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。

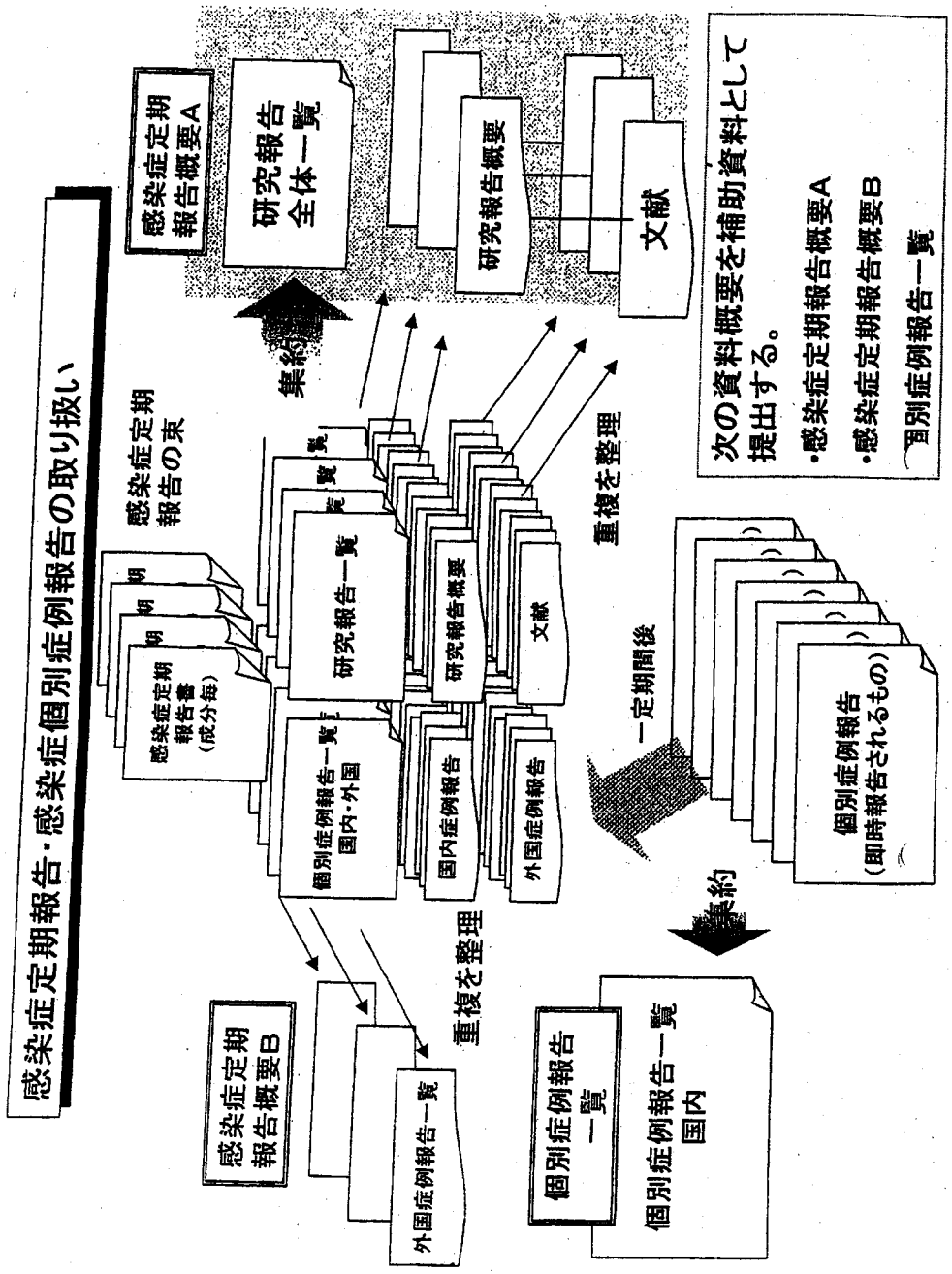
① 研究報告は、同一文献による重複を廃した別紙のような形式の一覧表を作成し、当該一覧表に代表的なものの報告様式（別紙様式第2）及び該当文献を添付した**「資料概要A」**を事務局が作成し、送付する。

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３月２日）

平成２１年９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９月１日以降に報告された感染症定期報告に含まれる研究報告（論文等）について、重複している分を除いた報告概要一覧表を作成した。

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

感染症定期報告の報告状況(2009/9/1～2009/11/30)

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
100022	2009/10/1	90550	A型肝炎	Eurosurveillance 2009 April 16; 14(15)	2008年9月1日-3月9日、スペイン・バルセロナにおいてA型肝炎に感染した150症例が報告された。この数は、前の2年の同時期と比べて3倍である。症例のほとんどの症例は、男性と性的関係を持つ男性(MSM)でありことを報告した87名を含む、成人男性に発生した。これは、MSM集団におけるA型肝炎感染のアウトブレイクの可能性を示唆しており、感染リスクの高いコミュニティーへのより効果的なワクチン接種プログラムの必要性を強調している。	1
100057	2009/11/2	90717	B・C型肝炎	Transfusion 2009; 49: 648-654	2005年8月、カナダ血液サービスは入れ墨や耳もしくは体のピアスに対する供血延期の期間を12ヶ月から6ヶ月に短縮した。本研究では、この変更が血液の安全性および安定供給に及ぼす影響を評価した。最近の供血者40,000名を対象とし、普及率を調べた結果、入れ墨、耳、体のピアスについてそれぞれ調査回答者の13.7、53.6、10.4%であり、過去6ヶ月以内の実施は最大0.7%であった。National Epidemiology Donor Databaseを用いて算出した供血延期期間変更前および後の感染症(TD)マーカー率は、100,000供血当たり21.6および19.2であった。症例対照試験はTD陽性供血者とマッチした対照者間のリスク因子を比較して行われ、最近の入れ墨やピアスはHCVまたはHBVのリスク因子ではなかった。延期期間の短縮により、供血延期の件数は入れ墨で20%、ピアスで32%減少した。供血期間の短縮後、検出できるほどの安全性に対する影響は少なく、血液供給においては期待効果以下ではあるが有効であった。	2
100057	2009/11/2	90717	B型肝炎	Hepatology 2009; 49: S156-165	B型肝炎の再燃とは、非活動型もしくはB型肝炎が治癒した患者にB型肝炎ウイルス(HBV)の急激な増幅が起きることである。最も説明が成されている例として、B型肝炎の再燃はリンパ腫または白血病の癌化学療法を受けている非活動性もしくはほとんど活動していないB型肝炎表面抗原(HBsAg)キャリアに起きている。通常は化学療法の間血清中HBV DNAが上昇し、化学療法中止後に免疫再構築による疾病増悪およびHBV DNAクリアランスと続く。いつくかの無作為化プラセボ対照試験は、抗ウイルス剤の予防投与によって再燃を防ぐことができることを示した。癌化学療法や移植を行っているHBsAg陽性者に定期的予防が推奨されるが、HBsAgスクリーニングを行う患者の選定や使用する抗ウイルス剤の種類や期間、およびHBsAg陰性のB型肝炎治癒患者への予防など疑問はある。再燃の分子生物学的メカニズムや異なる患者集団における診断、治療および予防の最適化についての研究が望まれる。	3
100034	2009/10/26	90666	B型肝炎	Transfusion 2009 July; 49; 1314-1320	HBsAg(hepatitis B surface antigen)に陽性を示した供血者とHBV(hepatitis B virus)感染者とのHBVgenotypeを比較するため、HBsAg陽性供血者の遺伝子型を決定した。2006年10月-2007年9月の日本人供血者のデータは日本赤十字社から提供を受け、1887例についてHBVの主な6genotypes(A-F)をELISA(enzyme-linked immunosorbent assay)法によって決定した。HBsAg陽性ドナーについてHBVコア抗原に対するIgM抗体の有無の確認を行った。供血者と患者間で示されたHBVgenotype分布における有意差はC/B遺伝子型比で認められ、この比率は供血者で低く(2.0-3.9)、患者で高かった(5.3-18.2)。また、genotypeBの比率は10歳代の13.8%から増加し、50歳代では42.4%であったが、genotypeC比率は10歳代の83.1%から50歳代の55.1%に減少した。HBcAgに対するIgM抗体およびNAT(nucleic acid test)両者に陽性であるドナーでは、genotypeAおよびBは男性のみであった。日本人供血者におけるHBVgenotypeの年齢特異的な分布は、B/C遺伝子型比に特徴があり、米国もしくは西欧諸国由来であるHBVgenotypeAの性特異的分布は、日本人男性ドナーに観察された。	4

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100005	2009/9/28	90523	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。	
100022	2009/10/1	90550	B型肝炎	日本肝臓学会第37回東部会O-85	日本の首都圏において、HBVの中でも慢性化率の高いgenotypeAは急速に増加しており、新規日本人キャリアからの二次感染が疑われることが急性B型肝炎症例の検討から明らかになった。	
100022	2009/10/1	90550	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。	
100022	2009/10/1	90550	E型肝炎	Emerging Infectious Disease 2009; 15 ;704-708	E型肝炎ウイルス(HEV)のgenotype3は日本においては不顕性感染とされているが、重篤な肝炎を発症した国内8症例について、強毒性をもたらすHEVの遺伝的特徴を解析するため遺伝子配列を決定した。系統樹解析の結果、いずれも他のgenotype3とは区別され、JIO株と名付けられた固有のクラスターに分類された。このJIO関連ウイルスは他のHEVgenotype3とは異なる18のアミノ酸をコードしており、また、JIOクラスターのヒトHEV株のほぼすべてに共通する置換はヘリカーゼ領域(V239A)に位置し、V239Aはgenotype4では一般的であることから、毒性の増強と関連が示唆された。また、genotype3に属するswJ19株に感染した5匹のブタから遺伝子を解析した結果、同様にヘリカーゼにV239A置換が存在していたことから、JIO関連ウイルスが人獣共通であることが疑われた。	5
100022	2009/10/1	90550	E型肝炎	第57回日本輸血・細胞治療学会2009; 55; 244	北海道で献血者のHEV感染の実態を解析するため、2005年1月-2008年11月に北海道内の献血者1,075,793名について20本プールによるHEV NATを実施した。HEV NAT陽性者は140名であり、献血時のHEV抗体保有率は3割以下、感染初期の献血が多かった。陽性者のHEVのgenotypeは9割以上が3型で4型も認められた。陽性者の約7割は献血前に動物内臓肉の喫食歴があり、陽性者の半数にはその後ALT値の上昇が見られた。北海道内の献血者集団に於けるHEV RNA陽性頻度は高く、zoonotic infectionが起きていると考えられる。	6
100022	2009/10/1	90550	HHV-8感染	J Infect Dis. 2009; 199(11); 1592-1598	米国内で輸血を介したHHV-8感染の調査を行った。供血者-受血者のペアを明確にした米国内調査を行うため、1970年代に登録されたTTVS(Transfusion-transmitted Viruses Study)の参加者にHHV-8血清学的検査を行った。HHV-8抗体陽性率は、供血者では2.8%、受血者では7.1%、輸血されず手術を行った対照患者では7.7%、カポジ肉腫のある対照患者では96.3%であった。1例の受血者はセロコンバージョンしたが、、この患者にはHHV-8陽性の血液ユニットは輸血されなかった。また、輸血されず手術を行った対照患者1例もセロコンバージョンした。セロコンバージョン率は、受血者が1.6(1000人-年あたり)であり、輸血を受けていない手術を行った対照患者では3.6(1000人-年あたり)であった。輸血群と非輸血群におけるHHV-8 seroconversion率には統計学的な差はなく、かつ過去の集団の特徴(例:白血球除去施行前)は現在の輸血を介した伝播が稀であることを示している。	7

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100034	2009/10/26	90666	HIV	Nature Medicine 2009; 15: 871-872	2001年以降、フランスのレファレンス研究所はHIVの遺伝子多様性を調査しており、2004年に血清検査でHIV陽性であった62歳の女性の血清試料(RBF168)を分析した。この血清は女性がカメルーンからパリに移住したすぐ後に採取された。女性は現在AIDSの症状はない。RBF168からウイルスを分離し、ウイルス遺伝子を解析した結果、RBF168はゴリラのサル免疫不全ウイルス(SIVgor)と最も近縁であった。この新しいウイルスは新しいHIV-1のプロトタイプであると思われるが、HIV-1のグループM,N,Oとは異なり、グループPと命名された。RBF168株が発見される前は、HIVグループOが最もSIVgorに近縁であったが、変異の大きさから、現在のSIVgorから直接出現したのではなく、SIVgorのゴリラからヒトへの伝播が起因していると考えられた。これらの結果より、HIVの感染源としてチンパンジーに加えてゴリラが示された。	8
100022	2009/10/1	90550	HIV	Pediatrics 2009; 124: 658-666	米国において9、15および39ヶ月の子供3例は、臨床症状から検査が行われた結果、HIV感染と診断された。2例については、母親がHIV感染者であるが、母乳は与えず、また周産期感染は否定された。3例目は、母親ではなく養育していた叔母がHIV感染者であった。全例とも、HIV感染者である養育者が食べ物を噛んで与えており、2例では噛み与えた大人に口腔内出血があった。EnvのC2V3C3またはgp41コード領域とgagのp17コード領域を用いた系統発生解析の結果は、3例中2例は養育者の噛み与えによってHIV感染が起きたという疫学的結論を支持した。	9
100022	2009/10/1	90550	HIV	第83回日本感染症学会総会 2009 April 23-24; 314	名古屋医療センターにおいて、4例にHIV-2の感染が疑われた。HIV抗体陽性かつ血中HIV-1RNAコピー数が検出限度以下を示した4例(外国籍男性3例、日本国籍女性1例)の末梢血白血球より抽出したDNAを鋳型にPCRによりgagおよびenv領域の増幅後、遺伝子配列を決定した。4例中3例はHIV-2であることを確認し、日本国籍女性については確定診断に至らなかった。解析に成功した3例の内、1例はサブタイプA,他の2例はサブタイプ判定には至らなかった。日本国内においてもHIV-2 のスクリーニングを強化する必要がある。	10
100022	2009/10/1	90550	HTLV	47 news. 2009 Jun 27	厚生労働省研究班は2006-2007年に初めて献血した全国約119万人を対象に、HTLV-1の調査を実施し、3787人の感染が確認され、国内感染者数は約108万人と推計した。約20年前の前回調査の120万人と比べて大きな変化はなかった。研究班班長である山口一成国立感染症研究所客員研究員は、感染者の地域別割合の高かった九州で減少し、大都市圏(関東・中部・近畿)で増加したが、これは感染者が多い九州からの人の移動が背景にあると指摘した。	11
100057	2009/11/2	90717	Q熱	Eurosuveilance 2009; 14(19); 2009 May 14	オランダは2007および2008年のアウトブレイク後再びQ熱報告が2009年4月から急増し、1月1日-5月11日の間、総計345症例が報告された。男女比は約1.7:1で、年齢中央値は49(38-61)歳であった。ほとんどの患者が2007および2008年の報告と同様、Noord-Brabant地方の同地域の住民であるが、感染領域は拡大傾向にある。オランダにおけるQ熱の主な臨床症状は肺炎であり、2008年に報告された患者は、545例が肺炎、33例が肝炎、115例が他の発熱性疾患を発症した。Noord-Brabant地方には大規模なヤギ農場が集中しており、流産の増加している農場が発生源と疑われる。小型反芻動物へのワクチン接種義務化が始まっており、2010年には効果が出ると考えられる。	12
100057	2009/11/2	90717	アメリカ・トリパノソーマ症	CBER (http://www.fda.gov/cber/gdlns/chagas.htm)	CBERから、輸血用全血、血液成分製剤、ヒト細胞・組織及びヒト細胞・組織由来製剤のTrypanosoma cruziが伝播する危険性を低減するための血清学的検査実施についてのガイダンス案を公表。	

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100057	2009/11/2	90717	アメリカ・トリパノソーマ症	Emerg Infect Dis 2009; 15:653-655	ブラジルで2006年1～11月に発生したアメリカ・トリパノソーマ症のアウトブレイク(178症例)について、調査の結果、アサイー果実を潰す際に、原虫を媒介するサシガメの排泄物が混入した可能性が考えられた。	
100009	2009/9/28	90527	アメリカ・トリパノソーマ症	FDA Guidance for Industry(draft) "Use of Serological Tests to Reduce the Risk of Transmission of Trypanosoma cruzi Infection in	Trypanosoma cruzi抗体検出用のELISA検査システムがCBERにより許可されたことをうけ、米国において、全血、血液成分及びHCT/Psにおけるトリパノソーマ症伝播のリスク低減のためのドナースクリーニングについて、FDAよりドラフトガイダンスが公表された。最終版発表後1年以内にこのガイダンスに適合することが推奨されることとなる。	13
100057	2009/11/2	90717	アメリカ・トリパノソーマ症	ProMED-mail20090406.1328	ベネズエラでグアヴァジュースの摂取によるアメリカ・トリパノソーマ症のアウトブレイクが発生し、同学校に通う児童47名と教師3名が感染。児童3名が死亡。	
100009	2009/9/28	90527	ウイルス感染	N Engl J Med 2009; 360: 2099-2107	New Yorkの62歳の男性は、シカダニウイルスに感染したシカダニの咬傷後に髄膜脳炎で死亡した。これまでシカダニウイルスのヒト感染は報告されていないが、この症例はシカダニウイルスが致命的脳炎の原因でありえることを示している。	
100009	2009/9/28	90527	ウイルス感染	PLoS Pathogens 2009; 4; e1000455	2008年に南アで発生した致死性出血熱のアウトブレイクにおいて、30年ぶりに新規の旧世界アレナウイルスが分離された。発見された地名(Lusaka, Johannesburg)より、Lujo virusと命名された。	14
100003	2009/9/17	90498	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。	
100022	2009/10/1	90550	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。	
100034	2009/10/26	90666	ウイルス感染	ProMED-mail20090806.2782	2009年8月4日、ブラジルMazagaoで過去3ヵ月間に657例がオロポーチ熱に感染した事を当局は発表した。このうち29例はIEC(Instituto Evandro Chagas)によって確定診断がなされ、この病気の原因はCulicoides属ヌカカによる刺咬であると分かった。症状はデング熱やマラリアに似ており、発熱、頭痛および全身性筋肉痛である。初発例は2009年3月に発生し、4月および5月には報告が激増し、MazagaoのVelhoおよびCarvaoで600を超えた。オロポーチウイルスはブラジルで2番目のアルボウイルス熱の原因ウイルスであり、ブラジルでは過去30年間に約50万人の発熱例が起きている。オロポーチ熱のアウトブレイクはアマゾン地域でのみ報告がある。	15
100040	2009/10/27	90673	ウイルス感染	Virilogy blog 2009 May 29	2008年に南アで発生した致死性出血熱のアウトブレイクにおいて、30年ぶりに新規の旧世界アレナウイルスが分離された。発見された地名(Lusaka, Johannesburg)より、Lujo virusと命名された。	

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100022	2009/10/1	90550	ウイルス感染	日本感染症学会第83回総会 P224 O-171	2007年に初めて報告された新興感染症コウモリオルソレオウイルス(別名:マラッカウイルス)による急性上気道炎の報告である。2007年11月にインドネシア・バリ島から帰国した男性は帰国数日前から発熱、関節痛が出現し、帰国後も強い上気道炎症を呈し、オルソレオウイルス感染症と判明した。本ウイルスはコウモリを宿主とし、本患者はコウモリとの接触はなかったが、渡航先で上気道症状を呈する現地住民との接触があった。本患者では回復期に抗体が検出されたが、他の接触者は全て陰性であった。	16
100022	2009/10/1	90550	ウエストナイルウイルス	CDC (http://www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount08_detailed.htm)	2008年、米国におけるウエストナイルウイルス感染症例は46州から1356例が報告され、うち687例では脳炎や髄膜炎を発症、死亡に至ったのは44例だった。	
100057	2009/11/2	90717	細菌感染	第83回日本感染症学会総会 2009 April 23-24; 224 O-172	2002-2003年に高知県で日本紅斑熱が疑われた患者18名の保存血液を解析した結果、2名からヒトアナプラズマ(Anaplasma phagocytophilum:A.p.)に特異的なp44/msp2遺伝子が検出され、ヒトアナプラズマ症の国内における存在を初めて確認した。1例はヒトアナプラズマ症で、もう1例はA.p.と日本紅斑熱リケッチア(Rickettsia japomicar.R.j)の混合感染症であった。	17
100003	2009/9/17	90498	細菌感染	日本細菌学会第82回総会 P2-182 (2009 March 12,13,14)	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。	
100003	2009/9/17	90498	レトロウイルス	第56回日本ウイルス学会 2008 October 27 2P111	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。	
100022	2009/10/1	90550	感染症	第57回日本輸血・細胞治療学会 2009; 55; 245	日本赤十字社が2008年に収集し、報告した輸血関連感染(疑)症例149例の現状と解析結果である。149例の病原体別内訳は、HBV61例、HCV38例、細菌46例、HEV2例、HIV1例およびCMV1例であった。HBV4例、HEV2例および細菌2例については献血者検体から病原体を検出し、いずれも輸血と感染症との因果関係は高いと評価された。また、輸血後B型肝炎を発症した1例は、劇症肝炎により死亡した。日赤では2008年8月よりCLEIA法および新NATシステムを導入し、安全性の向上に努めている。	18
100009	2009/9/28	90527	インフルエンザ	CDC/MMWR 2009; 58: 1-3	2009/4/17米CDCはカリフォルニア南部の小児2例の熱性呼吸器疾患をブタインフルエンザA(H1N1)感染であると特定した。アマンダジン、リマンダジンに抵抗性があり、過去に報告されていない固有の遺伝子断片の組み合わせが含まれていた。ブタ接触歴は無く感染源は不明。	
100022	2009/10/1	90550	インフルエンザ	Virus Res. 2009; 140; 85-90	中国のブタからヒト様H1N1インフルエンザウイルスが検出され、ブタがヒトにおけるパンデミックを引き起こす古典的なインフルエンザウイルス保有宿主である証拠が示された。	

