dehydration.

More Information

The United Nations Office for the Coordination of Humanitarian Affairs in Zimbabwe has reported that new cases and deaths due to cholera are increasing. Although Zimbabwe has reported several smaller cholera outbreaks in recent years, this outbreak is more severe and may worsen with the onset of the rainy season. On December 3, the government of Zimbabwe declared a national emergency and appealed for international assistance. The humanitarian community has already been responding to this outbreak with water, sanitation, and hygiene initiatives in outbreak areas. WHO and its Health Cluster partners are finalizing a "Cholera Response Operational Plan" to evaluate and control the current outbreak.

For more information about the cholera outbreak in Zimbabwe, including maps:

- Weekly Situation Report (/travel/forward.aspx?t=aHR0cDovL29jaGFvbmxpbmUudW4ub3JnL0RlZmF1bHQuYXNweD9hbGlhcz1vY2hhb25saW5lLnVuLm9yZy96aW1iYWJ3ZQ%3d%3d-uddp6JMnq70%3d) —United Nations Office for the Coordination of Humanitarian Affairs (February 3, 2009)
- Cholera in Zimbabwe (/travel/forward.aspx?t=aHR0cDovL3d3dy53aG8uaW50L2Nzci9kb24vMjAwOF8xMl8wMi9bi9pbmRleC5odG1s-SD6LRlB9hkU%3d) —World Health Organization (December 2, 2008)
- Relief Web (/travel/forward.aspx?t=aHR0cDovL3d3dy5yZWxpZWZ3ZWIuaW50L3J3L2RiYy5uc2YvZG9jMTE1P09wZW5Gb3JtJnJPTE%3d-HYAld4y5GyY%3d) , Zimbabwe—United Nations, Office of the Coordination of Humanitarian Affairs, (January 31, 2009)

For more information for travelers:

- Warden Message about cholera, November 26, 2008 (/travel/forward.aspx?t=aHR0cDovL2hhcmFyZS51c2VtYmFzc3kuZ292LzExLzI2LzMvDQuaHRtbA%3d%3d-l2qel6aC740%3d) —American Embassy in Harare, Zimbabwe Warden messages (/travel/forward.aspx?t=aHR0cDovL2hhcmFyZS51c2VtYmFzc3kuZ292L3dhcmRlbi5odG1s-PuVXy907AcA%3d)
- Travel Warning about cholera, December 12, 2008 (/travel/forward.aspx?t=aHR0cDovL2hhcmFyZS51c2VtYmFzc3kuZ292L3ppbWJhYndlX3RyYXZlbHdhcm5pbmoyLmh0bVw%3d-dhUsw6uJ%2bDU%3d) —American Embassy in Harare, Zimbabwe

- Cholera (yellowBookCh4-Cholera.aspx) (from *CDC Health Information for International Travel 2008*)
- Safe food and water (contentSafeFoodWater.aspx) (CDC Travelers' Health website)

For more information about cholera, see the following CDC links:

- Cholera (http://www.cdc.gov/nczved/dfbmd/disease_listing/cholera_gi.html) (from CDC, Division of Foodborne, Bacterial, and Mycotic Diseases)
- Cholera (yellowBookCh4-Cholera.aspx) (from *CDC Health Information for International Travel 2008*)

To find medical care in Zimbabwe:

- On the web: List of local medical specialists (/travel/forward.aspx?t=aHR0cDovL2hhcmFyZS51c2VtYmFzc3kuZ292L21fZGJjYWxfaW5mb3JtYXRpb24uaHRtbA%3d%3d-U8dFKbSICao%3d) (Embassy of the United States, Harare, Zimbabwe)
- By phone: 263-4-250593/4 Consular section of the United States Embassy, Harare, Zimbabwe: American Citizen Services

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