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100022	2009/10/1	90550	新型インフルエンザ(H1N1)	N Engl J Med 2009; 360; 2605-15	4月15日から5月5日の間、米国の41州において、総計642症例からヒトにおける新規ブタインフルエンザA(H1N1)ウイルスの感染を確認した。	19
100064	2009/11/26	90745	新型インフルエンザ(H1N1)	The Canadian Press 2009 September 16	オーストラリアの研究グループは新型A1N1ウイルスに感染し重症となった妊婦では、ウイルスと戦い、体がワクチンに反応する助けとなる、特定の抗体が低値である事を発見した。ICUで治療中のブタインフルエンザ感染患者すべての抗体レベルを個々のサブタイプまで調べた結果、IgG2のレベルが低値であった。妊婦女性についてのみ調べた結果であるが、このIgG2欠損が、ほとんどの人はインフルエンザ症状のみで治癒するが少数例は危篤となる理由が説明できる可能性がある。	20
100005	2009/9/28	90523	新型インフルエンザ(H1N1)	CBER 2009 April 30	新型インフルエンザ(H1N1)の輸血を介した感染可能性について。輸血により季節性インフルエンザに感染した例はこれまで報告されたことが無く、新型インフルエンザについても報告されていない。現時点で、輸血のメリットは新型インフルエンザの理論的リスクをはるかに上回る。なお、血漿分画製剤については製造工程におけるクリアランスが十分であることが確認されている。	
100009	2009/9/28	90527	新型インフルエンザ(H1N1)	CDC/MMRW 2009; 58: 521-524	05～06年、06～07年、07～08年の季節性インフルエンザワクチン接種コホートの保存ペア血清を用いて、新型インフルエンザウイルスの交差反応性を検討した。18-64歳ではワクチン接種前に6～9%、60歳以上では3%が交差反応を示した。ワクチン接種後には交差反応を示した例が18-64歳で2倍程度に増え、60歳以上では全く増えなかった。	
100003	2009/9/17	90498	新型インフルエンザ(H1N1)	CDC/MMWR 2009; 58: 1-3	2009年4月、南カリフォルニア周辺郡の小児2人がブタインフルエンザA(H1N1)ウイルスに感染した。2症例から検出されたウイルスは、米国やそれ以外の国でも報告されたことがないブタ又はヒトインフルエンザウイルスの遺伝子片を併せ持っていた。いずれの小児もブタとの接触はなく、感染源は不明である。	
100009	2009/9/28	90527	新型インフルエンザ(H1N1)	CDC/MMWR 2009; 58; 773-778	2009年5月28日、Dallas County Department of Health and Human Services (DCHHS)は5月18-28日に、ダラス郡(County)内で入院した、新型インフルエンザA感染に関連した神経系の合併症を伴う4例の小児についてCDCに報告した。これまで季節性インフルエンザの気道感染に関連した神経系の合併症は報告されているが、新型インフルエンザに関しては報告がない。患者は7, 10, 11および17歳であり、ILI(influenza-likeillness: インフルエンザ様症状)の症状と痙攣もしくは精神状態の変化のため入院し、3例に脳波に異常が認められた。また、4例すべてに新型インフルエンザA(H1N1)ウイルスRNAが鼻咽頭検査では認められ、脳脊髄液からは認められなかった。4例すべては回復し、神経学的後遺症はなかった。	21

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100040	2009/10/27	90673	新型インフルエンザ(H1N1)	CFIA 2009 April 26	CFIA(Canadian Inspection Agency)はこれまでに米国南部やメキシコで発生したブタインフルエンザのヒト症例を報告してきた。今日までの情報は、ウイルスのヒト間での伝播が起きていることを示しており、PHAC(Public Health Agency of Canada)はこの状況に対するカナダ国民の応答を取りまとめており、CFIAは要求に応じたサポートや専門知識を提供している。現時点では、カナダのブタに病気や死亡の増加を示す兆候はないが、CFIAは生産者、獣医師や研究所に監視を強化し、ブタの病気を報告するよう要請している。ブタにおける疑わしい例は獣医師、州当局もしくはCFIAに報告し、重篤なインフルエンザ様症状を呈するヒトは医療従事者に連絡するよう推奨している。	22
100022	2009/10/1	90550	新型インフルエンザ(H1N1)	Eurosurveillance 2009; 14; 19244	2009年5月から6月における日本のインフルエンザA(H1N1)感染に関する疫学的な特徴がまとめられた。日本の16の都道府県から、インフルエンザA型(H1N1)ウイルス確定症例が合計401例報告された。最も感染の多かった2地域は、高校でアウトブレイクが発生し休校に至った大阪市および神戸市であり、6月4日までにこの2県で357例の感染が報告され、64%が15-19歳、10%が10-14歳であり、60歳以上は1%であった。既知の臨床症状が確認された217例の約90%はオセルタミビルもしくはザナミビルを投与され、2009年6月4日現在、重症患者および死亡例の報告はない。インフルエンザA(H1N1)に感染した患者の病状の程度は季節性インフルエンザと同程度であった。	23
100040	2009/10/27	90673	新型インフルエンザ(H1N1)	ProMEDmail-20090630.2359	2009年6月29日、ロッシュ社はデンマークにおいてH1N1インフルエンザに感染した患者がタミフル治療に抵抗性を示した事を報告した。ブタインフルエンザでは初症例である。H1N1のタミフル耐性株が蔓延している兆候はなく、2009年にタミフル耐性株が出現し、広く蔓延している季節性H1N1インフルエンザとは対照的である。英国HPA(Health Protection Agency)においても新型インフルエンザのアウトブレイク当初から抗ウイルス薬耐性株の監視を行っているが、英国での定型調査では、オセルタミビルもしくはザナミビル耐性は検出されていない。	24
100009	2009/9/28	90527	新型インフルエンザ(H1N1)	Sience 2009: 10.1126/SCIENCE.1176062	新型インフルエンザA(H1N1)ウイルスは世界中に急速に広まっている。パンデミックの可能性を判断するのはデータが限られているため難しいが、適切な保険対応を伝えるには必須である。メキシコでの大流行、国際的な広がりの早期情報およびウイルス遺伝的変異について分析することにより、感染力と重症度の早期評価を実施した。	
100040	2009/10/27	90673	新型インフルエンザ(H1N1)	WHO 2009 June 11	2009年6月11日、WHO事務局長Margaret Chan博士は声明を発表した。WHOはインフルエンザパンデミックの警戒レベルをフェーズ5から6に引き上げ、世界は2009インフルエンザパンデミックの始まりにある。各国は高い警戒態勢を維持し、感染防御の実施などについて協力するよう呼びかけた。	25
100061	2009/11/18	90726	新型インフルエンザ(H1N1)	農林水産省 新型インフルエンザに関する報道発表資料 2009 October 21	2009年10月21日、農林水産省は大阪府の養豚農場のブタから分離されたウイルスが新型インフルエンザであることを発表し、当該農場に対し、臨床検査および遺伝子検査により異常がないことを確認するまで飼育ブタの移動を自粛するよう要請した。(独)農研機構動物衛生研究所がHおよびN亜型検査(遺伝子解析)を実施した結果、本ウイルスはH1N1亜型であり、新型インフルエンザと同一である事を確認した。	26
100002	2009/9/16	90479	新型インフルエンザ(H1N1)	共同通信HP 2009 April 28 / WHO 2009 April 28	WHOは新型インフルエンザのPandemic Alertをフェーズ4に引き上げた。	

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100003	2009/9/17	90498	新型インフルエンザ(H1N1)	厚生労働省 新型インフルエンザに関する報道発表資料 2009 May 16	兵庫県神戸市における新型インフルエンザ(インフルエンザA／H1N1)が疑われる患者発生についての報告。国内最初の新型インフルエンザ患者が確認された。患者は10代後半の男性。本人に渡航歴はない。国立感染症研究所からの検査の結果、A型(＋)、ヒトH1(−)、ヒトH3(−)、新型H1(+)であったため、新型インフルエンザ(インフルエンザA/H1N1)が否定で、新型インフルエンザが疑われる患者として神戸市に届出があった。患者は感染症法に基づき、神戸市内の感染症指定医療機関に入院した。	
100009	2009/9/28	90527	コクシジオイデス症	CDC/MMWR 2009; 58: 105-109	カリフォルニア州におけるコクシジオイデス症の報告数及び入院数は2000～2006年の間毎年増加しており、1995～2000年の3倍以上(8/10万人)となった。米国のコクシジオイデス症全体の約60%を占めるアリゾナ州でも同様で、2006年には5,535例(91/10万人)と増加している。米国全体でも、1996年の1,697例から2006年には8,917例(6.97/10万人)に増加しており、流行地への訪問や居住歴のあるインフルエンザ様症状や肺炎、播種性感染症の患者では本症が鑑別されるべきである。	
100003	2009/9/17	90498	コレラ	CDC/Travelers' Health 2009 February 4 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。	
100022	2009/10/1	90550	チクングニヤウイルス感染	CDC 2009 August 17	2009年8月17日、米国CDCはアジアでのチクングニヤ熱のアウトブレイクに注意喚起をした。2009年1月以降、クングニヤ熱症例数の増加がアジアの一部で報告されている。チクングニヤ熱は感染した蚊を介してもたらされるウイルスによって発症し、突発性発熱、関節痛、悪寒、頭痛、吐き気や発疹などを伴う。タイでは2009年7月22日現在、南部でアウトブレイクが起こり、34，200超の症例(死亡例なし)を報告した。マレーシアでは2009年7月18日現在、2900症例の発症を報告し、インドでは2009年4月29日現在、2700例の疑い症例(死亡例なし)が報告された。渡航者へのアドバイスとして、チクングニヤ熱を防ぐ薬物治療やワクチンはないため、CDCは、虫除けを使用し、蚊にさされないよう自己防衛し、発症を自覚した際には、医療機関を受診するよう奨めている。	27
100057	2009/11/2	90717	バベシア症	2009 Feb 23; New York City, Department of Health	2008年9月以降の6ヶ月間、ニューヨーク市において輸血関連バベシア症の報告急増。市衛生局は医療従事者に対し、3ヶ月以内に輸血又は臓器移植の既往歴があり、発熱/溶血性貧血を呈する患者の鑑別診断にバベシア症を考慮するよう勧告した。	
100009	2009/9/28	90527	パルボウイルス	Transfusion (Malden) 2009; 49: 1488-1492	米国において、パルボウイルスB19(B19V)のGenotype3がアメリカ人供血者から初めて検出された。B19Vを検出するための広範囲な特異性のあるPCRを用い、81,000人以上の供血者から集めた約440,000の臨床サンプルを調べ、更にはB19Vタイタ-とDNA解析および抗体濃度を調べた。この評価の結果、DNA配列分析によってB19VGenotype3に感染していると確認された米国人1人のドナーから28日の間に8回の血漿ドネーションを行っていることが明らかとなった。ウイルス価はピーク時で1011IU/MLを示し、下がるに遅れてIgMレベルが上昇し、IgGレベルは約7日遅れて上昇した。	28

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
100005	2009/9/28	90523	ヒトパルボウイルス	FDA/CBER Guidance for Industry 2009 July	FDAが血漿由来製品の製造業者向けに提供するガイダンス。血漿由来製品の製造に使用される原料血漿および転用血漿用の製造過程において、ヒトパルボウイルスB19を検出するための核酸増幅検査(nucleic acid test;NAT)を行う事を推奨している。すべての血漿由来製品について、製造プール中のパルボウイルスB19DNAのウイルス負荷が10000IU/mLを超えない事を保障するために、 ○すべての血漿由来製剤に対し、製造用プール血漿中のHPV B19 DNAの濃度が10^4 IU/mLを超えないように、工程内検査としてHPVB19 NATを実施すべきである。 ○血漿由来製剤の製造に投入する血漿ユニットのスクリーニングには、ミニプールサンプルに対してHPV B19 NATを実施すること。HPV B19 NATで用いるプライマーおよびプローブは、このウイルスの既知のすべての遺伝子型を検出できるものを用いること。 ○ 血漿由来製剤の製造に投入する血漿ユニットに、製造用プール血漿のHPV B19 DNA濃度が10^4IU/mLを超えるような高値を示すものが見つかった場合は、当該血漿ユニットは使用しないこと。	29
100003	2009/9/17	90498	マラリア	CDC/MMWR 2009; 58; 229-2	近年、5番目のマラリア原虫として、サルマラリアであるPlasmodium knowlesiのヒトへの感染例がマレーシア及びその周辺において多数確認されており、人畜共通感染症の病原体として新興している可能性が示されている。	
100084	2009/11/26	90745	マラリア	Clinical Infection Deiseases 2009; 49; 852-860	ヒトにおけるPlasmodium knowlesi感染の臨床的な特徴および検査結果を調べる目的で、急性P. knowlesi感染患者の背景と経過について系統的に調べ、2006年7月-2008年2月に、Kapit病院でPCRにより急性マラリアと確定された、治療歴の無い非妊娠成人から臨床データおよび検査結果を収集した。152例のうち、P.knowlesi、P.falciparumもしくはP.vivaxに感染した症例は107(70%)、24(16%)および21(14%)であり、非特異的発熱症状のあるP.knowlesi感染患者の入院時寄生虫値の中央値は1387parasite/ulであり、全例が血小板減少を示した。ほとんどのP.knowlesi感染患者には合併症はなく、クロロキンおよびプリマキン治療で治癒した。WHOの熟帯性マラリアの判断基準により7人は重症であった。入院時のP.knowlesi寄生虫血症は呼吸困難の独立した決定因子であり、入院時の血清クレアチニンレベル、血清ビリルビンおよび血小板数と同様であった。2例のP.knowlesi感染患者が死亡し、死亡率は1.8%(95%信頼区間、0.2-6.6%)であった。P.knowlesiは広範囲の疾病を引き起こすが、多くの場合合併症伴わず、治療に速やかに反応し、約10人に1人が死亡を伴う合併症となる。	30
100009	2009/9/28	90527	リケッチア症	第83回日本感染症学会総会 2009 April 23-24	平成20年8月、仙台市においてリケッチア症を疑う患者が発生した。生検材料を用いたPCRにより陽性であったが、シークエンス解析により、ロシアや中国の患者から報告されているR.heilomgiangensisに一致した。国内に、日本紅斑熱とは異なる紅斑熱ケッチア症が存在することが示された。	
100002	2009/9/16	90479	レンサ球菌感染	日本化学療法学会第57回総会 201	50代後半の男性が右母指のウオノメをカッターで自己切除したところ黒変し、その範囲は急速に拡大。右下肢の腫脹が起こり入院。右母指には悪臭と壊疽を伴う重度の蜂巣炎、X線所見で右大腿部にガス像を認めた。Streptococcus dysgalactiae subsp. dysgalactiaeによる初めてのヒト感染例と考えられる。	

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
100022	2009/10/1	90550	BSE	OIE (http://www.oie.int/eng/info/en_esbmonde.htm.)	1989年から2008年までに、世界各国(英国を除く)から国際獣疫事務局(OIE)に報告されたBSEの報告数である。	
100022	2009/10/1	90550	BSE	OIE (http://www.oie.int/eng/info/en_esbru.htm.)	1987年以前から2008年までに、英国から国際獣疫事務局(OIE)に報告されたBSEの報告である。	
100013	2009/9/29	90532	クロイツフェルト・ヤコブ病	Transfusion 49(5) ; 977-984	米国での調査研究の結果は、輸血によるCJD伝播については根拠に欠けるとしている。2004年以降、英国ではvCJDの輸血による伝播が報告され、変異型でないCJDもしくは古典的CJDの伝播のリスクについて懸念が高まってきた。1995年、米国赤十字社はCDCと共同で輸血によるCJD伝播の懸念を評価する詳細な疫学的データを得るために、供血後にCJDと診断された供血者(CJDドナー)の長期後ろ向き調査を開始し、CJDドナーの血液成分を投与された受血者を特定した。本結果からは、CJDの輸血による伝播を示す根拠は示されなかった。CJDドナーによる異常プリオンの輸血伝播のリスクは、vCJDドナーによる伝播のリスクと比べて顕著に低いことを後押しする結果となった。	
100022	2009/10/1	90550	クロイツフェルト・ヤコブ病	Transfusion Epub 2009 January 5	米国。輸血のCJD伝播リスクについて。後にCJD発症した供血者36例と受血者436例を調査。受血者のうち生存91例、死亡329例、不明16例。受血後にCJDを発症した例は特定されず。	
100022	2009/10/1	90550	異型クロイツフェルト・ヤコブ病	BMJ 2009 May 21	英国イングランドおよびスコットランドで扁桃摘出術により摘出された匿名の扁桃腺検体を対象に、プリオンプロテイン(PrPCJD)に関連した陽性率をcross sectional opportunistic survey (随時横断調査)により調査した。2008年9月末までに63,007の検査を行い、このうち12,753検体は最もvCJDが発症した1961-85年の出生コホート由来であり、19,908検体はBSEに曝露された可能性のある1986-95年コホートから集められた。2種類の酵素免疫法両方に明確に陽性を示す検体は無く、276検体はいずれかの検査に初回陽性を示し、その繰り返し陽性率は15%であった。免疫組織化学法もしくは免疫ブロット法を行った結果、この276検体を含め、陽性を示す検体はなかった。1961-85年の出生コホート由来の扁桃検体におけるPrPCJD陽性率は0/32661であり、1961-85年の出生コホート由来については、0であり、過去の虫垂組織の調査結果よりは低かったが、矛盾はなかった。	31
100009	2009/9/28	90527	異型クロイツフェルト・ヤコブ病	Department of Health 2009 June 5	血友病患者の脾臓中に異常プリオン蛋白質が発見されたことを受け、CJD事故委員会の要請により「vCJD Risk Assessment Calculations for a Patient with Multiple Routes of Exposure」報告書がDepartment of Healthによって作成された。感染可能性のある種々の経路を設定し、それぞれの相対的な感染確率を検討した報告である。	32

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
100040	2009/10/27	90673	異型クロイツフェルト・ヤコブ病	EMEA CPMP 2009 July 23	2009年7月23日、EMA(EMEA)は「CJDと血漿・尿由来医薬品に関するCHMPの見解書(CHMP position statement)」を改訂する必要性についてconcept paperを発表した。このCHMP 見解書が最後に改訂されたのは2004年6月であり、2004年以降、白血球非除去赤血球輸血と関連した4例のvCJD感染や、動物モデルにおける尿中に検出されたTSE感染性など、更なるエビデンスが蓄積してきた内容について改訂する。また、後にvCJDを発症した供血者由来の血液製剤を投与された血友病患者の膵臓に異常プリオン蛋白が検出されが、その調査結果も考慮する必要がある。2005および2007年にEMEAで開催されたCJDと血漿・尿由来医薬品に関する会議結果も今回の改訂に盛り込む。更に、血漿由来医薬製品のリスク評価に影響を及ぼす今後の状況についても考慮する。改訂されたCHMP意見書は3ヶ月間の意見公募を経て2010年に適用される。	33
100009	2009/9/28	90527	異型クロイツフェルト・ヤコブ病	FDA TSE advisary committee 2009 June 16	英国でvCJDに関連した凝固因子製剤を11年前に投与された血友病患者のvCJD感染の報告を受けて、米国におけるリスク管理戦略を再評価した。その結果は、米国で承認されている第Ⅷ因子製剤からのvCJD感染のリスクは極めて低いと考えられるが断言はできない、という従来と同様の評価である。	34
100003	2009/9/17	90498	異型クロイツフェルト・ヤコブ病	HPA 2009 February 17	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。	
100009	2009/9/28	90527	異型クロイツフェルト・ヤコブ病	HPA 2009 May 22	2004年にHealth Protection Agencyは扁桃腺に蓄積されたvCJD関連プリオンタンパク質の大規模な調査により、無症候性vCJD保有率を検討するNational Anonymous Tissue Archive(NATA)を開始。既に63000例の扁桃腺組織の収集・解析を行っており、100000例まで収集する計画であるが、現在のところ陽性サンプルは一つもなかった。	
100009	2009/9/28	90527	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。	
100022	2009/10/1	90550	異型クロイツフェルト・ヤコブ病	Nature 2009; 457: 1079	最近、非定型BSEが日本、カナダ、米国、複数のヨーロッパ諸国で発生している。非定型BSEの可能性があるプリオン遺伝子の突然変異は豪州や新西蘭でも発生する可能性があり、反芻動物の厳密な飼料管理等、将来のアウトブレイクの防止に必要な規制を緩和すべきではない。	
100022	2009/10/1	90550	異型クロイツフェルト・ヤコブ病	ProMED-mail20090108.0076	英国CJDサーベイランスユニットの統計によると、2009年1月5日時点でvCJD死亡患者数総数には変化はなく167例のままであり、英国におけるvCJD流行は減少しつつあるとする見解に一致する。	

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
100009	2009/9/28	90527	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。	
100040	2009/10/27	90673	異型クロイツフェルト・ヤコブ病	Vox Sanguinis 2009; 97: 226-233	異常プリオン蛋白(PrPsc)に特異的に結合するリガンドを用いた新しいクロマトグラフィ法が開発された。vCJD(variant Creutufeldt-jakob)伝播リスクの観点から安全性を向上させるために、SD(solvent/detergent)処理された血漿分画製剤OctaplasLGの製造過程に本法を導入し、PrPsc除去効果を調べた。Octaplas製造の途中および最終製品にPrPscが含まれた脳ホモジネートをスパイクし、リガンドゲル1mL当りのbinding capacity(結合能)およびヒト由来PrPscに対するリガンドゲルの特異性を調べた。PrPscの検出および定量にバリデートされたWestern blot法が用いられた。その結果、reduction factor(RF)は≧3.0log10であり、ゲルのPrPsc結合能は≧6log10ID50/mlと非常に高かった。また、ゲルは動物(ハムスターとマウス)およびヒト(sporadicおよびvariant CJD)由来であるPrPscに特異的に結合する。この新しいPrPsc除去ゲルはOctaplasLGからvCJDの病原因子を除去できる非常に高い性能を示した。	35

別紙様式第2-1

No. 1

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 5. 18	該当なし	
一般的名称	人血清アルブミン					
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)		研究報告の公表状況	Tortajada C, de Olalla PG, Pinto RM, Bosch A, Cayla J. Euro Surveill. 2009 Apr 16;14(15). pii: 19175.	公表国 スペイン	

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
○2008年9月～2009年3月に発生したスペインのバルセロナにおける男性と性的関係を持つ男性(MSM)間のA型肝炎のアウトブレイク 2008年9月1日～2009年3月9日の期間に、バルセロナにおいてA型肝炎症例150例が報告され、これは過去2年間の同期間と比較して3倍に増加した。ほとんどの症例は、MSMであることを報告した87名を含む、成人男性に発生した。以上のことは、MSM集団にアウトブレイクが発生中である可能性を示し、このコミュニティを標的とした有効な予防接種プログラムの必要性を強調している。	赤十字アルブミン20 赤十字アルブミン25 赤十字アルブミン20%静注4g/20mL 赤十字アルブミン20%静注10g/50mL 赤十字アルブミン25%静注12.5g/50mL 血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
2008年9月1日～2009年3月9日の期間に、スペイン、バルセロナにおいてA型肝炎症例150例が報告され、MSM集団におけるアウトブレイクの可能性が示されたとの報告である。 これまで、本製剤による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製剤の安全性は確保されていると考える。	本製剤の安全性は確保されていると考えるが、本製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。また、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。

別紙2

JRC2009T-025

Rapid communications

Outbreak of hepatitis A among men who have sex with men in Barcelona, Spain, September 2008 – March 2009

C Tortajada (ctortaja@aspb.cat)[1], P G de Olalla[1], R M Pinto[2], A Bosch[2], J Cayla[1]
1. Public Health Agency of Barcelona, Barcelona, Spain
2. Enteric Virus Laboratory of the Department of Microbiology of the University of Barcelona, Barcelona, Spain

Between 1 September 2008 and 9 March 2009, 150 cases of hepatitis A were reported in Barcelona, representing a threefold increase compared with the same period in the previous two years. The majority of the cases occurred in adult men, including 87 who reported having sex with men. This indicated the possibility of an outbreak ongoing in the population of men who have sex with men (MSM) and emphasised the need to target this community with more effective vaccination programmes.

Introduction

In Spain, hepatitis A is a reportable disease defined by acute hepatitis symptoms combined with the presence of immunoglobulin M antibodies to hepatitis A virus (IgM anti-HAV) [1]. Physicians and laboratories report cases to the local public health agencies. The Public Health Agency of Barcelona is the relevant office for the city of Barcelona, covering a population of 1,600,000 inhabitants. The Health Department of the Government of Catalonia collects cases from all the regional agencies of Catalonia and reports them to the National Centre of Epidemiology in Madrid.

Since September 2008, an increase in the number of reported cases of hepatitis A in the municipality of Barcelona has been observed. Between 1 September 2008 and 9 March 2009, a total of 150 confirmed cases of hepatitis A were reported from the area. In the same period in 2006-7 and 2007-8 the numbers of notified cases were 54 and 55 respectively.

The notification data indicated that the increase may affect predominantly men who have sex with men (MSM). An outbreak alert was raised after five cases had been notified in one day, including four men aged 23-25 years of whom three were known to be MSM. For comparison, in the previous two years, the average number of notifications ranged from 0 to 12 cases per month. This prompted us to undertake a survey among the reported adult male cases, to determine whether they belonged to the group of MSM and whether they engaged in activities associated with an increased risk of hepatitis A infection [2-5].

The outbreak is still ongoing and notifications occur at a frequency of one case per day.

Methods

For the purpose of the outbreak investigation, a case was defined as a man over 18 years old who had sex with men, was resident in Barcelona city and had symptoms of acute hepatitis with onset from 1 September 2008 and positive result of IgM anti-HAV test.

To identify cases according to the above definition, all reported hepatitis A patients who were male and older than 18 years, resident in Barcelona city and had symptoms onset from September 2008 were interviewed with a modified questionnaire based on the standard questionnaire for hepatitis A of the Health Department of the Government of Catalonia but with additional questions on sexual behaviour. The interviews were done by telephone or e-mail. Cases that had been reported before the outbreak alert but could fulfil the case definition criteria were re-interviewed retrospectively, using the modified questionnaire.

Questions included having sex with men, number of sexual partners, visiting bathhouses, bars and discos, use of the internet to look for sexual partners, having group sex, and working as sex worker during the two months before symptoms onset, as well as hepatitis A immunisation status and infection with human immunodeficiency virus (HIV).

Contact-tracing was performed according to standard procedures, as done routinely by the local Public Health Agency for every case of hepatitis A reported. During the interview, the patient is asked to identify close contacts. These people are then contacted directly by the Agency and informed about the risk of infection and offered vaccination or postexposure prophylaxis. Vaccination and immunoglobuline is provided free of charge in the Agency offices or, in some cases, administered by healthcare workers visiting the contacts.

Sera from 14 cases who fulfilled the case definition were sent to the Enteric Virus Laboratory of the Department of Microbiology of the University of Barcelona for genetic analysis.

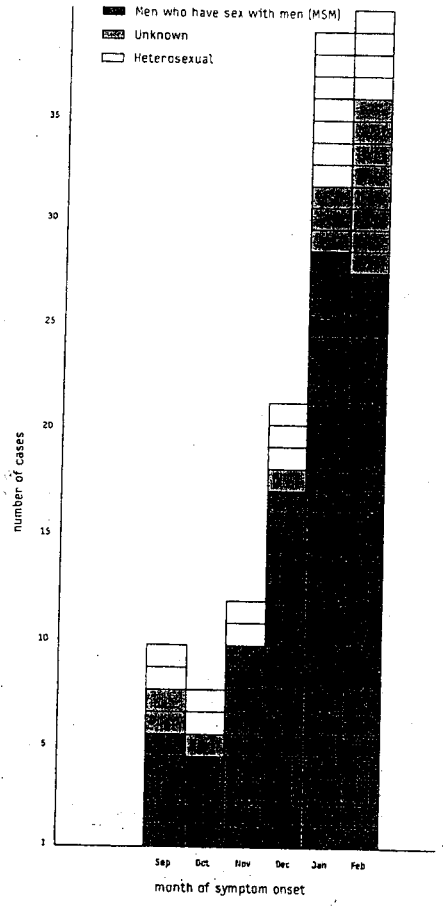
Results

From 1 September 2008 to 9 March 2009, a total of 150 laboratory-confirmed hepatitis A cases were reported. Of the 150 cases, 137 (91%) were older than 18 years, and of these, 126

(84% of the total) were men and 11 (7% of the total) were women. In the equivalent period in 2006-7, of the 54 hepatitis A cases reported, 29 (54%) were older than 18 years, including 21 (39%) men. Similarly, in 2007-8, there were 55 cases in total, 24 (43%) of whom were over 18 years old, including 13 (23%) men.

FIGURE

Number of cases of hepatitis A among men older than 18 years, by month of onset of symptoms and sexual behaviour, Barcelona, 1 September 2008 - 9 March 2009 (n=122, preliminary data)



Source of data: Public Health Agency of Barcelona, Spain

Of the 126 adult male patients, 107 were interviewed using the modified questionnaire. In response, 87 (69%) declared to have had sex with men and 20 (16%) defined themselves as heterosexual. For the remaining 19 notified cases (15%) this information was not available (Figure).

As a result, 87 persons fulfilled the case definition criteria. The median age of these cases was 33 (IC 95%: 31-34) years. Ten (11%) were HIV-positive. Only one had been vaccinated against hepatitis A and another one had received only one ddse of the vaccine.

A considerable proportion of MSM cases reported engaging in activities that may be associated with increased risk of infection. The mean number of sexual partners was four (IC 95%: 3-6), 14 cases (16%) used the internet to look for sexual partners, 26 (30%) frequented discos or bars and 19 (22%) visited bathhouses.

The virological analysis showed HAV genotype IA in sera obtained from 14 patients. The results of phylogenetic analysis are not available yet.

Control measures

Vaccination against hepatitis A of all cases' contacts and postexposure prophylaxis of close contacts and sexual contacts within 15 days of the last exposure has been recommended. Vaccination and immunoglobuline is offered free of charge in the Public Health Agency of Barcelona.

We performed contact-tracing and offered vaccination and immunoglobuline to those identified. In cases when patients did not have or did not want to give this information (address or telephone), we advised them to inform their partners and close contacts to get the vaccination or immunoglobuline.

In addition, we have also strengthened the existing recommendations for vaccination of MSM by distributing fliers and posters in collaboration with the Spanish "Coordinadora Gai-Lesbiana" a federation which coordinates the activity of gay non-governmental organisations (NGO) and other associations.

The vaccination program for hepatitis A and B in gay bathhouses, which has been in place in Barcelona since 2004, has been reinforced, as well, by increasing the number of visits of healthcare workers and by covering more establishments.

To raise awareness about the possible outbreak, e-mail alerts were sent to microbiology laboratories, local practitioners and hospitals to enhance notification.

Gay organisations were informed about the hepatitis A outbreak affecting MSM, and information about the outbreak was published on some gay websites.

Discussion

An increase in the number of reported hepatitis A cases in Barcelona has been observed since September 2008. Of the 150 cases reported between 1 September 2008 and 9 March 2009, 87 were identified as MSM.

An increase in the number of notifications has recently been observed in other regions of Spain, as well. The data available are from the period between week 36 of 2008 and week 4 of 2009. Andalucia has reported an increase from 175 and 125 cases for that period in 2006-7 and 2007-8, respectively, to 350 in 2008-9; Madrid has reported an increase from 95 and 75 to 230 and Castilla – La Mancha has registered an increase from 15 and 20 cases to 60 [6]. It is not clear whether these increases are due to outbreaks and whether they affect a particular risk group but investigations are ongoing.

In Spain vaccination for hepatitis A is not included in the routine immunisation schedule, but is recommended for certain risk groups, including MSM [7].

In recent years, 2002-3 and 2004, two outbreaks of hepatitis A among MSM, affecting 48 and 60 people respectively, were detected in Barcelona. Most of them (80%) were bathhouse users [data from the Public Health Agency of Barcelona, not published]. Similar venues have also been associated with hepatitis A outbreaks elsewhere in Europe [2-5]. The strain identified in the current outbreak is different from the one detected in the MSM outbreaks in 2002-3 and 2004.

Since 2004 a special vaccination programme for hepatitis A and B has been targeted at those who frequent gay bathhouses. Healthcare workers from the Public Health Agency of Barcelona visit these venues and offer information about hepatitis A, B, C and sexually transmitted infections (STI), perform rapid tests for HIV and administer vaccinations for hepatitis A and B. To date, 3,000 bathhouse guests have used this opportunity [data from the Public Health Agency of Barcelona, unpublished].

The scenario in the present outbreak seems to be different from the previous two outbreaks since only 22% of the cases identified as MSM were bathhouse users.

Interventions aimed at the sexual contacts of the cases were difficult to carry out since in a considerable proportion of the cases the partners could not be identified in the course of contact-tracing process.

All but two cases among MSM were unvaccinated. Vaccination of MSM could help to control this outbreak and is crucial in preventing future ones. Thus information campaigns and immunisation programmes which effectively reach the MSM community are needed.

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別紙様式第2-1

No. 5

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. 5. 18	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	Goldman M, Xi G, Yi QL, Fan W, O'Brien SF. Transfusion. 2009 Apr;49(4):648-54. Epub 2009 Jan 2.	公表国 カナダ	
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社)					

研究報告の概要

○入れ墨、ピアスに対する供血延期の再評価
背景:2005年8月に、カナダ血液サービスは、入れ墨や耳・体のピアスに関連する供血延期期間を12ヶ月から6ヵ月に短縮した。本試験では、この変更が血液の安全性および安定供給に及ぼす影響を評価した。
試験デザインおよび方法:最近の供血者40,000名を対象とした匿名郵送調査により、これら行為の実施率を調べた。National Epidemiology Donor Databaseを用いて、感染症(TD)マーカー率を算出した。TD陽性供血者とマッチする対象者間のリスク因子を比較する症例対照試験を実施した。供血延期率は、延期期間の変更前後に評価した。
結果:入れ墨、耳のピアス、ボディピアスの実施率は、それぞれ調査回答者の13.7%、53.6%、10.4%であり、最大0.7%の行為が過去6ヵ月間に行われていた。TDマーカー率は低く安定し、供血延期期間変更前は100,000供血当たり21.6、変更後は100,000供血あたり19.2であった。昔行った入れ墨はHCVリスクと関連付けられたが(オッズ比、5.43; 95%信頼区間1.82～16.2)、最近の入れ墨やピアスは、HCVまたはHBVのリスク因子でなかった。延期期間の短縮により、供血延期の件数は入れ墨で20%、ピアスで32%減少した。
結論:入れ墨およびピアスに対する供血延期期間の短縮後、検知できるほどの安全性に対する影響はなく、血液供給においては、期待値以下ではあるが、好ましい効果があった。現在の血液の安全性に及ぼす影響はごくわずかであることから、他の一時的供血延期の期間について再評価すべきである。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
カナダ血液サービスにおいて、入れ墨や耳・体のピアスに関連する供血延期期間を12ヶ月から6ヵ月に短縮した後、検知できるほどの安全性に対する影響はなく、血液供給においては、期待値以下ではあるが、好ましい効果があったとの報告である。	日本赤十字社では、輸血感染症対策として問診時に過去1年以内に入れ墨を入れた人は献血不適としている。ピアス穴を開けた人については、状況によって1ヵ月～1年間、粘膜を貫通している場合は無期限に献血延期としている。今後も情報の収集に努める。

(2)

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BLOOD DONORS AND BLOOD COLLECTION

Reassessment of deferrals for tattooing and piercing

Mindy Goldman, Guoliang Xi, Qi-Long Yi, Wenli Fan, and Sheila F O'Brien

BACKGROUND: In August 2005, the Canadian Blood Services decreased the deferral period for tattooing and ear or body piercing from 12 to 6 months. This study assessed the impact of this change on blood safety and availability.

STUDY DESIGN AND METHODS: The prevalence of these activities was assessed on an anonymous mail-out survey of 40,000 recent donors. Transmissible disease (TD) marker rates were calculated using the National Epidemiology Donor Database. A case-control study was performed comparing risk factors in TD-positive donors with matched controls. Donor deferral rates were assessed before and after the change in deferral period.

RESULTS: The prevalence rates of tattoo, ear piercing, and body piercing were 13.7, 53.6, and 10.4 percent in survey respondents, respectively, with up to 0.7 percent of activity likely to represent deferrable risk. TD marker rate was low and stable at 21.6 per 100,000 donations before and 19.2 per 100,000 donations after the change in deferral length. Remote tattoo was associated with hepatitis C virus (HCV) risk (odds ratio, 5.43; 95% confidence interval, 1.82-16.2), but neither recent tattoo nor piercing was a risk factor for HCV or hepatitis B virus. Shortening of the deferral period reduced deferrals by 20 percent for tattoo and 32 percent for piercing.

CONCLUSION: There was no measurable adverse effect on safety and a positive but less than expected effect on blood availability after shortening the deferral period for tattoo and piercing. The length of other temporary deferrals should be reassessed, since their current contribution to blood safety may be negligible.

Blood donor selection criteria are an important part of blood safety. Criteria must balance recipient and donor risk, against the ever-increasing need for blood and the challenges of ensuring adequacy of supply. It is important to reassess both the need for and the duration of specific deferral criteria, particularly as other aspects of blood safety, such as transmissible disease (TD) testing and good manufacturing procedures, are strengthened.[1] Tattooing and ear and body piercing are reasons for temporary deferral of varying lengths in different regulatory jurisdictions. A US Food and Drug Administration (FDA) memorandum issued in April 1992 stipulated a 12-month deferral for donors who have had ear piercing or tattoo in which sterile procedures were not used.[2] A decade later, an FDA Blood Products Advisory Committee voted to continue these deferrals, but recommended a reexamination of the duration of deferral.[3] Presentations made to the committee at that time underlined the limited evidence of any safety benefit of these criteria.[3]

Blood donation does not exist in a vacuum, but is affected by societal trends in behaviors and infectious disease rates, which will influence donor deferral and TD rates. The frequency of both tattooing and body piercing is increasing in the general population, particularly in younger individuals, as assessed by population surveys and individual observations on a stroll down any city

ABBREVIATIONS: CBS = Canadian Blood Services; DHAQ = donor health assessment questionnaire; IVDU = intravenous drug use; TD = transmissible disease.

From Canadian Blood Services Donor and Transplantation Services and the Department of Epidemiology; and the Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada.

Address reprint requests to: Mindy Goldman, MD, FRCP(C), Executive Medical Director, 1800 Alta Vista Drive, Ottawa, ON, Canada K1G 4J5; e-mail: mindy.goldman@blood.ca.

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street on a summer day.[4-7] Temporary deferrals result in donation loss on that day and may also decrease donor return rates, particularly when they happen early in an individual's donation career.[8] In Canada, the deferral period for these activities decreased from 12 months to 6 months in August 2005. We aimed to examine the impact of this change on safety by assessing both TD rates and the association between these behaviors and TD before and after the change in deferral period. We also estimated the prevalence of piercing and tattoos in our donor population and assessed the positive impact of a shorter deferral period on adequacy of supply.

MATERIALS AND METHODS

Anonymous donor survey

An anonymous questionnaire was mailed to a total of 40,000 whole blood donors on a monthly basis throughout 2006. The sample was stratified by region proportional to the number of donors in each region, and first-time donors were oversampled such that there were 20,000 first-time and 20,000 repeat donors in the sample. A sample was drawn from donors who had donated during a given month, and the questionnaire mailed within 2 weeks of the end of the month. To increase the response rate, a second questionnaire with an accompanying letter and reminder card were sent 2 and 4 weeks after the initial questionnaire, respectively. The questionnaire included a code that denoted the region of index donation, donation status, and whether it was the first or second mailing, but did not include donor identifiers. In total, 20,037 donors (50%) completed a survey questionnaire, including 7382 first-time donors (37%). Of total responders, 4357 (21.7%) were from the second mailing. To identify possible duplicate questionnaires an algorithm comparing the first and second mailings for age, sex, donation status, donation times, country of birth, first three digits of residence postal code, marital status, ethnic origin, and highest level of education was applied. The handwriting on potential duplicate questionnaires was compared, and if duplication was likely, the second mailing item was removed. Frequencies of demographic characteristics of respondents were compared with those in the 2006 general donor base to confirm representativeness. To account for the differential sampling probability (first-time and repeat donors), sampling weights were created for each of the respondents based on their representation in the 2006 donor population by age, sex, donation status, and region.

Donors were asked if they had ever had a tattoo, ears pierced, or any other body piercing and whether or not they had participated in the activity in the past 6 months. The survey was approved by the Canadian Blood Services (CBS) Research and Ethics Board.

Assessment of donor deferral rates

All donors are queried about tattoo, ear piercing, and body piercing, in the self-administered section of the CBS donor health assessment questionnaire (DHAQ). For donors who answer affirmatively, the date and type of activity are noted on the DHAQ, and the donor is coded in the CBS donor database. However, deferral codes are not entirely specific for a given risk factor and include donors with other risk factors, such as needle-stick injury. Manual revision of the DHAQ was done for the central and north eastern regions of Ontario, which include Toronto, Ottawa, and surrounding areas. These two regions represent about 23 percent of CBS collections. The exact reason and start date of deferral was obtained from the DHAQ. For the purpose of analysis these were divided into two groups: Group 1, the 16 months before the change in donor deferral period (April 1, 2004, to July 31, 2005) and Group 2, the 16 months after the change in deferral duration (September 1, 2005, to December 31, 2006). The month of August 2005 was excluded to avoid the inclusion of potential errors relating to operational issues in the early phase of implementation.

TD testing

Antibody to human immunodeficiency virus (HIV)-1/2, hepatitis C virus (HCV), and human T-lymphotropic virus (HTLV)-I/II, and hepatitis B surface antigen (HBsAg) were detected with a chemiluminescent assay (Abbott PRISM HIV O Plus, Abbott Diagnostics Division, Wiesbaden, Germany). Confirmatory testing for HIV was performed using the HIV-1 Western blot (Calypte Biomedical Corp., Rockville, MD), for HCV using a third-generation recombinant immunoblot assay (Chiron Corp., Emeryville, CA), for HBsAg using the Abbott PRISM confirmatory assay, and for HTLV-I/II using the HTLV Western blot assay (Version 2.4, Genelabs Diagnostics Ltd., Singapore Science Park, Singapore). Nucleic acid testing (NAT) was performed for HIV and HCV (Roche Molecular Systems, Branchburg, NJ) using 24-unit minipools.

National Epidemiology Donor Database

The National Epidemiology Donor Database is maintained with computer software (SAS, SAS Institute, Inc., Cary, NC) and contains donation and demographic data such as age, sex and geographic location on all Canadian blood donors except those in the province of Québec. All allogeneic blood donations (whole blood, plasma, and platelet donations) were included in the TD rates.

Case-control study

A case-control study to examine predictors of TD in blood donors was carried out in 2005 and 2006. Because very few

donors test positive for the presence of HIV or HTLV in Canada, we have focused on risk factors for HCV- and HBsAg-positive donors. The method has been described previously.[9] In brief, all donors who tested positive for the presence of HBsAg or HCV in 2005 or 2006 were invited to participate in a telephone interview about risk factors. For each positive donor who participated, 4 control donors who had tested negative for all markers matched according to age (±5 years), sex, donation type, donation status (first time or repeat), and geographic region were randomly selected. All TD-positive donors received a standard notification letter informing them of their test results and permanent deferral from donation and advising them to seek medical attention. Donors were subsequently sent a letter inviting them to participate in the telephone interview and then were telephoned to conduct the interview. Once an HBsAg- or HCV-positive donor had completed an interview, control donors were selected and invited to participate in the same way. If a control donor refused to participate or could not be contacted, another was randomly selected among the eligible donors until 4 control donors had been interviewed for each positive donor. The telephone interview used a scripted questionnaire that asked about known and potential risk factors and demographic factors.[9] The interview was completed by 181 of 318 TD-positive donors (57%) and 737 of 1252 matched controls (59%). The study was approved by the CBS Research and Ethics Board.

Statistical analysis

Donor survey data

The percentage of donors with a risk factor was calculated and the 95 percent confidence interval (CI) was estimated using the normal approximation method or the Poisson exact method for small percentages.

TD rate

The rate for each TD marker was expressed as the number of positive donations per 100,000 donations, and CIs were estimated using the Poisson exact method.

Case-control study

Odds ratios (ORs) and 95 percent CIs were estimated for the studied potential risk factors separately for HBsAg- and HCV-positive donors. To determine the independent association of the risk factors with positivity, multiple logistic regression models were constructed separately for each marker. Only those risk factors that had significant ($p < 0.05$) ORs in univariate analysis were included in the model. To determine whether there was any difference in the ORs before and after the change in deferral duration, models for before and after were constructed separately for each marker and the ORs compared.

Deferral data

Deferral data were tabulated (frequency and percentage) for each specific deferral reason in the two time periods as well as the duration between the risk behavior and the deferral date (<6 or ≥6 months). The differences in proportions between two time periods (Groups 1 and 2) were compared using the chi-square test. A relative decreasing rate was calculated as: (number of deferred donors in Period 1 – number of deferred donors in Period 2)/number of deferred donors in Period 1 multiplied by 100(%). The deferral frequencies of each group were compared using the chi-square test for a one-way frequency table. In all analyses, a p value of less than 0.05 was considered to be significant.

RESULTS

Prevalence of tattoo, ear piercing, and other body piercing

As shown in Table 1, the prevalence of tattoo, ear piercing, or body piercing is high in donors. Furthermore, it is relatively common for donors to have engaged in these behaviors in the past 6 months (the duration of deferral when the 2006 donor survey was performed). After adjustment for donation status, there were approximately 5265 CBS donors in 2006 (95% CI, 4616-5911) who had one of these risk factors in the past 6 months but who had donated within the past few weeks.

TD rates

TD rates for all CBS donors did not change over the duration of the study. In the 16 months before the change in the duration of deferral there were 270 confirmed positive donations for all TD markers and 1,247,706 total donations for a rate of 21.6 per 100,000 (95% CI, 19.1 to 24.4). In the 16 months after shortening of the duration of deferral there were 249 confirmed positive donations and 1,295,561 total donations, for a rate of 19.2 per 100,000 (95% CI, 16.9 to 21.8; $p > 0.05$).

TABLE 1. Prevalence of tattoo and piercing, 2006 donor survey (n = 20,037)*

Risk factor	Ever	In the past 6 months
Tattoo	13.7 (13.2-14.1)	0.4 (0.3-0.5)
Ear piercing	53.6 (52.8-54.2)	0.7 (0.6-0.8)
Body piercing, other than ear piercing	10.4 (10.0-10.8)	0.3 (0.2-0.4)

* Data are reported as percentage (95% CI).

Importance of tattoo and piercing as risk factors for HCV and HBV

Tables 2 and 3 show the risk factors identified in all CBS donors confirmed positive for the presence of HCV or HBV in 2005 and 2006. Separate models were constructed for before and after the deferral change and there was no difference in the ORs when the two time periods were compared for either HCV or HBV; hence the data are presented for the 2-year period. For HCV, tattoo was found in 22.7 percent of cases and 10.9 percent of controls with an adjusted OR of 3.47 (95% CI, 1.49 to 8.07). To determine the impact of the date of receiving a tattoo, the model was also constructed with tattoo divided into those donors who had received a tattoo more than 10 years ago and those donors who had only received a tattoo in the past decade. Having received a tattoo more than 10 years ago was a significant predictor of HCV positivity (OR, 5.43; 95% CI, 1.82-16.2), but receiving a tattoo within the past decade was not (OR, 2.35; 95% CI, 0.77-7.22). Ear or body piercing was not a risk factor for HCV on univariate or multiple logistic regression analysis. Major risk factors for HCV, shown in Table 2, were intravenous drug use (IVDU), country of birth in Africa or Asia, sex with an IVDU, blood transfusion, and needle-stick injury. For HBV, neither tattoo nor piercing was an important risk factor for infection on univariate or multiple logistic regression analysis. Major risk factors for HBV, shown in Table 3, were country of birth in Asia or Africa, living in a closed institution, a family history of death from liver disease, or living with someone who had hepatitis or liver disease.

TABLE 2. HCV risk factors, logistic regression model, 2005-2006*

Risk factors	Case (n = 88)	Control (n = 349)	Adjusted OR	95% CI
IVDU	18 (20.5)	1 (0.3)	69.02	8.05-592.02
Born in Africa or Asia	14 (16.3)	14 (4.0)	14.44	5.18-40.25
Sex with IVDU	14 (17.3)	7 (2.1)	8.80	2.46-31.50
Blood transfusion	21 (25.6)	27 (7.2)	6.70	3.04-14.80
Needle-stick injury	14 (15.9)	14 (4.0)	4.04	1.45-11.29
Tattoo	20 (22.7)	38 (10.9)	3.47	1.49-8.07

* Data are reported as number (%).

TABLE 3. HBV risk factors, logistic regression model, 2005-2006*

Risk factors	Case (n = 69)	Control (n = 275)	Adjusted OR	95% CI
Ethnic origin				
East or Southeast Asia	24 (34.8)	7 (2.5)	151.41	38.6-593.84
Arab or Africa	14 (20.3)	5 (1.8)	74.42	17.34-319.29
South or West Asia	9 (13.0)	16 (5.8)	23.08	6.48-82.17
European	18 (26.1)	236 (85.8)	1.00	
Other	4 (5.8)	11 (4.0)	9.59	1.64-56.03
Lived in a closed institution	8 (11.6)	6 (2.2)	39.67	2.00-17.82
Death in the family resulting from liver disease	9 (13.6)	7 (2.6)	22.85	4.77-109.39
Living with someone who had hepatitis or liver disease	15 (23.8)	13 (4.7)	5.68	1.49-21.72

* Data are reported as number (%).

Impact of change in deferral period on deferral rates

There were 329,203 donor visits in Group 1 and 341,848 donor visits in Group 2, for the two Ontario regions examined. Table 4 summarizes the number of donors deferred for tattoo or ear or body piercing in these two time frames. Deferrals are divided into whether the donor stated that the activity had occurred less than 6 months or 6 to 12 months before the attempted donation. After the decrease in the deferral period (Group 2), no donors should have been deferred for tattoo or piercing that occurred more than 6 months before their donation attempt. The 10 donors in this category may have been deferred in error, shortly after the criteria were changed. For comparison, the number of donors temporarily deferred for other risk factors in the self-administered portion of the DHAQ is noted for the two time frames. These deferrals varied in length from 1 day for activities such as dental cleaning to 12 months for activities such as contact with an individual with hepatitis or jaundice. Overall, the 1017 deferrals for tattoo and piercing in Group 1 and the 723 deferrals in Group 2 represent 35.5 and 28.4 percent of total donor deferrals based on the DHAQ before and after change in the deferral duration, respectively ($p < 0.0001$). This does not include deferrals due to donor hemoglobin (Hb), malaria risk travel, or vital signs assessment. The number of donors deferred for tattoo decreased by 21 percent while the number of donors deferred for piercing decreased by 32 percent after the change in deferral duration; the number of other temporary donor deferrals based on the self-administered portion of the questionnaire decreased by 3 percent, which was not significant ($p = 0.80$). In Group 1, risk activities were not evenly distributed in the 6 to 12 months versus less than 6 months before the donation attempt ($p < 0.0001$). For tattoo and piercing, respectively, 61 and 65 percent of reported risk activities occurred less than 6 months before donation. Since many of the other temporary deferrals in the comparison group were of very short duration, one would expect the majority of these to occur less than 6 months before the donation attempt, as seen in Table 2.

TABLE 4. Impact of change in deferral duration, Central and North Eastern Ontario

Deferral reason and interval before donation attempt	Group 1, n = 329,203 (April 1, 2004, to July 31, 2005)			Group 2, n = 341,848 (September 1, 2005, to December 31, 2006)		
	<6 months	>6 months	Total	<6 months	>6 months	Total
Tattoo	187	117	304	237	4	241
Piercing	465	248	713	476	6	482
Other temporary deferrals self-administered questions	156	35	191	146	40	186
Total deferrals DHAQ*	2074	787	2861	2335	208	2543

* Not including deferrals due to donor Hb, malaria risk travel, or vital signs assessment.

DISCUSSION

Our results demonstrate that there was no increase in TD rates after a shortening of the deferral period for tattoo or ear and body piercing. Furthermore, engaging in these activities, at least in the past 10 years, was not a risk factor for HCV and HBV positivity, the only two markers with enough positive donors to permit analysis. Piercings and tattoos, occurring in the past 6 months, were not infrequent in people who had recently successfully donated and had negative TD testing results. Shortening of the deferral period had a positive effect on our inventory, although less than one would have expected.

Body adornment by tattoo and body piercing are increasingly common, with prevalence rates of 8 to 25 percent for tattoos and 14 to 51 percent for body piercing reported in recent surveys conducted in various population groups.[4-7] It is therefore not surprising that tattoo and piercing are relatively common reasons for temporary donor deferral, both for CBS and for other blood suppliers.[10,11] Deferral rates are particularly high in younger donors, who are early in their donation career and may potentially have a negative impact on donor return rates.[8,10] Tattoo and piercing result in temporary deferral periods of 6 to 12 months in various jurisdictions; in some cases, shorter deferrals are permitted if additional testing is performed for HBV or HCV or if the donor states that single use needles were used.[12-14] In the United States, after the FDA granted licence amendments to several blood suppliers, AABB Standards were amended to permit donations if tattoos have been applied in a state-regulated entity with sterile needles and ink that has not been reused; however, this is only possible in states that regulate tattoo establishments.[15,16]

Deferrals for tattoos and piercing were implemented in Canada and other jurisdictions in the 1980s, when TD testing, quality standards, and deferral for other higher risk behaviors did not provide the same level of safety that we have achieved today.[17] The current contribution of these criteria to blood safety has not been extensively evaluated. In our study there was no change in the TD marker rate after shortening of the deferral period, in spite of acceptance of donors who would otherwise have been deferred. If these behaviors were important risk factors, one would expect an increase in TD rates immediately after implementation of the change. Zou and coworkers[18] from the ARC found that returning donors who had been temporarily deferred for potential infectious disease risk did not have a higher prevalence of positive TD markers, compared to other donors.

There are conflicting studies on the importance of tattoo and piercing as risk factors for HBV and HCV in the general population.[3,19,20] However, causal associations are generally difficult to establish and interpretation is limited by the different populations studied and by potential confounding effects of other established risk factors such as incarceration and IVDU, particularly since these carry much stigma and may be less readily acknowledged by study participants than piercings and tattoos. In any event, neither ear or body piercing or tattoos (in the past 10 years) were predictors of HCV or HBV positivity in our study, in spite of their high prevalence in donors, and shortening the length of deferral had no effect on this. Although we could not assess the association between piercings or tattoos and HIV or HTLV due to their low prevalence in donors and in the general population, it may be expected that if these were independent predictors of blood-borne pathogen transmission, they would be identified as such for HCV and/or HBV since these are more prevalent infections in the Canadian population and in the donor population. Furthermore, failure to report these risk factors appears to be fairly common, with an estimated 5265 donors having engaged in one of these behaviors in the last 6 months in 2006, and yet TD rates are very low in Canada, underscoring the nonspecificity of these behaviors as identifiers of risk.

Studies on TD marker rates in the blood donor population have consistently demonstrated much higher rates for first-time versus repeat donors, indicating that almost all infections in the donor population are related to remote rather than recent infections and risk factors.[21-24] There have been several studies examining risk factors in TD-positive donors.[8,23-26] In a large, case-control study performed by the REDS group in 1994 to 1995, ear or body piercing was a weak risk factor for HCV positivity, while tattoo was a risk factor on univariate analysis alone.[25]

Similar results were obtained on an earlier US study.[26] Results of earlier studies may not reflect risks associated with more recent piercings or tattoos, since these activities are currently much more common in the general population and less likely to have occurred in nonprofessional settings, such as jails. More recent studies from Holland and Australia are difficult to interpret because of the lack of a control group or analysis to remove confounding effects of IVDU and incarceration, which may be particularly important for HCV transmission.[23,24]

In Canada, a decrease in the deferral period from 12 to 6 months did result in decreased donor deferral rates for tattoo and piercing. However, a 50 percent decrease in the deferral interval only led to a decrease of 21 percent in deferrals related to tattoos and 32 percent in deferrals related to piercing. Analysis of the interval between donation attempt and reporting of risk behavior in Group 1 demonstrates an uneven distribution of reported risk throughout the 12-month deferral period, with increased reporting of more recent risk. Our donor survey data also indicate that many donors who have donated recently have engaged in one of these behaviors within the previous 6 months. Since there were likely a few weeks between the time when the donor made her or his last donation and completed their survey questionnaire, it is possible that a minority of donors engaged in the behavior after donating, however, most likely failed to report deferrable risk. Donors may judge that more temporally remote risk behaviors that did not result in infection do not actually require reporting and may also have decreased recall of more remote behaviors.[17] In spite of the less-than-expected donation gain, a decrease in deferral period was still advantageous, as it will result in approximately 2000 additional donations annually, without any adverse effect on safety. Additionally, the data generated provide reassurance that a further reduction of the length of deferral would not be expected to have any impact on safety. Interestingly, preliminary results from a study in Spain demonstrated that a reduction in donor deferral period from 12 to 4 months for a variety of risk activities, including tattoos and piercing, did not result in any increase in TD marker rates, but led to a less-than-expected decrease in deferral rates of 17 percent.[27]

In summary, tattoos and piercing are frequent in donors, reflecting their increasing popularity in the general population. Our data suggest that deferral of donors for recent tattoo or piercing has a very limited contribution to blood safety in Canada, since decrease in the deferral period did not change the TD marker rate. Additionally, undisclosed risk is common, the TD marker rate is extremely low, and recent tattoo or piercing are not independent risk factors for HBV or HCV infections in donors. Given that window periods for HCV and HBV are estimated at less than 10 and less than 45 days, respectively, for HCV minipool NAT and HBsAg tests currently performed in Canada, a decrease in the duration of deferral to 4 months, which is the current EU standard, would not be expected to have any negative impact on safety.[21] The value of other temporary deferrals should similarly be reassessed.

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研究報告の概要

○B型肝炎の再燃

B型肝炎の再燃とは、非活動性B型肝炎またはB型肝炎が治癒した患者で、B型肝炎ウイルス(HBV)が急増することである。再燃は自然に起こる場合もあるが、一般的には癌、自己免疫疾患または臓器移植の免疫抑制療法によって引き起こされることが多い。再燃は、一過性で非顕在性となる場合もあるが、疾患増悪を引き起こし、重症化して急性肝不全に至ることもある。ほとんどの再燃例は自然治癒するが、免疫抑制が続く場合慢性肝炎を発症し、進行性肝障害や肝硬変に至る場合がある。もっともよく報告されている再燃例は、リンパ腫または白血病の癌化学療法治療を受けている非活動性またはほとんど活動性のないB型肝炎を有するB型肝炎表面抗原(HBsAg)キャリアに起きている。通常は化学療法時に血清HBV DNA値が上昇し、化学療法中止後に免疫再構築による疾患増悪およびHBV DNAのクリアランスが起こる。特殊なパターンとしては、臓器および骨髄移植後に再燃が起こり慢性感染を生じる。複数の無作為化プラセボ対照試験で、抗ウイルス剤の予防投与により再燃が予防できることが示された。以上により、癌化学療法または移植を受けるHBsAg陽性者に対してルーチンの予防が推奨されるが、重大な疑問が残る。どのような患者にHBsAgのスクリーニングを行うべきか、全員に治療を行うべきか？どの抗ウイルス剤を、どのくらいの期間使うべきか？ B型肝炎が治癒したHBsAg陰性患者に予防を行うべきか？今後の研究では、異なる患者集団を対象として、再燃の分子学的発症機序、および診断、治療、予防の最適な方法について、取り組む必要がある。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
癌、自己免疫疾患または臓器移植の免疫抑制療法によってB型肝炎再燃が誘発されることが多く、癌化学療法または移植を受けるHBsAg陽性者に対してルーチンの予防が推奨されるとの報告である。輸血後HBV感染の調査には、化学療法後のB型肝炎再燃の可能性を考慮する必要がある。日本肝臓学会から示された「免疫抑制・化学療法により発症するB型肝炎対策ガイドライン」の中で再燃時の対応が提示されている。	日本赤十字社では、薬事法及び関連法令に従い輸血副作用・感染症情報を収集し、医薬品医療機器総合機構を通じて国に報告している。HBV感染に関する新たな知見等について今後も情報の収集に努める。

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JRC2009T-026

Reactivation of Hepatitis B

Jay H. Hoofnagle

Reactivation of hepatitis B refers to the abrupt increase in hepatitis B virus (HBV) replication in a patient with inactive or resolved hepatitis B. Reactivation can occur spontaneously, but more typically is triggered by immunosuppressive therapy of cancer, autoimmune disease, or organ transplantation. Reactivation can be transient and clinically silent, but often causes a flare of disease that can be severe resulting in acute hepatic failure. Most instances of reactivation resolve spontaneously, but if immune suppression is continued, re-establishment of chronic hepatitis occurs which can lead to progressive liver injury and cirrhosis. The best-described instances of reactivation occur in hepatitis B surface antigen (HBsAg) carriers with inactive or minimally active disease who are given cancer chemotherapy for lymphoma or leukemia. Typically, serum HBV DNA rises during chemotherapy, followed by a disease flare and HBV DNA clearance with immune reconstitution after chemotherapy is stopped. Special forms of reactivation occur after solid organ and bone marrow transplantation in which chronic infection often results. Several randomized, placebo-controlled trials have shown that reactivation can be prevented by antiviral prophylaxis. Routine prophylaxis is therefore recommended for persons with HBsAg undergoing cancer chemotherapy or transplantation, but major questions remain. Which patients should be screened for HBsAg and should all be treated? Which antiviral should be used and for how long? Should persons with resolved hepatitis B without HBsAg receive prophylaxis? Future research should address the underlying molecular mechanisms of reactivation as well as its optimal means of diagnosis, treatment, and prevention in different patient populations. (HEPATOLOGY 2009; 49:S156-S165.)

Introduction

Reactivation of hepatitis B is a well-characterized syndrome marked by the abrupt reappearance or rise of hepatitis B virus (HBV) DNA in the serum of a patient with previously inactive or resolved HBV infection. Reactivation is also often, but not always, accompanied by reappearance of disease activity or a flare of hepatitis in previously minimal or inactive disease. Reactivation can be spontaneous, but is most commonly triggered by cancer chemotherapy, immune suppression, or alteration in immune function. Reactivation can lead to clinically apparent acute hepatitis, which can be severe and result in acute liver failure and death. Nevertheless, a large number of cases of reactivation are subclinical and resolve spontaneously, or result in persistent infection which may go undetected until advanced liver disease is present or the disease has been transmitted to sexual or family contacts.

The importance of reactivation of hepatitis B rests on its potential severity and the ease of its prevention with prophylactic oral antiviral therapy. In addition, reactivation reveals fundamental features of HBV and its ability to persist in a latent replicative form for prolonged periods despite other evidence of viral clearance. Importantly, the lack of recognition of reactivation and its complex virological and biological features often cause confusion and delayed recognition until it has already occurred and caused clinical consequences. Furthermore, reactivation can be misdiagnosed as superimposition of another form

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Abbreviations: AASLD, American Association for the Study of Liver Diseases; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; anti-HBe, antibody to hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; TNF, tumor necrosis factor.

From the Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH), Bethesda, MD.

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Address reprint requests to: Jay H. Hoofnagle, M.D., Building 31, Room 9A27, 31 Center Drive, NIH, Bethesda, MD 20892. E-mail: Hoofnagle@exmx.niddk.nih.gov; fax: 301-480-3276.

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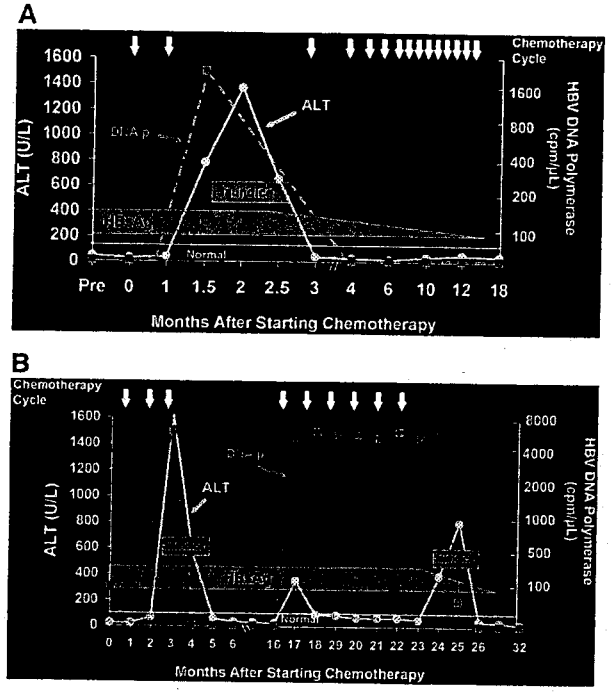

Fig. 1. (A) Reactivation of hepatitis B in an HBsAg carrier with testicular cancer undergoing cyclic chemotherapy. After the second course of chemotherapy, he presented with jaundice and marked elevations in ALT and HBV DNA polymerase activity in serum. Testing of stored serum demonstrated HBsAg without HBeAg or detectable HBV DNA before chemotherapy. The acute hepatitis eventually resolved and he tolerated further courses of chemotherapy without recurrent reactivation. In follow-up 18 months later, he was HBsAg-negative and anti-HBs positive. (B) Reactivation of hepatitis B in an HBsAg carrier with non-Hodgkin's lymphoma undergoing cyclic chemotherapy. After the third course of chemotherapy, she presented with jaundice and marked elevations in ALT and HBV DNA polymerase activity. Testing of stored serum demonstrated HBsAg without HBeAg and low levels of HBV DNA polymerase in serum before chemotherapy. The acute hepatitis eventually resolved, but she developed HBV reactivation again when chemotherapy was restarted. Prospective monitoring demonstrated the rise in HBV DNA with the first course of treatment, but only mild ALT elevations and no clinical symptoms until chemotherapy was stopped, at which point she suffered a severe bout of icteric hepatitis. Approximately 6 months later, she was found to have cleared HBsAg and tested positive for anti-HBs. Modified with permission from Hoofnagle et al.[3]

of liver disease (drug-induced liver disease, alcoholic liver disease) occurring in a previously stable, inactive HBV carrier. There is a need for a wider awareness about reactivation of hepatitis B, when and where it occurs and how it should be prevented or managed.

Virological and Clinical Features of HBV Reactivation

HBV reactivation occurs in many situations in which a person with mild or inactive hepatitis B is exposed to immunosuppressive agents or suffers from immune deficiency. Reactivation has been shown to occur with chemotherapy for solid cancers and leukemia[1-5] particularly when using rituximab;[6] with immune modulation using prednisone or infliximab for autoimmune conditions;[7,8] with progression of human immunodeficiency virus (HIV) infection;[9] after solid organ transplantation (heart, lung, kidney);[10,11] and, most commonly and dramatically, after bone marrow[12,13] and liver transplantation.[14]

The typical course of reactivation is shown in Fig. 1, which shows the course of two hepatitis B surface antigen (HBsAg)-positive patients who received cancer chemotherapy in the early 1980s before the availability of antiviral therapy which might alter the course and outcome.[3] HBV reactivation can be separated into three phases: (1) increase in HBV replication; (2) appearance of hepatic injury; and (3) recovery (Table 1).

Reactivation starts with the abrupt increase in viral replication that typically occurs soon after initiating immune suppression or chemotherapy. The degree of increase in viral replication is measured by the rise in HBV DNA in serum (the examples show HBV DNA polymerase activity, an insensitive, early quantitative measure of viral replication). In patients without hepatitis B e antigen (HBeAg), this marker may reappear in the serum. The second phase of reactivation starts when immunosuppression is withdrawn or decreased and hepatocellular injury or hepatitis arises, as shown by rises in serum aminotransferase levels and, in more severe instances, symptoms and jaundice. During this phase, HBV DNA levels may start to fall. The third phase of reactivation is recovery, as the evidence of liver injury resolves and HBV markers return to baseline levels.

Table 1. Three Phases of HBV Reactivation

Phase	Feature	Diagnostic Markers	Comments
1	Increase in Viral Replication	HBV DNA HBeAg HBsAg	Rise of > 1 $\log_{10}$ IU/mL In HBeAg negative Reverse seroconversion
2	Appearance of Disease Activity	ALT Symptoms Jaundice	Rise of > 3 times baseline Indicative of more severe injury
3	Recovery	HBV DNA ALT HBsAg	Fall to baseline values Fall to baseline values May be cleared late

Not all patients with reactivation have all three phases. In some patients, HBV DNA reappears and rises to high levels, but there is no immune reconstitution and no liver injury arises. These patients also typically do not recover completely, a pattern that is common in patients who remain immunosuppressed, such as solid organ and bone marrow transplant recipients.[10-13] In other patients, the hepatitis phase is severe and can be fatal so that recovery does not occur.[1,4] In other instances, the hepatitis phase persists and a chronic hepatitis is established, of varying severity. Finally, recovery may be marked by a return to the previous inactive state of hepatitis B or may actually result in more complete recovery. In the examples shown in Fig. 1, both patients ultimately became HBsAg-negative and developed antibody to HBsAg (anti-HBs). The examples also show that restarting chemotherapy and immune suppression does not necessarily cause recurrence of reactivation (Fig. 1A), but in some instances can (Fig. 1B).

The Frequency of HBV Reactivation

The frequency of reactivation is not well defined. In a landmark study from the 1980s, investigators from Hong Kong carefully followed 100 patients with lymphoma while undergoing cancer chemotherapy for virological, serological, and biochemical evidence of reactivation.[4] Almost half of the 27 HBsAg-positive patients (48%) developed reactivation during or shortly after chemotherapy, compared to 0 of 22 patients with no serological markers for ongoing or previous hepatitis B. Importantly, two of 51 patients (4%) with serological evidence of resolved hepatitis B (without HBsAg, but with antibody to hepatitis B core antigen [anti-HBc] in serum) developed reactivation with reappearance of HBsAg in serum. This latter pattern is commonly referred to as "reverse seroconversion" and represents an extreme form of HBV reactivation. In this initial prospective study, half of patients who developed reactivation became jaundiced, and 20% of patients with jaundice died. While the incidence of reactivation has varied in different case series, the fatality rate of HBV reactivation has been consistently greater than 10%, far higher than the fatality rate of typical acute hepatitis B and similar to fatality rates of hepatocellular drug-induced liver injury.

A recent meta-analysis of the role of prophylaxis with lamivudine in preventing reactivation of hepatitis B has provided support for these early results on the frequency of its occurrence.[15] Among 13 studies enrolling 424 patients who did not receive prophylaxis, the combined rate of HBV reactivation was 50%, ranging in individual studies from 24%-88%. Subsequent studies have assessed risk factors for developing reactivation; the likelihood of HBV reactivation is higher in patients with HBeAg or HBV DNA before chemotherapy[16] and with the use of corticosteroids in the chemotherapy regimen.[17] Actually, the most important factor—the aggressiveness of the cancer chemotherapy or rigor and duration of immune suppression—could not be analyzed in these studies because of the homogenous populations enrolled.

The role of degree of immunosuppression in the frequency and severity of HBV reactivation is highlighted by reports of severe reactivation following more aggressive forms of chemotherapy or immune suppression such as with the use of rituximab[8] or fludarabine[18] in the therapy of lymphoma. Rituximab is a monoclonal antibody against CD20, a major cell surface marker on B cells, which effectively reduces B cell numbers and antibody levels. The rate of HBV reactivation with rituximab therapy has not been defined but appears to be high. Thus, in the 12 individual case reports of HBV reactivation associated with rituximab therapy in the literature, the mortality rate was 83%, and five cases occurred in patients who were HBsAg-negative before therapy (reverse seroconversion).[8,18-28] In cases of reverse seroconversion, the reappearance of HBsAg and HBV DNA typically occurs late, after several cycles of chemotherapy with rituximab, and generally at a time when anti-HBs and anti-HBc have fallen to low or undetectable levels (Fig. 2).[26]

HBV Reactivation After Immune Suppression for Nonmalignant Disease

Reactivation is not limited to patients with cancer undergoing chemotherapy (Table 2). Simple immune suppression as is given to patients with autoimmune or allergic diseases who have either HBsAg or anti-HBc in serum can also induce reappearance of HBV replication and disease activation, although at a lower rate than occurs with cancer chemotherapy.[7] Thus, reactivation of hepatitis B is uncommon with immune suppression using azathioprine and low doses of corticosteroids, but has been reported (rarely) with long-term use of methotrexate.[29-31] Although rare reports of reactivation have been described in patients receiving corticosteroids alone, more

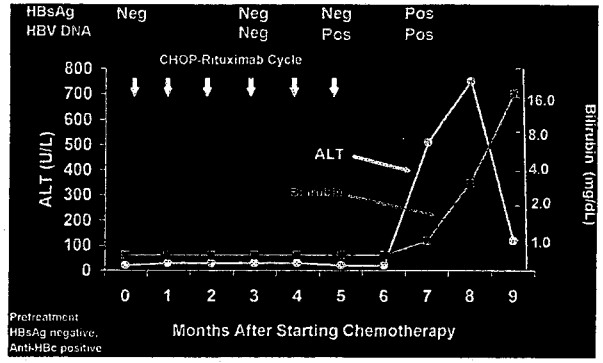

Fig. 2. Fatal reactivation of hepatitis B with reverse seroconversion in a patient with large B-cell lymphoma treated with rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, and dexamethasone). The patient was HBsAg-negative but anti-HBc-positive before therapy, becoming HBV DNA-positive during the last of six cycles of chemotherapy and subsequently developing HBsAg and rising levels of ALT and bilirubin leading to acute liver failure and death. Modified from Yamagata et al.[26]

striking examples occur after the use of potent immune suppression such as with anti–tumor necrosis factor-alpha therapies (infliximab).[8] Thus, there have been more than a dozen published reports of severe reactivation (three being fatal) after use of infliximab for Crohn's disease, rheumatoid arthritis, or ankylosing spondylitis which has resulted in a "black box" warning.[8,32-36] The rates of reactivation have been difficult to ascertain, because only rare patients receiving these therapies have pre-existing HBsAg or anti-HBc, and prophylaxis with nucleoside analog is now common. In a study from Spain,[8] patients who were both HBsAg-positive and who did not receive prophylaxis with lamivudine developed severe reactivation after treatment with infliximab, whereas no patient given lamivudine prophylaxis during infliximab therapy developed reactivation.

Organ Transplantation and HBV Reactivation

Solid organ transplantation usually requires long-term moderate-to-severe immune suppression to prevent rejection and, consequently, is a setting for occurrence of HBV reactivation in susceptible patients. Before the introduction of antiviral prophylaxis, the rates of HBV reactivation after renal transplantation ranged from 50%-94%.[10,37-39] Reactivation was frequently subclinical and resulted in chronic hepatitis rather than acute reactivation episodes. For this reason, the frequency and consequences of HBV reactivation were often overlooked. A similarly high rate of reactivation occurs after heart transplantation.[11] Rates of reverse seroconversion after kidney and heart transplantation have not been well defined, but may be rising in recent years with the use of more potent antirejection regimens.[10] Currently, patients evaluated for heart, lung, and kidney transplantation are routinely tested for HBsAg and anti-HBc and, if positive, considered for antiviral prophylaxis and long-term antiviral treatment.[40] At issue is the long-term benefit of this approach and whether antiviral therapy must be continued indefinitely.

Liver transplantation offers a special and somewhat confusing example of reactivation. Because the infected liver is removed at transplantation, the reappearance of HBsAg and HBV DNA afterwards in HBV-infected transplant recipients is considered reinfection rather than reactivation. Reinfection is almost universal after liver transplantation in patients who are HBsAg-positive, but can be reliably prevented by appropriate use of hepatitis B immune globulin and antiviral therapy.[40,41] Reinfection after liver transplantation for patients with anti-HBc without HBsAg appears to be uncommon, and such patients are usually not given immunoprophylaxis or long-term therapy.[41]

Reactivation in the setting of liver transplantation occurs when the organ donor rather than recipient is positive for HBsAg or, more frequently, for anti-HBc. Indeed, the most dramatic examples of reverse seroconversion occur with the transplantation of a liver from a donor with anti-HBc without HBsAg into a recipient without HBV infection.[14,42-46] Retrospective analyses indicate that approximately 70% of such transplants result in HBV infection in the recipient and almost always results in chronic infection which can be progressive and severe.[14]

Table 2. Different Causes and Forms of HBV Reactivation

Spontaneous
Progressive Immunodeficiency (HIV Infection)
Sudden Withdrawal of Antiviral Therapy
Cancer Chemotherapy
Immunosuppression for Autoimmune or Allergic Conditions
Solid Organ Transplantation (Kidney, Heart, Lung)
Liver Transplantation (Reactivation in Graft)
Bone Marrow Transplantation

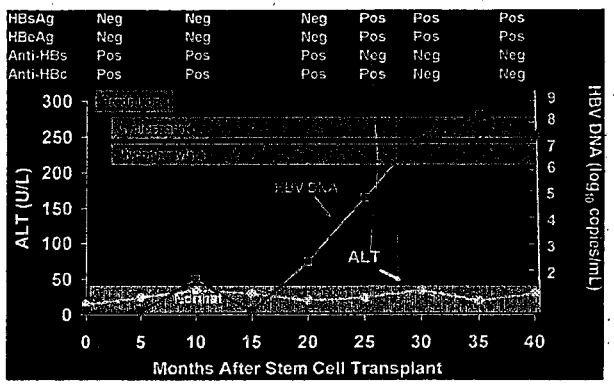

Fig. 3. Reverse seroconversion occurring 20 months after successful bone marrow transplantation for chronic myelogenous leukemia in a patient who was HBsAg-negative but anti-HBs–positive and anti-HBc–positive before transplant. Levels of anti-HBs and anti-HBc fell during 16 months after transplantation, and HBV DNA arose shortly thereafter. HBsAg was detected once HBV DNA levels rose above 1000 copies/mL. The patient required continued immunosuppression with prednisone, cyclosporine, and mycophenylate mofetil for graft-versus-host disease. Serum ALT levels remained normal. Modified from Knoll et al.[12]

The reappearance of hepatitis B in the recipient of a liver donor with serological evidence of recovery from hepatitis B (anti-HBc with or without anti-HBs in the absence of HBsAg) indicates that HBV can become latent and that virus with replicative capabilities remains in the liver in patients who have recovered from hepatitis B. Indeed, blood from such donors can be infectious for hepatitis B,[47] and persons who have recovered from acute or chronic hepatitis B have been shown to harbor HBV DNA in liver despite absence of active liver disease or presence of HBsAg or HBV DNA in serum.[48-50]

For these reasons, donors with anti-HBc (even without HBsAg) are not used in liver transplantation, unless they are given to patients undergoing transplantation for hepatitis B (and thus who will receive antiviral prophylaxis) or are given with informed consent to a patient who receives long-term prophylaxis with an antiviral agent.[40,41] Reactivation can be prevented by prophylactic antiviral therapy in this situation, but the long-term efficacy and safety of this latter approach have yet to be fully documented.[51-55]

Bone Marrow Transplantation and HBV Reactivation

Perhaps the most dramatic examples of HBV reactivation have been described in patients undergoing bone marrow transplantation. In typical allogeneic bone marrow transplantation, the recipient bone marrow is ablated using high doses of chemotherapy and then replaced by the infusion of donor marrow from someone who may or may not have immunity to hepatitis B. Thus, bone marrow transplantation represents the most extreme form of immune suppression/ablation. Reactivation of hepatitis B is almost universal among patients with HBsAg undergoing bone marrow transplantation.[56,57] In addition, reverse seroconversion is common, although it is often not detected or is misdiagnosed.[12,13,58-60] In retrospective analyses using sensitive serological and virological markers, a high proportion of persons with anti-HBc without HBsAg in serum redeveloped HBV DNA and HBsAg after bone marrow transplantation, occurring in three of six patients (50%) in a study from Germany[12] and in seven of 14 patients (50%) in a study from Japan.[13] Serial testing demonstrated that the bone marrow recipients gradually lost anti-HBs reactivity, with levels of antibody falling to undetectable between 1 and 3 years after transplantation. With loss of anti-HBs (and anti-HBc), HBV DNA appeared and levels increased; once HBV DNA levels rose above ~1000 copies/mL (~200 IU/mL), HBsAg typically appeared in the serum (Fig. 3). In the case series, most patients did not develop clinically apparent hepatitis, but among those with clinically apparent disease, fatalities are not infrequent. Importantly, reactivation and particularly reverse seroconversion usually occurred late, between 1 and 3 years after the bone marrow transplantation, and further follow-up may show that a higher proportion of patients would eventually become infected. Because of multiple publications of fatal instances of reverse seroconversion after bone marrow transplantation, current recommendations are for all potential marrow recipients to be tested for HBsAg, anti-HBs, and anti-HBc and patients with HBV markers should receive antiviral prophylaxis. Although this approach appears to be effective, the late development of reactivation after bone marrow transplantation suggests that long-term, if not lifelong, antiviral prophylaxis may be necessary.[61-66]

Spontaneous Reactivation

Chronic hepatitis B is a dynamic condition, and patients with inactive infection (the inactive HBsAg carrier state) can revert spontaneously to the immune-active

phase with reappearance of high levels of HBV DNA and disease activity.[67-69] Indeed, a not uncommon pattern of disease in patients with HBeAg-negative chronic hepatitis B is a relapsing course with periods of normal alanine aminotransferase (ALT) levels and no or low levels of HBV DNA followed by acute episodes of marked ALT elevations and HBV DNA detectability.[70] This pattern represents recurrent HBV reactivation and can present in a fashion resembling acute viral hepatitis[71,72] and appears to have a high likelihood of resulting in cirrhosis.[69,70] Spontaneous reactivation of chronic hepatitis B is often misdiagnosed,[73] yet this pattern of disease activity has been found to be quite responsive to antiviral therapy with nucleoside analogs which block the episodic flares of disease.[70]

Reactivation of Hepatitis B in HIV-Infected Patients

The progressive immunodeficiency that accompanies chronic infection with HIV can lead to reactivation in patients with chronic HBV infection and reverse seroconversion in patients with anti-HBc without HBsAg in serum. Testing of stored serum specimens from patients with HIV infection followed in clinical research cohorts has identified several instances in which anti-HBs reactivity is gradually lost and HBsAg with HBV DNA and ALT elevations appears.[74-76] Many of the antiretroviral agents used to treat HIV infection also have activity against HBV, and in several instances, patients have had sudden exacerbation of chronic hepatitis B when HIV medications are adjusted and drugs with activity against HBV (lamivudine, tenofovir, emtricitabine) are discontinued.[77] A similar severe flare in hepatitis that is potentially fatal can occur in HIV-uninfected individuals who abruptly stop lamivudine therapy.[78] For these reasons, patients with HIV infection should be tested for HBV markers and patients with HBsAg and/or anti-HBc should not be switched away from agents with anti-HBV activity.

Prevention of Reactivation

Controlled clinical trials[79,80] and several subsequent meta-analyses[15,81,82] have shown that prophylaxis with nucleoside analogs (most commonly lamivudine) decreases the incidence of HBV reactivation and the frequency of clinical hepatitis and death from HBV-associated liver injury in patients undergoing cancer chemotherapy. Initiating therapy once reactivation has occurred is typically done for control subjects in these trials and appears to be ineffective.

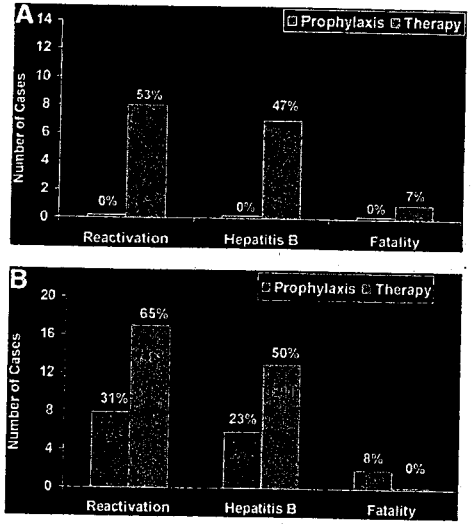

Fig. 4. Rates of HBV reactivation, hepatitis, and fatal hepatitis in two prospective, randomized controlled trials of prophylactic versus delayed (therapeutic) lamivudine in patients with malignant lymphoma undergoing cancer chemotherapy. (A) Study from Hong Kong in 30 patients.[79] (B) Study from Taiwan in 52 patients[80]; numbers in the horizontal bars represent number of cases that arose during the period of prophylaxis versus number of cases that arose afterward.

There have been two prospective, randomized controlled trials of lamivudine prophylaxis against HBV reactivation in patients with HBsAg who were undergoing chemotherapy for malignant lymphoma. Both studies were conducted in Asia, one from Hong Kong[79] and one from Taiwan.[80] Both studies enrolled HBsAg-positive patients only (not those with anti-HBc without HBsAg) who were scheduled to undergo chemotherapy for previously untreated lymphoma. In the study from Hong Kong,[72] 30 patients were enrolled and randomized to receive prophylactic lamivudine (100 mg daily starting 1 week before chemotherapy and stopping 6 weeks after completion of the last cycle of chemotherapy) or lamivudine treatment only if reactivation were documented to occur. Reactivation was defined by a 10-fold rise of serum HBV DNA levels and "hepatitis" was defined by a three-fold increase in ALT levels in patients with HBV reactivation. Reactivation occurred in eight of 15 control subjects (53%) but 0 of 15 patients given lamivudine prophylactically ($P = 0.002$) (Fig. 4A). Seven of the eight instances of HBV reactivation were accompanied by hepatitis (88%), two were icteric (25%), and one was fatal (12%).

A second study was recently published from Taiwan[80] which employed a similar design, and, indeed, was discontinued early because of the results of the study from Hong Kong. In this multicenter trial, 52 HBsAg-positive patients with newly diagnosed non-Hodgkin's lymphoma were randomized to receive either prophylactic or therapeutic lamivudine. The prophylactic group received 100 mg daily starting 1 week before chemotherapy and continuing for 2 months after completion of chemotherapy. The therapeutic group received lamivudine if serum ALT levels rose during therapy. Definitions of HBV reactivation (1 $\log_{10}$ rise in HBV DNA levels) and hepatitis (three-fold rise in ALT levels) were similar in the two studies. Among 26 patients receiving lamivudine prophylactically, only three (12%) developed HBV reactivation while on therapy compared to 14 of the 25 control patients (56%) ($P = 0.002$). Most control patients with HBV reactivation also fulfilled criteria for hepatitis (82%), and five patients developed jaundice. In contrast, the cases of reactivation in the prophylactic group were mild and were not accompanied by jaundice. Two of the patients who developed reactivation despite lamivudine therapy were found to harbor lamivudine-resistant HBV which had not been detected before therapy. Most importantly, HBV reactivation and hepatitis were also common after therapy was stopped, occurring in similar proportions of the prophylactic (19%) and the therapeutic (14%) groups (Fig. 4B). In addition, cases of reactivation occurring after prophylactic therapy tended to be clinically apparent: three patients developed jaundice and two died of liver failure.

Thus, both studies clearly demonstrated that prophylactic lamivudine decreased the rate of HBV reactivation and hepatitis; however, the larger trial from Taiwan, which had a more rigorous design and follow-up, demonstrated that HBV reactivation is not completely eliminated by prophylactic lamivudine treatment, perhaps because of development of lamivudine resistance, and that continuation of therapy for 2 months after stopping chemotherapy was not adequate to prevent delayed reactivation.

Prospective trials of antiviral prophylaxis have not been performed in other situations with high risk for HBV reactivation (bone marrow transplantation, solid organ transplantation, HIV infection, immune modulation for autoimmune conditions), but small case series with historical controls indicate that reactivation appears to be decreased, if not eliminated, if prophylaxis is provided.[8,83-87] Given the safety and tolerability of current nucleoside analogs for hepatitis B and given that prophylaxis against reactivation of hepatitis B appears to be effective, it would seem appropriate to recommend its application widely. Indeed, clinical guidelines from expert groups in Asia, Australia, Europe, Canada, and the United States all recommend prophylaxis against reactivation of hepatitis B in high-risk situations.[88-91]

Conclusions and Recommendations

Reactivation of HBV is a common occurrence after immune suppression and can be clinically severe and result in death from acute liver failure or progressive liver disease and cirrhosis. HBV reactivation can be prevented in some instances by prophylactic use of antiviral agents. Nevertheless, it is difficult to make rigorous recommendations regarding the prevention and control of HBV reactivation. Issues include: which patients should be screened for evidence of hepatitis B before starting immune suppression or chemotherapy? Should screening tests include both HBsAg and anti-HBc? Which patients should be offered prophylaxis against reactivation? Which antiviral agent should be used? And for how long? Using what tests to monitor therapy for both efficacy and safety?

Recommendations regarding reactivation have been published by several academic societies[88-90] and by the Centers for Disease Control and Prevention,[91] but the recommendations differ and are frequently complex and require special expertise or knowledge about hepatitis B and its risk factors and serology. Based on the current literature about reactivation as well as the realization that chemotherapeutic and immunosuppressive regimens continue to evolve and have become more rigorous and aggressive with newer immunosuppressive agents and regimens, simple recommendations can be made, although not all are convincingly supported by medical evidence.

All patients who are to undergo cancer chemotherapy, marked immunosuppressive treatments or solid organ or bone marrow transplantation should be screened for evidence of ongoing or previous hepatitis B (for HBsAg and anti-HBc).

Persons found to be HBsAg-positive should be evaluated for indications for therapy of hepatitis B and, if found to warrant treatment, started on appropriate therapy before starting cancer chemotherapy or immune suppression. Such therapy should continue for the duration of chemotherapy and for as long as dictated by the chronic hepatitis B.

Persons found to have the inactive HBsAg carrier state or immune-tolerant chronic hepatitis B should receive antiviral prophylaxis before starting chemotherapy or immune suppression.

Persons found to have anti-HBc without HBsAg in serum should be considered for antiviral prophylaxis if they are scheduled for organ or bone marrow transplan-

tation or if aggressive or prolonged chemotherapy or immune suppression is planned.

Prophylaxis against HBV reactivation should continue for at least 6 months after stopping chemotherapy. In situations in which immune suppression is continued for the long term, long-term prophylaxis should be considered.

Although lamivudine or adefovir may be adequate for short-term prophylaxis, antiviral nucleoside analog with a higher barrier to resistance should be considered for patients in whom long-term prophylaxis is likely, particularly if high levels of HBV DNA are present before immune suppressive therapy.

Needs for Future Research

The complexity of reactivation of hepatitis B and the many issues surrounding its management call for prospective studies of its incidence, pathogenesis, treatment, and prevention. At present, recommendations have to be based on our understanding of reactivation, uncontrolled observations, and limited studies of its prevention. Because the oral nucleoside analogs active against hepatitis B are relatively potent and are well tolerated, prevention is easy to recommend. More difficult is to decide when to stop therapy and how to monitor patients before or during prophylaxis. Although future controlled studies of prophylaxis versus no prophylaxis are not warranted, controlled trials of different approaches to prophylaxis are reasonable and would provide valuable information. Thus, prospective clinical trials might compare the efficacy of lamivudine versus entecavir or tenofovir, or evaluate discontinuation of prophylaxis at 2 versus 12 months after stopping chemotherapy. Studies of nonliver organs from donors with anti-HBc without HBsAg might be developed that compared limited, short-term prophylaxis to continued antiviral therapy. These studies should include careful virological analyses and ancillary studies directed at elucidating the nature of HBV latency, factors that lead to an increase in HBV replication and liver cell injury, and features of the innate and adaptive immune system that lead to immune clearance of HBV after acute reactivation.

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No. 3

医薬品 研究報告 調査報告書

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研究報告の概要

○日本のB型肝炎ウイルス(HBV)陽性供血者のHBV genotypeの年齢、性別特異的な分布

背景:日本の急性・慢性HBV感染患者において、B型肝炎ウイルス(HBV)genotype分布の報告が増加しているが、供血者のHBV genotypeについての報告はほとんどない。B型肝炎表面抗原(HBsAg)陽性供血者のHBV genotypeを感染患者と比較するために、すべてのHBsAg陽性供血者のgenotypeを決定した。

試験デザインおよび方法:2006年10月～2007年9月の日本の供血者のデータを、日本赤十字社のデータベースから入手した。利用可能な検体数は1979検体であり、1887検体でHBV genotypeを決定した。HBVの6つの主要genotype(A-F)を、酵素結合免疫吸着検定法を用いて調べた。HBsAg陽性ドナー全員について、抗HBVコア抗原IgM抗体の有無を酵素免疫測定法を用いて調べた。

結果:ドナーと患者の間のHBV genotype分布に関する有意差はC/B遺伝子型比率でみられた。比率は供血者(2.0～3.9)で低く、患者(5.3～18.2)で高かった。genotype Bの比率は、10代のドナーの13.8%から50歳台の42.4%まで増加するが、genotype C比率の差は、10代ドナーの83.1%から50代では55.1%に減少する。抗HBVコア抗原IgM抗体および核酸増幅検査陽性供血者において、genotype AとBは男性のドナーに限定された。

結論:日本の供血者において、HBV遺伝子型の年齢特異的な分布が、genotype C/Bの比で観察された。米国または西欧諸国を起源とするHBV genotype Aの性別特異的な分布が、日本の男性ドナーに観察された。

報告企業の意見	今後の対応
日本のHBsAg陽性供血者においてHBV遺伝子型の分布を調べたところ、genotype Cは若年層で、Bは中高年層でより多く、genotype Aはほとんどが男性供血者であった。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おり、安全性は確保されていると考える。	特別な対応を必要としないが、HBV感染に関する新たな知見等について今後も情報の収集に努める。

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
クロスエイトM静注用250単位
クロスエイトM静注用500単位
クロスエイトM静注用1000単位

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

4

MedDRA/J Ver 12.0.1

Age- and gender-specific distributions of hepatitis B virus (HBV) genotypes in Japanese HBV-positive blood donors

Akira Yoshikawa, Yuko Gotanda, Yoshiharu Suzuki, Masako Tanaka, Harumichi Matsukura, Toshio Shiraishi, Keiji Matsubayashi, Emi Kon, Ko Suzuki, Hisao Yugi, and the Japanese Red Cross HBV Genotype Research Group

BACKGROUND: There are an increasing number of reports on the hepatitis B virus (HBV) genotype distribution in acute or chronic HBV-infected patients in Japan; however, reports on the HBV genotype of blood donors are few. To compare the HBV genotypes of hepatitis B surface antigen (HBsAg)-positive blood donors with infected patients, all the HBsAg-positive donors' genotypes were determined.

STUDY DESIGN AND METHODS: Data on Japanese blood donors from October 2006 to September 2007 were obtained from the Japanese Red Cross database. The number of available samples was 1979, and the HBV genotypes were determined in 1887 samples. The six major genotypes of HBV (A-F) were determined by enzyme-linked immunosorbent assay. The presence of the immunoglobulin M (IgM) antibody against the HBV core antigen was determined by enzyme immunoassay among all HBsAg-positive donors.

RESULTS: A significant difference in the HBV genotype distribution between donors and patients was in the C/B genotype ratio. The ratios were low in blood donors (2.0-3.9) and high in patients (5.3-18.2). The genotype B ratio increases from 13.8% in teenage donors to 42.4% in those in their 50s; however; the genotype C ratio decreases from 83.1% in teenage donors to 55.1% in those in their 50s. In both IgM antibody against hepatitis B core antigen and nucleic acid test–positive donors, genotypes A and B were restricted to male donors.

CONCLUSIONS: The age-specific distribution of HBV genotypes in Japanese blood donors was observed in the B/C genotype ratio. The gender-specific distribution of HBV genotype A, which originated from the US or Western countries, was observed in male Japanese donors.

The hepatitis B virus (HBV) genotype is important in epidemiologic studies, analysis of modes of infection, and medical treatment. There are eight HBV genotypes designated as A to H on the basis of greater than 8% nucleotide variation over the entire genome.[1-3] HBV genotypes are distributed in distinct geographical localizations.[1-6] HBV genotype A is detected in America, Northern Europe, and India.[4] Genotypes B and C are prevalent in Asia.[5] Genotype D is detected around the Mediterranean Sea.[4] Genotype E is restricted to Africa,[2] and Genotypes F and H are prevalent in South and Central America.[6] Genotype G has been found in France, Germany, the United States, and Mexico.[3]

The clinical significance of HBV genotype has been reported. The HBV genotype may affect hepatitis B e antigen (HBeAg) seroconversion rates, mutational patterns in the precore and core promoter regions, response to interferon, and the severity of liver disease.[4,5,7,8] Comparisons between Genotypes A and D in Europe and America, and between Genotypes B and C in Asia, have been reported. Genotypes A and B are more sensitive to interferon than Genotypes C and D.[9]

ABBREVIATIONS: HBeAg = hepatitis B e antigen; JRC = Japanese Red Cross; MSM = men who had sex with other men.

From the Japanese Red Cross Saitama Blood Center, Saitama; the Japanese Red Cross Tokyo Blood Center, Tokyo; the Japanese Red Cross Osaka Blood Center, Osaka; the Japanese Red Cross Hokkaido Blood Center, Hokkaido; the Blood Services Department, Japanese Red Cross Headquarters, Tokyo; and the Japanese Red Cross Tokyo Nishi Blood Center, Tokyo, Japan.

Address reprint requests to: Akira Yoshikawa, Japanese Red Cross Saitama Blood Center, 1370-12 Takahagi, Hidaka-shi, Saitama-ken 350-1213, Japan; e-mail: yoshikawa@saitama.bc.jrc.or.jp.

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Despite the distinct geographical localization of HBV genotypes, the rate of Genotype A has increased in Japanese blood donors as well as Japanese acute HBV patients.[10] To provide an overview of the present state of HBV infection and the HBV genotype distribution in Japanese blood donors, the HBV genotypes of hepatitis B surface antigen (HBsAg)-positive donors from October 2006 to September 2007 were determined.

MATERIALS AND METHODS

Data of blood donors

Data of Japanese blood donors were obtained from the Japanese Red Cross (JRC) database. The number of total blood donors was 4,974,911, and the number of HBsAg-positive donors was 2043 (0.041%). The number of first-time blood donors was 594,096, and the number of HBsAg-positive first-time blood donors was 1362 (0.23%) from October 2006 to September 2007.

The number of available samples was 1979, and the HBV genotypes could be determined in 1887 samples. The HBV DNA load of the other 92 samples was too low for the determination of the HBV genotypes.

Determination of HBV genotypes and subgenotypes

The six major HBV genotypes (A-F) were determined by enzyme-linked immunosorbent assay (ELISA; HBV Genotype enzyme immunoassay [EIA], Institute of Immunology, Tokyo, Japan). This method involves the use of monoclonal antibodies directed to five epitopes exposed on the pre-S2 region of the HBV genome.[11] When a genotype could not be determined by the ELISA, they were determined by direct sequencing of the surface region using a cycle sequencing kit and a genetic analyzer (BigDye Terminator and ABI PRISM 3100, respectively, PE Applied Biosystems, Foster City, CA). To analyze the sequences, two different computer programs were used (SEQUENCHER MAC, Version 4.1, Hitachi Software Engineering, Tokyo, Japan; or GENETYX MAC, Version 9.0, Software Development Co., Tokyo, Japan). The primers from HBsAg region were used as follows: S1-1 (sense, 5′-TCGTGTTACAGGCGGGGTTT-3′[nts]192-211), S1-2 (antisense, 5′-CGAACCACTGAACAAATGGC-3′[nts]689-5-704), S2-1 (nested sense, 5′-CAAGGTATGTTGCCCGTTTG-3′[nts]455-474), and S2-2 (nested antisense, 5′-GGCACTAGTAAACTGAGCCA-3′[nts]668-687).

The subgenotypes Aa (Asian type) and Ae (European type) were determined on the basis of the α region of 1556 bases (nt 2333-3221 and 1-667) and the subgenotypes Ba (Asian type) and Bj (Japanese type) were determined on the basis of the precore region of nucleotide 1838.[12,13] The primers from α region were as follows. For first polymerase chain reaction (PCR), HB104 (sense, 5′-AGACCACCAAATGCCCCTATC-3′[nts]2297-2317) and S1-2 (antisense) were used. For nested PCR, HB106 (nested sense, 5′-CCCCTATCYTATCMACACTTCCG-3′[nts]2310-2332) and S2-2 (nested antisense) were used. The primers from precore region were as follows. For first PCR, PC1-1 (sense, 5′-CATAAGAGGACTCTTGGACT-3′[nts]1653-1672) and PC1-2 (antisense, 5′-AAAGAATTCAGAAGGCAAAAAAGA-3′[nts]1949-1972) were used. For nested PCR, PC2-1 (nested sense, 5′-AATGTCAACGACCGACCTTG-3′[nts]1679-1698) and PC2-2 (nested antisense, 5′-TCCACAGAAGCTCCGAATTC-3′[nts]1922-1941) were used.

Serologic screening and nucleic acid amplification technology

The Japanese screening system was described previously.[14] Briefly, samples were screened for HBsAg by reverse passive hemagglutination and confirmed by EIA (AxSYM, Abbott Laboratories, Abbott Park, IL) and for HBV core antibody (anti-HBc) by hemagglutination inhibition.[14] The sensitivity of reverse passive hemagglutination for HBsAg was approximately 2 ng/mL. The presence of the immunoglobulin M antibody against the HBV core antigen (IgM-HBcAb) was determined by EIA (Abbott Laboratories) among all the HBsAg-positive donors from October 2006 to September 2007.

The nucleic acid amplification technology (NAT) system has been described elsewhere.[15] The present pool size of JRC is 20. The 95% HBV DNA detection limit of the AMPLINAT MPX test system was found to be 30 (22-60) copies/mL based on a plasma standard quantified in the Amplicor Monitor assay (Roche, Indianapolis, IN)[16] and was found to be 15 IU/mL (60 copies/mL) according to validation studies with the WHO standard by JRC. Serologically positive and alanine aminotransferase (ALT)-elevated (>60 IU/mL) samples were excluded from NAT screening.

Statistical analysis

The proportional distributions of genotypes were compared using Fisher's exact test, chi-square test with Yates' correction, and F-test. A p value of less than 0.05 was considered significant.

RESULTS

The number of total blood donors and that of first-time blood donors of every age group from October 2006 to September 2007 are shown in Fig. 1. The median age of total donors was 37 years and that of first-time donors was 24 years. The male/female ratio of total donors was 1.89 (1.29 for those 20-29 years old and 2.13 for those 30-39 years old) and that of first-time donors was 1.39. The rate

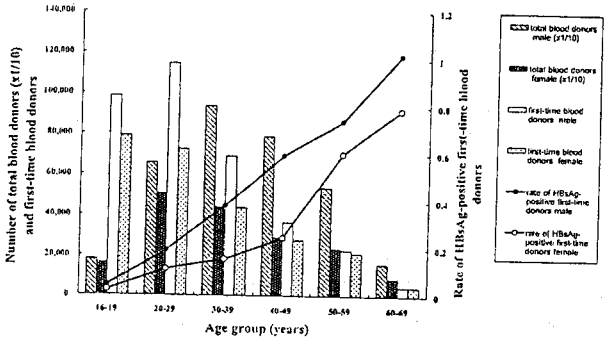

Fig. 1. Number of total and first-time blood donors and rate of HBsAg-positive first-time blood donors. Left axis shows male and female total and first-time blood donors. The number of total blood donors was multiplied by 1/10. Therefore, the number of first-time blood donors was approximately 10% of total blood donors. The median age of total blood donors was 37 years and that of first-time blood donors was 24 years. The right axis shows the rate of HBsAg-positive male and female first-time blood donors. The rate of HBsAg-positive first-time blood donors was found to increase with age. Blood donors aged 16 to 19 years were born after 1986, the year a selective vaccination program to prevent mother-to-infant infection by HBV was started. Blood donors aged 60 to 69 years were born at around World War II.

TABLE 1. Distribution of HBV genotypes in Japanese blood donors and patients

			Number	Genotype (%)			
				A	B	C	D-F and mix
Blood donors	Total HBsAg positive		1887	5.6	30.8	62.6	1.0
	First-time		1349	5.0	31.0	62.3	1.7
	Repeat		538	6.9	30.3	62.3	0.5
	IgM-HBcAb positive		61*	21.7	15.0	63.3	0.0
	NAT-positive†		68	19.1	16.2	63.2	1.5
Patients‡	Chronic	Kobayashi et al.[18]	1077	1.9	9.4	87.7	1.0
		Orito et al.[19]	720	1.7	12.2	84.7	1.4
		Takeda et al.[20]	80	0.0	6.3	93.7	0.0
		Hayashi et al.[21]	123	3.3	15.4	81.3	0.0
	Acute	Takeda et al.[20]	98	18.4	4.1	74.5	3.0
		Hayashi et al.[21]	123	21.1	8.1	67.5	3.3
		Sugauchi et al.[22]	485	19.0	12.0	68.0	1.0

* The genotype of one sample could not be determined.
† The number of NAT-positive donors was not included in the total HBsAg-positive donors. Twenty-two HBcAb-positive cases were excluded.
‡ The representation of patients was modified as a percentage.

of HBV-positive first-time blood donors increased with increasing age (Fig. 1). The rate of HBV-positive first-time blood donors in Japan decreased yearly from 1.07% in 1995 and 0.22% in 2007 (data not shown).

The HBV genotype distribution in HBsAg-positive blood donors from October 2006 to September 2007 is shown in Table 1. The number of first-time donors was 1349 and that of repeat donors was 538. Among repeat donors, HBsAg seroconverted donors were approximately 10%, because JRC accepted the donors' right to refuse to receive the notification of human immunodeficiency virus (HIV), hepatitis C virus (HCV), and HBV infections. Therefore, some HBsAg-positive donors donate repeatedly. All the HBsAg-positive samples were tested for IgM-HBcAb. Sixty-one samples were IgM-HBcAb positive ($1.2 \leq s/n$). Thirty-three of the 61 samples were from first-time donors and 28 samples were from repeat donors. In addition to the 1887 HBsAg-positive donors, 90 HBV NAT–positive (HBsAg-negative and HBV DNA–positive) donors were detected. Twenty-two HBV NAT–positive donors were considered not to be in the serologic window period and were excluded because they were HBcAb and HBV DNA positive but IgM-HBcAb and HBsAg negative. If high-sensitive tests were implemented, some of NAT-positive donors including these 22 donors became HBsAg positive.

Comparison of the genotypes of donors and patients

To compare the genotypes of donors and patients, five references[18-22] are cited in Table 1. The HBV Genotype A distribution in total HBsAg-positive donors (5.6%) was similar to that of chronic patients (0.0%-3.3%) and that of acute patients (18.4%-21.1%) was similar to that of IgM-HBcAb– (21.7%) or NAT-positive (19.1%) donors. A significant difference in HBV genotype distribution between donors and patients was in the C/B genotype ratio. The ratios were low in blood donors (2.0-3.9) and high in patients (5.3-18.2; $p < 0.01$). However, there was no significant difference in the C/B genotype ratio between chronic patients (5.3-14.9) and acute patients (5.7-18.2).

Age-specific distribution of genotypes

The distribution of genotypes among the same age group is shown in Fig. 2. The following calculation was conducted from the data in Table 2. The distribution of Genotype B increases from 13.8% (9/65) in 16- to 19-year-old donors to 42.4% (189/446) in 50- to 59-year-old donors ($p < 0.01$); however, the Genotype C ratio decreases from 83.1% (54/65) in 16- to 19-year-old donors to 54.9% (245/446) in 50- to 59-year-old donors ($p < 0.05$). The genotype distribution among age groups is shown in Table 2. Genotype A was found in approximately 90% (23.6% + 37.7% + 28.3%) of 20- to 49-year-old donors. On the other hand, Genotype C was found in every age group, whereas Genotype B was most prevalent in those 50 to 59 years old (32.5%).

Gender-specific distribution of genotypes and subgenotype

The male/female ratio of total donors was 1.89 (3,253,849/1,721,062), that of first-time donors was 1.39 (345,986/248,110; $p < 0.01$), that of Subgenotype Ae was 13.8 (69/5; $p < 0.01$), that of Subgenotype Aa was 4.2 (25/6), that of Subgenotype Ba was 2.45 (98/40), that of Bj was 2.49 (276/111; $p < 0.05$), and that of Genotype C was 2.58 (851/330; $p < 0.01$; Table 3). The significance was compared with the male/female ratio of total donors using the chi-square test. Subgenotype Ae is male-specific.

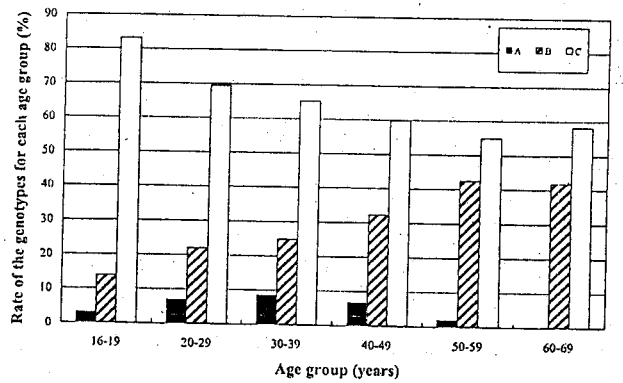

Fig. 2. Ratio of HBV Genotypes A, B, and C within each age group. The numbers of HBsAg-positive donors were 65 (16-19 years), 364 (20-29 years), 469 (30-39 years), 433 (40-49 years), 446 (50-59 years), and 110 (60-69 years). The ratio of Genotype C decreased from 83.1% (54/65) for those aged 16 to 19 years to 54.9% (245/446) for those aged 50 to 59 years; however, that of Genotype B increased from 13.8% (9/65) for those aged 16 to 19 years to 42.4% (189/446) for those aged 50 to 59 years.

TABLE 2. Age-specific distribution of each HBV genotype

Genotypes	Total number (%)	Age (years)					
		16-19	20-29	30-39	40-49	50-59	60-69
A	106 (100)	2 (1.9)	25 (23.6)	40 (37.7)	30 (28.3)	9 (8.5)	0 (0)
B	581 (100)	9 (1.5)	80 (13.8)	117 (20.1)	140 (24.1)	189 (32.5)	46 (7.9)
C	1181 (100)	54 (4.6)	253 (21.4)	306 (25.9)	259 (21.9)	245 (20.7)	64 (5.4)
D-F and mix	19 (100)	0 (0)	6 (31.6)	6 (31.6)	4 (21.0)	3 (15.8)	0 (0)
Total	1887 (100)	65 (3.4)	364 (19.3)	469 (24.9)	433 (23.0)	446 (23.6)	110 (5.8)

TABLE 3. Age- and gender- specific distributions of HBV genotype or subgenotype

Gender	Age (years)	Total	HBV genotype and subgenotype						
			Aa	Ae	Ba	Bj	B (a/J)*	C	D-F
Male	16-39	687	19	42	54	85	16	463	8
	40-69	684 + 1†	6	27	44	191	22	388	6
Female	16-39	211	3	3	24	24	3	150	4
	40-69	304	3	2	16	87	15	180	1
Total	16-69	1887	31	74	138	387	56	1181	19

* Subgenotype could not be determined.
† Subgenotype could not be determined in one sample Aa or Ae.

TABLE 4. HBV genotype or subgenotype of IgM-HBcAb–positive and NAT-positive donors

Gender	Age (years)	Total	HBV genotype and subgenotype				
			Ae	Ba	Bj	C	E
Male	16-39	78 + 1*	23	9	3	43	0
	40-69	24 + 1†	3	5	2	14	0
Female	16-39	23	0	0	1	21	1
	40-69	2	0	0	0	2	0
Total	16-69	129	26	14	6	80	1

* Genotype of one sample could not determined.
† Subgenotype could not be determined in one sample Aa or Ae.

The trend toward male-specific infection is clear in HBV-positive donors who were infected recently. They are shown as IgM-HBcAb–positive donors (61 donors) and NAT-positive donors (68 donors) excluding HBcAb-positive (22 donors; Table 4). Both IgM-HBcAb– and NAT-positive donors were predominantly male except for those infected with Genotype C.

Although we could not exclude the possibility of reactivations completely in the case of IgM-HBcAb–positive donors, most reactivation cases would be excluded by the interview with donors whether they had medical history or not. The male/female ratio of those infected with Genotype C aged 16 to 39 years is low (2.05: 43/21), and the male/female ratio of those aged 40 to 69 years is high (7.0:14/2; $p < 0.05$).

DISCUSSION

The rate of HBV-positive donors has declined yearly in Japan. However, recently, the distribution of Genotype A has increased in blood donors and acute HBV patients.[10,17-22] The male/female ratio of those infected with Genotype A is different from the ratio of those infected with other genotypes. Particularly, IgM-HBc– or NAT-positive donors are restricted to males.

It is suggested that Subgenotype Ae might have been brought to Japan from the United States by a young male. This might be supported by the finding that the HBV Genotype A was predominant among HBV-HIV dually infected Japanese men who had sex with other men (MSM).[17] The sequences of Genotype A spread by MSM were highly homologous to those of the strains isolated in the United States. Although it has been reported that there is a tendency for Genotype A to spread among men rather than among women,[4] we could not explain whether this phenomenon might be related to MSM.

In addition to Subgenotype Ae, we have recently found Genotype H in a Japanese HBsAg-negative and NAT-positive blood donor.[23] The sequence of Genotype H, which is prevalent only in the United States and Central America, was highly homologous to those of the strains isolated in Los Angeles.

There was no difference in the HBV genotype distribution between first-time donors and repeat donors as shown in Table 1. The only difference between first-time donors and repeat donors was found when the Genotype A distributions of donors aged 16 to 39 and 40 to 69 years were considered (data not shown). The Genotype A ratio in first-time donors aged 16 to 39 years was 5.90% (40/678), whereas that in repeat donors aged 16 to 39 years was 12.27% (27/220; $p < 0.01$). That ratio in first-time donors aged 40 to 69 years was 4.2% (28/671) and in repeat donors aged 40 to 69 years was 3.5% (11/318; not significant).

The result was quite different from our expectation, because it was expected that the HBV-positive risk of first-time donors would be higher than that of repeat donors as shown in the case of HCV-positive donors.[10] HBV Genotype A–positive young donors might have a clear understanding of their risks and intend to test whether they would be infected with HBV or HIV. This might be suggested when IgM-HBcAb–positive donors were considered; the rates of repeat donors/first-time donors of Genotypes A, B, and C were 7/6, 4/5, and 17/22, respectively (data not shown). However, we must examine the result precisely, because most repeat donors might refuse to receive the notification of HBV infection and donate repeatedly. It might be interesting to compare the length of seroconversion between HBV- and HCV-positive donors. In any case, to reduce the risk of posttransfusion HBV infection, we should restrain the right of refusing to receive the notification of HIV, HCV, and HBV infections.

The characteristic difference in HBV genotypes distribution between blood donors and patients is in the B/C genotype ratio. In older blood donors, the ratio of Genotype B is markedly higher ($p < 0.01$).

The HBV genotypes show a relationship to clinical severity as well as a distinctive geographical distribution.[4,7,18] Genotype C is associated with the development of cirrhosis and hepatocellular carcinoma as well as a lower response rate to interferon therapy and with a lower rate of seroconversion from HBeAg to anti-HBe and a higher HBV DNA level compared with Genotype B.[5] ALT levels were significantly lower in patients with HBV Genotype B than in those with HBV Genotype A, C, or D.[24] From these lines of evidence, donors infected with HBV Genotype B would not be aware of the infection and would donate. Although donors infected with HBV Genotype C would donate while they are young and asymptomatic, they would eventually be symptomatic and would not donate when they reach old age.

These facts might be similar to those in the United States and Western Europe where HBV Genotypes A and D are prevalent. Although there are conflicting reports concerning the severity of diseases between those infected with Genotypes A and D, it would be interesting to know whether the distribution of Genotype A and D would change depending on age in these countries. Compared with Genotype D, Genotype A is more prevalent in HBeAg-positive than in anti-HBe–positive patients.[24] Although Genotype A may induce more severe hepatocytic lesions than Genotype D,[4] Genotype A is more sensitive to interferon than Genotype D.[24] HBsAg clearance occurred more often in patients with Genotype A than in those with Genotype D.[25]

In Japan, Genotypes C and B are predominant in HBV-positive donors. There is a distinctive geographical distribution in Japan. In the northern part of Japan, the distribution of Genotype B is 44.7% (350/783) and that of Genotype C is 48.8% (382/783); however, in the southern part of Japan, that of Genotype B is 20.9% (231/1104) and that of Genotype C is 72.4% (799/1104) except for Okinawa. In Okinawa, the southernmost part of Japan, that of Genotype B is 74.2% (23/31) and that of Genotype C is 22.6% (7/31) (data not shown).

Although now, the age-, gender-, and geographic-specific distributions of HBV genotypes have been determined, the specific distribution of the genotypes may change in the near future. Because the Japanese government began a nationwide hepatitis B vaccination program in January 1986 for infants born to HBV-positive mothers to prevent perinatal HBV infection,[26,27] the vertical infection from mother to infants would be reduced and the horizontal infection by sexual contact would be increased. Therefore, the geographical distribution of HBV genotypes would change and the distribution of Genotype A would increase in younger males as shown in Tables 1 through 4. To decrease the risk of posttransfusion HBV infection, we should continue to study the epidemiology of HBV genotype distribution.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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No. 5

医薬品 研究報告 調査報告書

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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
○E型肝炎ウイルスgenotype 3の高病性株、日本 本邦において、通常は無症候性のE型肝炎ウイルス(HEV) genotype 3により、患者8名に重症肝炎が引き起こされた。毒性の強いHEVの遺伝的特性を理解するために、HEV genotype 3株に感染した患者8名とブタ5匹から得たウイルスの完全またはほぼ完全なヌクレオチド配列を決定した(swJ19)。系統発生解析では、これらの分離株が、他のgenotype 3分離株と異なるグループに分類され、JIOと称される独自のクラスターを形成することが明らかになった。ヒトのJIO関連ウイルスは、他のHEV genotype 3とは異なる18のアミノ酸をコードした。JIOクラスターのヒトHEV株のほぼすべてに共通する置換は、ヘリカーゼ領域(V239A)に位置し、毒性の増加と関係する可能性が考えられた。ブタ5匹由来の分離株にも特徴的なヘリカーゼのV239A置換が起こっており、JIO関連ウイルスの起源が人獣共通であることが疑われる。	赤十字アルブミン20 赤十字アルブミン25 赤十字アルブミン20%静注4g/20mL 赤十字アルブミン20%静注10g/50mL 赤十字アルブミン25%静注12.5g/50mL 血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
本邦において、通常は無症候性のE型肝炎ウイルスgenotype 3により患者8名に重症肝炎が引き起こされた。分離株が他のgenotype 3分離株と異なるグループに分類され、特徴的なアミノ酸置換が起こっていたとの報告である。 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および液状加熱の2つのウイルス除去・不活化工程が含まれているが、最近HEVの耐熱性を示唆する成績が発表され、液状加熱の有効性に疑念を生じている。しかし疫学的に見て、血漿分画製剤で最も長い歴史を持つアルブミンではHEVの侵淫度が遥かに高い過去においても世界的に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。	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。

(5)

RESEARCH

Virulent Strain of Hepatitis E Virus Genotype 3, Japan

Kazuaki Takahashi, Hiroaki Okamoto, Natsumi Abe, Manri Kawakami, Hiroyuki Matsuda, Satoshi Mochida, Hiroshi Sakugawa, Yoshiki Suginoshita, Seishiro Watanabe, Kazuhide Yamamoto, Yuzo Miyakawa, and Shunji Mishiro

Hepatitis E virus (HEV) genotype 3, which usually causes asymptomatic infection in Japan, induced severe hepatitis in 8 patients. To better understand genetic features of HEV associated with increased virulence, we determined the complete or near-complete nucleotide sequences of HEV from these 8 patients and from 5 swine infected with genotype 3 strain swJ19. Phylogenetic analysis showed that the isolates from the 8 patients and the 5 swine grouped separately from the other genotype 3 isolates to create a unique cluster, designated JIO. The human JIO-related viruses encoded 18 amino acids different from those of the other HEV genotype 3 strains. One substitution common to almost all human HEV strains in the JIO cluster was located in the helicase domain (V239A) and may be associated with increased virulence. A zoonotic origin of JIO-related viruses is suspected because the isolates from the 5 swine also possessed the signature V239A substitution in helicase.

Hepatitis E virus (HEV) infection is relatively common. Anti-HEV antibodies are found in 10%–20% of the general population in Japan and most Asian countries (*1*,*2*); however, only a small fraction of these infections induce overt hepatitis. Although the mechanisms underlying induction of liver damage by HEV have not been well characterized, HEV genotypes seem to have distinct disease-inducing potential. HEV sequences have been classified into 4 genotypes (*3*). Genotype 1 consists of epidemic strains in developing countries of Asia and Africa. Genotype 2 is represented by the prototype sequences from an epidemic in Mexico, which have also recently been detected in Africa. Genotypes 3 and 4 are distributed worldwide and have been implicated in sporadic cases of acute hepatitis E in humans and domestic pigs. HEV genotypes 3 and 4 are found in Japan, but fulminant or severe acute hepatitis develops more frequently in persons infected with genotype 4 (*4*–*6*). The severity of liver disease may therefore be influenced by the HEV genotype with which the patient is infected as well as host factors such as age, gender, and pregnancy status.

In 1997, we identified a strain of HEV from a patient in Japan who had acute hepatitis (designated JIO) that clustered with genotype 3 sequences. From 2004 through 2006, JIO-related viruses were isolated from 7 additional patients who had acute or severe hepatitis. To better understand genetic features of HEV associated with severe hepatitis, we compared the complete or near-complete sequence of JIO isolates from these 8 patients with other well-characterized genotype 3 and 4 isolates. To determine whether these human genotype 3 sequences were zoonotic in origin, we sequenced full-length viral genomes from 5 swine infected with the swJ19 strain of HEV. These 5 animals were part of a larger outbreak of HEV infection that occurred in swine at a single farm in southern Japan during 2000–2002. The GenBank/EMBL/DDBJ accession numbers for nucleotide sequences of HEV isolates are AB291951–7/AB291960 (for the human isolates) and AB443623-7 (for the swine isolates).

Author affiliations: Toshiba General Hospital, Tokyo, Japan (K. Takahashi, N. Abe, S. Mishiro); Jichi Medical University School of Medicine, Tochigi, Japan (H. Okamoto); Kurashiki Medical Center, Okayama, Japan (M. Kawakami); Matsuda Naika Clinic, Tottori, Japan (H. Matsuda); Saitama Medical University, Saitama, Japan (S. Mochida); Heart-Life Hospital, Okinawa, Japan (H. Sakugawa); Kyoto University Graduate School of Medicine, Kyoto, Japan (Y. Suginoshita); Kagawa Prefectural Central Hospital, Kagawa, Japan (S. Watanabe); Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama (K. Yamamoto); and Miyakawa Memorial Research Foundation, Tokyo (Y. Miyakawa)

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Methods

We enrolled 8 patients who were infected with HEV genotype 3 and had clinical features of hepatitis (Table 1). A zoonotic source of HEV infection was identified for 3 of these patients: pig liver for patient 4, pig meat for patient 6, and wild boar meat for patient 7. Prothrombin time, a surrogate marker of hepatic insufficiency, averaged 63.9% (± 29.1%) of the reference range among the 8 HEV genotype 3–infected patients. Hepatitis was particularly severe in patients 3, 5, 7, and 8; at the peak of disease, prothrombin times for these patients ranged from 27% to 46% of the reference range. These sporadic HEV cases were not clustered geographically; they were distributed across several regions of Japan, including southern (Okinawa) and northern (Saitama) prefectures (Figure 1). Informed consent was obtained from all patients after the nature and purpose of the study was explained to them.

To assess possible zoonotic origins of these human infections, we sequenced HEV strain swJ19 isolates from 5 of 11 swine with previously documented infections (*7*). These animals had been raised commercially at a farm in the southern part of Miyazaki Prefecture where HEV infections were detected during 2000–2002. All animals received humane care, and the study was approved by the institutional review committee of Toshiba General Hospital, Tokyo, Japan.

To determine whether infections could be linked to a common genotype 3 virus, we compared the genetic structure and sequence homology of 8 human and 5 swine HEV strains. The entire or near-complete nucleotide sequences of the 8 JIO strain isolates from the human patients and the swJ19 strain isolates from the 5 swine were determined by a method reported previously (*8*,*9*), with some modifications. In brief, nucleic acids were extracted from serum with the QIAamp MinElute Virus Spin Kit (QIAGEN GmbH, Hilden, Germany). HEV RNA genomes were reverse transcribed, and cDNA was amplified by PCR with primers specific for 23 overlapping regions of the HEV genome. Reverse transcription and first-round PCR were conducted by using the SuperScript III One-Step RT-PCR System (Invitrogen Corporation, Carlsbad, CA, USA); second-round PCR was conducted with the Platinum Taq DNA polymerase (Invitrogen). The 5′- and 3′-terminal sequences were amplified by using the SMART RACE cDNA Amplification Kit (Clontech Laboratories Inc., Mountain View, CA, USA) and Oligo (dt)20 Primer (Invitrogen), respectively. The sequences enriched in G-C were amplified with the TaKaRa LA Taq in GC Buffer (TaKaRa Shuzo Co. Ltd., Shiga, Japan). The sequences not amplifiable by the above PCR methods were subjected to PCR with primers deduced from adjacent 5′ and 3′ sequences. The final products were sequenced in the 377 DNA Sequencer with use of the BigDye Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA). Genetic analyses of HEV sequences were conducted by the unweighted pair-grouping method with arithmetic means by using computer software GENTYX-MAC Version 13 (Genetyx Corporation, Tokyo, Japan).

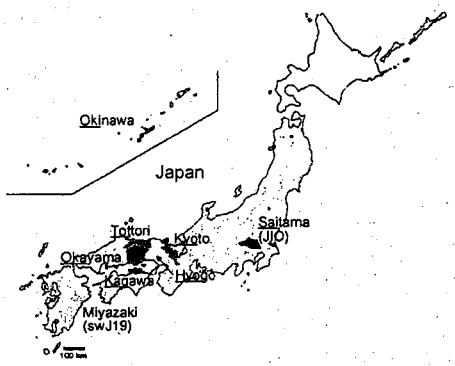

Figure 1. Map of Japan showing prefectures where human cases of hepatitis E virus have been found. Underlining indicates part of prefecture name included in isolate name; yellow indicates cases in swine; red indicates cases in humans.

Table 1. Profiles of 8 patients infected with hepatitis E virus, JIO strain, Japan*

Patient no.	Age, y/sex	Residence	Month of disease onset	Diagnosis	Nadir PT, %	Presumed route of transmission	Isolate name
1	50/M	Saitama	1997 Apr	Acute hepatitis	100	Unknown	JIO-Sai97L
2	76/M	Tottori	2004 Jan	Acute hepatitis	92	Unknown	JYM-Tot04L
3	63/M	Okinawa	2004 May	Acute hepatitis	46	Unknown	JYU-Oki04L
4	71/F	Okayama	2004 Dec	Acute hepatitis	75	Pig liver	JSS-Oka04L
5	65/M	Tottori	2005 Jun	Acute severe hepatitis	34	Unknown	JIY-Tot05L
6	78/M	Okinawa	2005 Jul	Acute hepatitis	92	Pig meat	JSO-Oki05L
7	63/M	Kagawa	2006 Mar	Acute hepatitis	45†	Wild boar meat	JTK-Kag06C
8	79/M	Kyoto	2006 Sep	Fulminant hepatitis	27	Unknown	JSW-Kyo-FH06L

*PT, prothrombin time.
†Only 1 determination was made.

Results

The prototypical isolate, JIO-Sai97L, had a genome length of 7,215 nt that contained a 5′ untranslated region (UTR), 3 open reading frames (ORFs), a 3′ UTR, and a poly-A tail. Lengths of HEV genomes from 6 other patients (JYM-Tot04L, JYU-Oki04L, JSS-Oka04L, JIY-Tot05L, JSO-Oki05L and JSW-Kyo-FH05L) were identical to that of JIO-Sai97L. An exception was the HEV isolate JTK-Kag06C from patient 7, which was slightly longer (7,236 nt). The 5 HEV isolates from swine (swJ19-1, swJ19-2, swJ19-5, swJ19-7, and swJ19-8) had genomes of 7,210 nt. The 3 ORFs of all swine and human HEV genomes had identical protein coding capacity. HEV isolates from all human patients had 97.9%–98.6% sequence homology with the prototypical JIO-Sai97L strain from patient 1. The 5 swine swJ19 isolates had 98.3%–99.9% sequence homology when compared with each other and 98.0%–99.8% homology when compared with the JIO strain from human patients.

Comparison of nucleotide sequences of the 13 human and swine HEV isolates in this study with those of published HEV genotype 3 sequences showed that the 13 complete and near-complete sequences described in this study closely matched those of 2 well-characterized genotype 3 viruses: JRA1 (89.4%–89.7% nucleotide identity) and swJ570 (88.9%–89.0% nucleotide identity). The 13 human and swine genotype 3 isolates displayed weak homology with other HEV genotypes. The B1 isolate of genotype 1 (GenBank accession no. M73218) was only 74.1%–74.7% similar to these genotype 3 viruses, the M1 isolate of genotype 2 (accession no. M74506) was only 73.6%–74.0% similar, and the T1 isolate of genotype 4 (accession no. AJ272108) was only 75.6%–76.0% similar.

Using the 13 complete or near-complete genomic sequences of HEV genotype 3 isolates described in this study (Figure 2), we constructed a phylogenetic tree. HEV sequences from the 8 patients (JTK-Kag06C, JYU-Oki04L, JSS-Oka04L, JIO-Sai97L, JSO-Oki05L, JSW-Kyo-FH06L, JIY-Tot05L, JYM-Tot04L) clustered on a branch separate from the other genotype 3 sequences, forming a distinct grouping related to the prototypical JIO strain. The swJ19 HEV sequences from the 5 swine (swJ19-1, swJ19-2, swJ19-7, swJ19-5, and swJ19-8) clustered closely with the JIO-related viruses from the human patients, indicating that the human and swine HEV isolates were highly similar (Figure 2, panel A). Another 18 swine isolates, from farms other than the 1 involved in the swJ19 outbreak, were phylogenetically distinct from those of the outbreak farms (Figure 2, panel B).

Another genotype 3 cluster was formed by 6 isolates from Hyogo Prefecture in western Japan (Figure 2, panel A). In this cluster were 5 HEV isolates from persons in whom hepatitis developed after they ate uncooked deer meat (*10*) and from serum from a local boar and a deer (*11*). Unlike the JIO-related viruses, which were broadly distributed from the most southern to northern Japanese prefectures, HEV strains responsible for the infections in Hyogo Prefecture were not commonly found in other parts

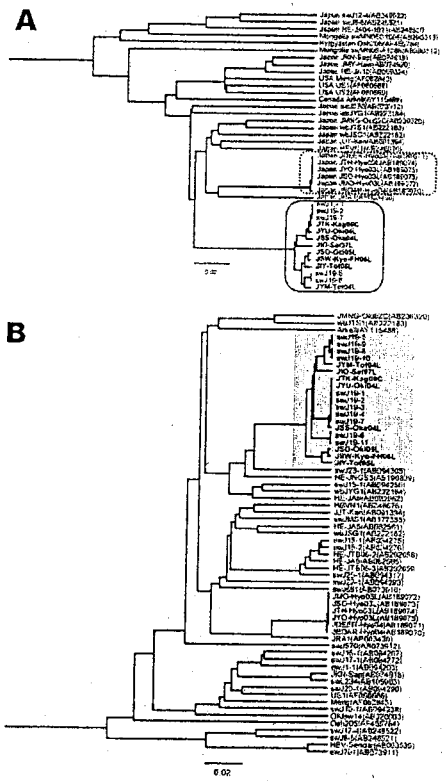

Figure 2. A) Phylogenetic tree (unweighted pair-grouping method with arithmetic means) constructed on the complete or near-complete nucleotide sequences of hepatitis E virus (HEV) genotype 3 isolates. Clustering of nucleotide sequences of 8 human patients infected with JIO strain of HEV and 5 swine infected with swJ19 strain of HEV is boxed by a solid line. Another clustering of local genotype 3 isolates from Hyogo Prefecture, Japan, is boxed by a dotted line. B) Phylogenetic tree (unweighted pair-grouping method with arithmetic means) constructed on a partial sequence of 412 nt in open reading frame (ORF) 2 (nt 5994-6405 of the US2 genome) of HEV genotype 3. Partial nucleotide sequences of 8 human JIO and 11 swine HEV swJI9 isolates (accession nos. AB094279–AB094289) are shown (shading). Analyses of full sequences of 5 of these 11 swine isolates were performed (swJ19-1, swJ19-2, swJ19-5, swJ19-7, and swJ19-8). Scale bars indicate nucleotide substitutions per site; **boldface** indicates isolates from humans.

of the country. Broad distribution of the JIO-related viruses seems to be unique in HEV epidemiology. In 2 (25%) of these 8 patients, pig liver or meat had been implicated in HEV infection.

Comparison of the 13 JIO-related viruses (Figure 2, panel A) with the other genotype 3 strains also showed 18 aa differences: 12 in ORF1, 3 in ORF2, and 3 in ORF3 (Table 2). Three mutations in the JIO strain were characteristic of genotype 4 viruses, which are typically more pathogenic than other HEV genotypes. ORF1 differences were found at amino acids 605 (serine to proline, S605P), 978 (isoleucine to valine, I978V), and 1213 (valine to alanine, V1213A). The V1213A substitution is potentially most relevant because it was not found in the prototypical isolate from patient 1 (JIO), who had mild clinical disease when infected in 1997, but was present in highly related isolates from the other 7 patients who had more severe hepatitis during 2004–2006. V1213A in ORF1 corresponds to V239A of the helicase domain, and its surrounding sequences were well conserved in HEV isolates of genotypes 3 and 4 (online Appendix Figure, available from www.cdc.gov/EID/content/15/5/704-appF.htm). Because V239A is common in genotype 4 isolates, we analyzed genomes of the genotype 3 JIO-related viruses for evidence of intergenotypic recombination. Comparison of 28 genotype 4 sequences with those of the JIO-related isolates showed no obvious signs of recombination (data not shown), which suggests that the V293A substitution arose independently in this genetically unique cluster of genotype 3 viruses. Notably, all 5 isolates recovered from swine on the Miyazaki Prefecture farm during the outbreak of 2000–2002 possessed the V239A substitution.

Discussion

Circumstantial evidence indicates that HEV genotype influences the severity of liver disease. Remarkably, HEV seroprevalence studies in Egypt found no clinical illness in any person, including pregnant women, although most (67.7%–84.3%) had been exposed to HEV genotype 3 (*13,14*). In contrast, results of a survey of 254 patients with HEV infection in Japan showed hepatitis associated with genotype 4 to be more severe than that associated with genotype 3 (*4*). Our results showed a clustering of 8 HEV isolates of JIO strain, genotype 3, recovered from patients with clinical hepatitis.

Despite the high disease-inducing activity of the HEV JIO strain, the 8 patients infected with this strain were distributed widely over Japan. This distribution is at odds with a local cluster of genotype 3 infections restricted to persons with hepatitis and to wild animals living in Hyogo Prefecture, Japan (Figure 2, panel A) (*11*). Wide regional distribution has also been reported for some HEV genotype 4 isolates (*15*). Why JIO strains caused more severe hepatitis than might be expected for a genotype 3 virus is

Table 2. Amino acid residues in 8 human and 5 swine hepatitis E virus isolates compared with those in the other genotype 3 isolates*

Amino acid position†	Conserved in genotype 3	Human no.								Swine no.					Conserved in genotype 4
		1	2	3	4	5	6	7	8	1	2	3	4	5	
ORF1															
154	A	A	T	A	A	T	T	A	T	A	A	T	A	T	T
547	R	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	R
598	R	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	K
605	S	P	P	P	P	P	P	P	P	P	P	P	P	P	P
721	A	T	T	T	T	T	T	T	T	T	T	T	T	T	A
807	A	S	S	S	S	S	S	S	S	S	S	S	S	S	A
978	I	V	V	V	V	V	V	V	V	V	V	V	V	V	V
979	S	K	K	K	K	K	K	K	K	K	K	K	K	K	E
1135	I	T	T	T	T	T	T	T	T	T	T	T	T	T	V
1213‡	V	V	A	A	A	A	A	A	A	A	A	A	A	A	A
1246	Q	H	H	H	H	H	H	H	H	H	H	H	H	H	D
1469	C	S	S	S	S	S	S	S	S	S	S	S	S	S	C
ORF2															
98	P	S	S	P	P	S	S	P	P	P	P	S	P	**S**	A
113	V/I	T	T	T	T	T	T	T	T	T	T	T	T	T	V
660	S	S	S	S	F	F	F	S	F	S	S	S	S	S	Y
ORF3															
91	S	N	N	N	N	N	N	N	N	N	N	N	N	N	S
97	A	A	V	V	V	V	V	V	V	V	V	V	V	V	A
98	P	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	P

*Eighteen amino acids of 8 human isolates (JIO strain) and 5 swine isolates (swJ19 strain) not shared by other genotype 3 isolates. The 3 at positions 605, 978, and 1213 (boldface) were the same as the corresponding residues in genotype 4 isolates.
†Corresponds to the position in hepatitis E virus (HEV)-US2 (GenBank/EMBL/DDBJ accession no. AF060669) (*12*).
‡V1213A in the open reading frame (ORF) 1 polyprotein corresponds to V239A in the HEV-US2 genotype 3 isolate helicase domain within ORF1 (online Appendix Figure, available from www.cdc.gov/EID/content/15/5/704-appF.htm).

not clear, but the reason may depend on the magnitude of virus replication. Alternatively, recombination between divergent HEV strains (*16*) may have played a role. This possibility prompted us to look for any recombination of JIO strains with genotype 4 strains that cause severe hepatitis in Japan. However, we found no evidence of recombination between the JIO strain of genotype 3 HEV with which the 8 persons were infected and 28 isolates of genotype 4 retrieved from the public and our own databases. The 18 aa substitutions were unique to the 8 human JIO and 5 swine sw19 isolates and not present in other genotype 3 viruses. Three differences in ORF1 (S605P, I978V, and V1213A) were common in wild type genotype 4 but not in genotype 3 isolates (Table 2). Because S605P and I978V are located in an ORF1 region that has high sequence divergence, they are unlikely to be responsible for an enhanced disease-inducing capacity. In contrast, V1213A changes at amino acid 239 of helicase, an enzyme capable of enhancing the efficiency of viral replication (*17*), were detected in 7 of the 8 patients (online Appendix Figure). Indeed, the helicase region of the prototypical JIO-Sai97L isolated in 1997 did not contain this amino acid polymorphism. Remarkably, all 5 swine isolates recovered in Miyazaki Prefecture during 2000–2002 belonged to the JIO strain and possessed V1213A (*hel*V239A). Taken together, the evidence strongly suggests a zoonotic origin for the 8 human HEV infections with JIO-related viruses.

Experimental and circumstantial evidence suggests that *hel*V239A may have enhanced the helicase activity of the genotype 3 JIO strain to levels comparable with those of the more pathogenic genotype 4 viruses. However, the role of *hel*V239A in enhancing helicase activity should be evaluated in vitro in future studies; its role in inducing hepatitis is yet to be confirmed. In addition, the effect of other mutations of JIO strains need to be fully explored before a conclusion can be drawn regarding the hepatitis-inducing capacities of this strain of HEV.

Findings from this study have public health implications. Because farm swine constitute a melting pot for generating various HEV mutants, at least in Japan where virtually all swine become infected with HEV within 4 months of birth, it is conceivable that virulent HEV mutant(s) arise on pig farms. Such occurrence has been described for influenza, for which point mutations are associated with increased virulence (*18,19*); for example, mutant influenza viruses that arose on chicken farms in Hong Kong in 1997 were transmitted to humans and had fatal consequences (*20,21*). In addition, although a vaccine against HEV has recently been developed (*22*), a vaccination strategy for humans and animals has yet to be defined. The results of our study indicate that selective vaccination of farm swine bearing HEV isolates of high virulence, such as those of the JIO strain in Miyazaki Prefecture, should be recommended to decrease the incidence of fulminant or severe acute hepatitis E in Japan and elsewhere in the world.

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Dr Takahashi is principal investigator in the Department of Medical Sciences at Toshiba General Hospital. His research interest is hepatitis viruses, most recently hepatitis E virus.

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Address for correspondence: Kazuaki Takahashi, Department of Medical Sciences, Toshiba General Hospital, 6-3-22 Higashi Oi, Shinagawa, Tokyo 140-8522, Japan; email: kazuaki6.takahashi@po.toshiba.co.jp

別紙様式第2-1

No. 6

医薬品 研究報告 調査報告書

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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) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○北海道内献血者におけるHEV感染の動向—4年間のまとめ—

【背景】北海道はHEV浸淫地区と考えられ、献血者におけるHEV感染の実態を解明するため、2005年から道内献血者のHEV RNAスクリーニング調査(HEV NAT)を実施してきた。

【方法】2005年1月から2008年11月にかけて、北海道内で献血した献血者、総数1,075,793名(男性663,155名、女性412,638名)について、20本プールによるHEV NATを行った。核酸抽出を行い、RT-PCRによりHEV RNAを検査した。また、陽性献血者について追跡調査および遡及調査を行い、喫食歴や自覚症状に関するアンケート調査、HEV抗体測定、HEV RNA定量、生化学検査、分子系統樹解析等を行なった。

【結果】HEV NAT陽性者総数は140名(男性103名、女性37名)で、2005年30名(男性17名、女性12名)、2007年31名(男性28名、女性3名)、2008年40名(男性31名、女性9名)であった。またHEV NAT陽性頻度(献血者延べ1万人当りの陽性者数)は、平均1.3人(男性1.6人、女性0.9人)、2005年1.0人(男性1.0人、女性1.1人)、2006年1.4人(男性1.6人、女性1.1人)、2007年1.2人(男性1.7人、女性0.3人)、2008年1.7人(男性2.0人、女性1.0人)であった。献血時のHEV抗体保有率は3割以下で、感染初期の献血が多かった。陽性者のHEV genotypeは3型と4型で、9割以上を3型が占めた。3型はさらに複数のクラスターに分類され、一部はブタ由来HEV株と高い相同性を示した。陽性者の約7割は献血前に動物内臓肉の喫食歴があり、また、陽性者の約半数は、その後ALT値の上昇が見られた。

【結論】北海道内の献血者集団におけるHEV RNA陽性頻度は高く、zoonotic infectionが起きていると考えられる。とくに男性におけるHEV陽性頻度は上昇傾向にあり、HEVは今後も十分な注意を要する肝炎ウイルスの一つである。

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

血液を原料とすることに由来する感染症伝播等

報告企業の意見

北海道内の献血者集団におけるHEV RNA陽性頻度は高く、特に男性においては上昇傾向にあり、zoonotic infectionが考えられるとの報告である。
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および液状加熱の2つのウイルス除去・不活化工程が含まれているが、最近HEVの耐熱性を示唆する成績が発表され、液状加熱の有効性に疑念を生じている。しかし疫学的に見て、血漿分画製剤で最も長い歴史を持つアルブミンではHEVの侵淫度が遥かに高い過去においても世界的に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。

今後の対応

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。

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O-051 北海道内献血者における HEV 感染の動向—4 年間のまとめ—

北海道赤十字血液センター検査部[1], 日本赤十字社血漿分画センター品質管理部 検査課[2]
松林圭二[1], 坂田秀勝[1], 佐藤進一郎[1], 加藤俊明[1], 池田久實[2]

【背景】北海道は HEV 浸淫地区と考えられ、献血者における HEV 感染の実態を解明するため、2005 年から道内献血者の HEV RNA スクリーニング調査 (HEV NAT) を実施してきた.
【方法】2005 年 1 月から 2008 年 11 月にかけて、北海道内で献血した献血者、総数 1,075,793 名 (男性 663,155 名, 女性 412,638 名)について、20 本プールによる HEV NAT を行った. Qiagen BioRobot 9604/MDx で核酸抽出を行い、TaqMan RT-PCR 法により HEV RNA を検査した. また、陽性献血者について追跡調査および遡及調査を行い、喫食歴や自覚症状に関するアンケート調査、HEV 抗体測定 (HEV Ab IgM, IgG, 特殊免疫研究所), HEV-RNA 定量, 生化学検査, 分子系統樹解析等を行なった.
【結果】HEV NAT 陽性者総数は 140 名 (男性 103 名, 女性 37 名) で、2005 年 30 名 (男性 17 名, 女性 13 名), 2006 年 39 名 (男性 27 名, 女性 12 名), 2007 年 31 名 (男性 28 名, 女性 3 名), 2008 年 40 名 (男性 31 名, 女性 9 名) であった. また HEV NAT 陽性頻度 (献血者延べ 1 万人当りの陽性者数) は、平均 1.7 人 (男性 1.6 人, 女性 0.9 人) で、2005 年 1.0 人 (男性 1.0 人, 女性 1.1 人), 2006 年 1.4 人 (男性 1.6 人, 女性 1.1 人), 2007 年 1.2 人 (男性 1.7 人, 女性 0.3 人), 2008 年 1.7 人 (男性 2.0 人, 女性 1.0 人) であった. 献血時の HEV 抗体保有率は 3 割以下で、感染初期の献血が多かった. 陽性者の HEV genotype は 3 型と 4 型で、9 割以上を 3 型が占めた. 3 型はさらに複数のクラスターに分類され、一部はブタ由来 HEV 株と高い相同性を示した. 陽性者の約 7 割は献血前に動物内臓肉の喫食歴があり、また、陽性者の約半数は、その後 ALT 値の上昇が見られた.
【結論】北海道内の献血者集団における HEV RNA 陽性頻度は高く、zoonotic infection が起きていると考えられる. とくに男性における HEV 陽性頻度は上昇傾向にあり、HEV は今後も十分な注意を要する肝炎ウイルスの一つである.

O-052 輸血前後感染症検査の実施状況と検査を契機に見出された C 型肝炎の 1 症例

埼玉県済生会栗橋病院臨床検査科
落合仁美, 佐藤祥子
TEL : 0480-52-3611 FAX : 0480-52-0301 E-mail : kensa@saikuri.org

【はじめに】当院では 2005 年 3 月より、輸血前後感染症検査を実施している. 今回、2008 年 11 月までの検査状況と、検査を契機に見出された C 型肝炎の 1 症例を報告する.
【方法】1) 輸血前検査は、初回輸血または前回輸血から 3 ヵ月を経過した患者を対象とし、輸血施行を確認した時点で実施した. 2)輸血後検査は、最終輸血後 3 ヶ月を経過した時点で、輸血歴リストを提示し、主治医が必要と判断した患者について実施した.
【結果】1) 輸血前検査実施件数は 1270 件 (内科系 61.4%、外科系 38.6%)、平均年齢は 70.6 歳であった. 2) 輸血後検査実施件数は 640 件 (50.4%)、未実施件数は 630 件 (49.6%) であり、未実施の内訳は、死亡 468 件(74.3%)、ターミナル 26 件(4.1%)、退院不能 87 件(13.8%)、他院入院中 36 件(5.7%)、その他 13 件 (2.1%) であった. 3) 輸血前検査実施の際、HCV コア抗原の陽性となる症例を経験した.
【症例】87 歳女性. 1996 年、心臓カテーテル施行. 2004 年、乳癌手術. 2008 年 7 月、認知症が進行し、食欲不振・脱水にて入院. 同年 8 月、胃ろう造設術後、出血性ショックにて RCC6 単位、FFP10 単位の輸血を実施. 輸血前検査により、HCV 抗体陰性、HCV コア抗原陽性であることが判明. 輸血後、コア抗原量が上昇し、重症の肝機能異常が認められた後、HCV 抗体が陽性化したが、1 週間後には陰性化した. 免疫抑制状態・免疫寛容状態などが想定されたが、確定することはできなかった.
【まとめ】今回の症例では、輸血前検査を実施していたことで、輸血による感染ではなく、輸血前からの感染であったことを把握できた. 感染症は自覚症状がないこともあり、早期に発見し、必要な治療を開始することが重要である. その点からも輸血前感染症検査は意義があると思われた. 輸血後検査実施率が 50% に留まっている現状は、死亡率が高いことに起因し、輸血を施行する患者は高齢者が多く、予後が悪いことが考えられた.

別紙様式第2-1

No. 20

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 6. 15	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	Cannon MJ, Operskalski EA, Mosley JW, Radford K, Dollard SC. J Infect Dis. 2009 Jun 1;199(11):1592-8.	公表国 米国	
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○過去の米国の集団においてヒトヘルペスウイルス-8が輸血を介して伝播したエビデンスはない

背景:ヒトヘルペスウイルス(HHV)-8はカポジ肉腫の原因ウイルスである。最近の試験では、ヒトヘルペスウイルス-8が輸血を介して伝播する証拠が時折発見されている。しかし、これらの研究は米国外で行われており、供血者-受血者の関連が確認されていないため、米国の血液バンクの方針に反映するには限りがある。

方法:1970年代に登録されたTransfusion-Transmitted Viruses Study(TTVS)の参加者にHHV-8血清学検査を行うことにより、米国における輸血を介したHHV-8伝播を調べた。

結果:HHV-8抗体陽性率は、供血者が2.8%(29/1023)、受血者が7.1%(96/1350)、輸血を受けず手術を受けた対照患者が7.7%(46/599)、カポジ肉腫を有する対照患者が96.3%(77/80)であった。1名の受血者はセロコンバージョンしたが(0.08%[1/1259])、この患者はHHV-8血清陽性血液をまったく投与されておらず、感染が輸血関連ではなかったことが示された。輸血を受けず手術を受けた対照患者の1例がセロコンバージョンした(0.18%[1/556])。セロコンバージョン率は、受血者が1000人年あたり1.6(95%信頼区間[CI]、1000人年につき0.04-8.9)、輸血を受けず手術を受けた対照患者が1000人年あたり3.6(95%CI、1000人年につき0.09-20.1)であった。

結論:輸血群および非輸血群のHHV-8セロコンバージョン率に統計学的な差はなく、過去の集団の特徴(例、白血球除去施行前)からは、現在の輸血を介する伝播が稀であることが示される。

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

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
1970年代に登録された米国のコホートにおいて、ヒトヘルペスウイルス-8が輸血を介して伝播したエビデンスは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、本製剤によるHHV-8感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本製剤の安全性は確保されていると考える。	念のため今後も情報収集に努める。

①

Lack of Evidence for Human Herpesvirus–8 Transmission via Blood Transfusion in a Historical US Cohort

Michael J. Cannon,[1] Eve A. Operskalski,[2,3] James W. Mosley,[3] Kay Radford,[1] and Sheila C. Dollard[1]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia; Departments of [2]Pediatrics and [3]Medicine, Keck School of Medicine, University of Southern California, Los Angeles

(See the editorial commentary by Busch and Glynn, on pages 1564–6.)

Background. Recent studies have found evidence of occasional human herpesvirus (HHV)–8 transmission via blood transfusion. However, because these studies were conducted outside the United States or did not have linked donor-recipient pairs, they have a limited ability to inform US blood-banking policy.

Methods. We investigated HHV-8 transmission via blood transfusion in the United States by conducting HHV-8 serologic testing among participants of the Transfusion-Transmitted Viruses Study (TTVS), who enrolled during the 1970s.

Results. HHV-8 seroprevalence was 2.8% (29/1023) among blood donors, 7.1% (96/1350) among transfusion recipients, 7.7% (46/599) among surgical control patients who did not receive transfusions, and 96.3% (77/80) among control patients with Kaposi sarcoma. One transfusion recipient seroconverted (0.08% [1/1259]), but this patient did not receive any HHV-8–seropositive blood units, suggesting that the infection was not related to blood transfusion. One of the surgical control patients who did not receive transfusions also seroconverted (0.18% [1/556]). Rates of seroconversion were 1.6 per 1000 person-years (95% confidence interval [CI], 0.04–8.9 per 1000 person-years) for the transfusion recipients and 3.6 per 1000 person-years (95% CI, 0.09–20.1 per 1000 person-years) for the surgical control patients who did not receive transfusions ($P = .61$).

Conclusions. Rates of HHV-8 seroconversion in the transfusion and nontransfusion groups were not statistically different, and the historical nature of the cohort (e.g., before leukoreduction) suggests that any current transmission via blood transfusion is rare.

Human herpesvirus (HHV)–8 is necessary for the development of Kaposi sarcoma (KS), primary effusion lymphomas, and multicentric Castleman disease. Disease tends to occur, however, only in the presence of immunosuppression [1]. In the overall US population, HHV-8 seroprevalence is low (estimated at between 1% and 7% [2, 3]), but higher seroprevalences are found among men who have sex with men [4] and among persons with human immunodeficiency virus (HIV) infection or risk factors for HIV infection [5].

Initial studies found no evidence of HHV-8 transmission via blood transfusion [6–8]. However, these studies were limited by relatively small numbers of patients, many of whom received leukoreduced or acellular blood components. Later reports that HHV-8 infection was associated with injection drug use and, presumably, needle sharing [5, 9–12] led to larger-scale investigations of transmission via transfused blood [13–15]. These studies found evidence that HHV-8 was transmitted occasionally via blood transfusion, leading to renewed questions about the advisability of screening of blood for HHV-8 [16–19]. Nevertheless, all 3 studies had a limited ability to inform US blood-banking policy, either because they were conducted outside the United States or because they did not have linked donor-recipient pairs to prove transmission via transfusion.

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Reprints or correspondence: Dr. Michael J. Cannon, CDC, 1600 Clifton Rd., Mailstop A-47, Atlanta, GA 30329 (mcannon@cdc.gov).

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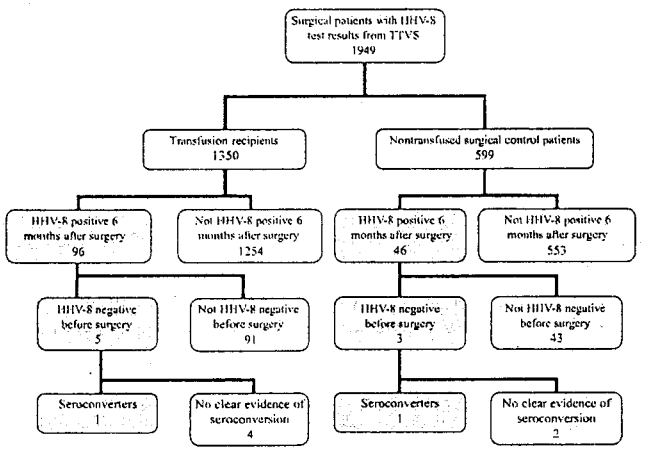

Figure 1. Testing algorithm and outcomes among the transfusion recipients and the surgical control patients who did not receive transfusions. All 4 blood donors for the 1 seroconverter who received a transfusion tested negative. HHV, human herpesvirus; TTVS, Transfusion-Transmitted Viruses Study.

To better evaluate the possibility of HHV-8 transmission via blood transfusion in the United States, we conducted HHV-8 serologic testing among participants of the Transfusion-Transmitted Viruses Study (TTVS). To our knowledge, this was the largest US study conducted with linked donor-recipient pairs and longitudinal follow-up specimens. The specimens were collected before the advent of several blood-safety improvements (such as HIV testing, more-stringent donor-deferral guidelines, transition to extended storage of blood components, and routine leukoreduction by filtration and apheresis techniques), making this study an important opportunity to detect HHV-8 transmission via blood transfusion in the United States.

METHODS

Study design and population. The TTVS was designed in the 1970s to prospectively identify cases of non-A, non-B hepatitis among a cohort of 1533 patients who had received transfusions and to create a repository for detecting the occurrence of virus transmission via blood transfusion [20]. The TTVS repository was funded by the National Heart, Lung, and Blood Institute (NHLBI) and is now housed at the NHLBI Biologic Specimen Repository. The TTVS repository has been used to demonstrate transmission of other viruses via transfusion, such as hepatitis B virus (HBV) and hepatitis C virus (HCV) [21–25]. TTVS participants consisted of blood donors, transfusion recipients (nearly all of whom underwent surgery), and surgical patients who did not receive transfusions (referred to hereafter as surgical control patients without transfusions). All transfusions occurred during the years 1974–1979. Donors could be linked to transfusion recipients, and both the transfusion recipients and the surgical control patients without transfusions had blood drawn before surgery and at multiple time points after surgery. The TTVS received institutional review board approval from the institutions at which it was performed. TTVS participants consented to future testing. The present analysis of HHV-8 was cleared by the Centers for Disease Control and Prevention (CDC) and the University of Southern California; specimens and associated data were delinked from participant identifiers so that the study did not fall under the category of human-subjects research.

For this study, we tested specimens from 1023 randomly selected TTVS blood donors (20.8% of the 4918 donors who had samples available), specimens from all transfusion recipients who had samples available 6 months after transfusion (n = 1350), and specimens from all surgical control patients without transfusions who had samples available 6 months after surgery (n = 599) (figure 1). To identify seroconverters, we tested the pretransfusion or presurgery specimens from all patients who were HHV-8 seropositive at 6 months. To determine the time of seroconversion, for all those who tested negative before surgery and positive 6 months after surgery, interim specimens were tested at monthly intervals. These serial specimens from individual patients were randomized and masked for testing. A small number of patients had specimens with repeated marginal reactivity; the specimens from these patients were grouped on the same slides and plates for retesting. We also tested any blood-donor specimens (masked to the laboratory) that were linked to seroconverters but were not part of the initial sample of tested donors. As an additional control, 80 specimens from HIV-positive patients with KS were randomly and blindly inserted among specimens from study patients. To help evaluate the performance of the HHV-8 assay, we also tested serial specimens from 7 randomly selected HHV-8–positive (i.e., positive before and 6 months after surgery) and 57 randomly selected HHV-8–negative (i.e., negative before and 6 months after surgery) surgical patients (both those who had received transfusions and those who had not). To compute seroconversion rates, person-time was measured as the time from surgery until the 6-month visit.

Serologic analysis. Specimens were tested at the CDC for antibodies against HHV-8 by an immunofluorescence assay (IFA), as described elsewhere [3, 13, 14]. Specimens were considered positive if they were reactive at a dilution of 1:80 or greater. Specimens that were equivocal or negative at a dilution of 1:80 were classified as not positive. To avoid false identification of seroconverters, we chose a conservative a priori definition of seroconversion: negative (not equivocal) at a dilution of 1:40 before surgery and positive at a dilution of 1:80 after surgery at ≥2 consecutive time points. All specimens that tested positive at a dilution of 1:80 were also tested at a dilution of 1:160.

Table 1. Human herpesvirus–8 seroprevalence in different groups in the Transfusion-Transmitted Viruses Study (TTVS).

Group	Proportion (%) positive
Control patients with KS[a]	77/80 (96.3)
Blood donors[b]	29/1023 (2.8)
Surgical control patients who did not receive transfusions	46/599 (7.7)
Transfusion recipients[c]	96/1350 (7.1)

NOTE. Data are the no. of positive specimens per the total no. tested. Specimens were considered positive if they were reactive at a dilution of 1:80 or greater by an immunofluorescence assay. KS, Kaposi sarcoma.

[a] Specimens from control patients with KS were randomly and blindly inserted among the other specimens.

[b] Donors were randomly selected from all the blood donors in the TTVS.

[c] Specimens were collected ~6 months after surgery.

RESULTS

HHV-8 seroprevalences in the 4 different study populations are described in table 1. Nearly all specimens from control patients with KS were positive (96.3%). Blood donors had the lowest seroprevalence (2.8%), and the transfusion recipients and the surgical control patients without transfusions had similar seroprevalences 6 months after surgery (7.1% and 7.7%, respectively). For the 4918 donors linked to the 1350 transfusion recipients, the type of transfused units were whole blood (61.3%), unknown (17.9%), packed cells (17.8%), plasma (2.0%), other (0.8%), washed frozen (0.1%), and platelets (0.1%). Of the 142 patients who were seropositive 6 months after surgery (figure 1), 8 were seronegative at their presurgery visits and were considered potential seroconverters.

Serial specimen testing was done for the 8 potential seroconverters, with each having a total of 8 specimens tested (1A, 1B, and 2A–2F in figure 2). Of the 8 potential seroconverters, 2 (2D and 2F in figure 2) were clearly seropositive only at their last (6-month) visit, suggesting that their 6-month postsurgery specimen may have been mislabeled or had a false-positive result or that the patient may have acquired a community HHV-8 infection near the end of the follow-up period. Another 4 patients (2A–2C and 2E in figure 2) had mixed reactivities that did not meet our definition of seroconversion. The remaining 2 potential seroconverters (1A and 1B in figure 2) had serial test results that met our a priori criteria for seroconversion (figures 1 and 2). On the basis of these 2 seroconverters, we computed the risk of seroconversion as 0.08% (1/1259) (95% confidence interval [CI], 0.0%–0.44%) for the transfusion recipients and as 0.18% (1/556) (95% CI, 0.0%–1.0%) for the surgical control patients without transfusions. Rates of seroconversion were 1.6 per 1000 person-years (95% CI, 0.04–8.9 per 1000 person-years) for the transfusion recipients and 3.6 per 1000 person-years (95% CI, 0.09–20.1 per 1000 person-years) for the surgical control patients without transfusions. The difference in rates was not statistically significant (P = .61). Rates of seroconversion determined using a more relaxed definition (i.e., negative at a dilution of 1:80 before surgery and positive at a dilution of 1:80 six months after surgery) were similar between the 2 groups (5.2% [5/96] for the transfusion recipients vs. 6.5% [3/46] for the surgical control patients without transfusions; P = .72) (figure 1).

The seroconverter who had undergone transfusion received a unit of blood from each of 4 donors (2 U of whole blood and 2 U of packed cells), none of whom was HHV-8 seropositive. Applying the HHV-8 seroprevalence of 2.8% to the 4918 donors who gave blood to the 1350 transfusion recipients, we estimate that ~138 seropositive units were transfused, 128 (92.9%) of which would have been given to HHV-8–seronegative transfusion recipients, none of whom seroconverted.

Serial testing was also done for patients whose serostatus was constant before surgery and 6 months after surgery (either positive or negative at both time points). For these 64 patients, serial HHV-8 testing results are shown in figure 2 (3A–3G and 4A–4H) and table 2. For the 7 HHV-8–positive patients, all serial specimens were positive at dilutions of 1:80 or greater at all visits. For the 57 HHV-8–negative patients, nearly all test results were negative, although a few were equivocal and 2 were positive (table 2).

DISCUSSION

In the present study—the largest US study to analyze HHV-8 infection among transfusion recipients and their linked donors—we found no evidence that HHV-8 is transmitted via

Figure 2. Human herpesvirus–8 serial test results among Transfusion-Transmitted Viruses Study surgical patients.

Table 2. Consistency of human herpesvirus–8 test results among serial specimens from patients in the Transfusion-Transmitted Viruses Study.

Group	Patients tested,[a] no.	No. of visits with specimen results that were			
		Negative	Equivocal	Positive at 1:80	Positive at ≥1:160
Positive before surgery and positive 6 months after surgery	7	0	0	1	43
Negative before surgery and negative 6 months after surgery	57	379	11	0	2

NOTE. Included are test results for specimens from the presurgery visits and from all follow-up visits through 6 months after surgery (mean no. of visits, 6.8).

[a] Patients were selected to be positive and negative control subjects for the seroconversion study.

blood transfusion. Two study patients met our a priori definition of seroconversion—they were negative by the IFA at a dilution of 1:40 before surgery and had at least 2 consecutive positive IFA results at a dilution of 1:80 after surgery. One seroconverter received only HHV-8–seronegative blood, and the other seroconverter was a surgical control patient without a transfusion.

The study design did not allow us to determine the cause of seroconversion in these 2 patients. It is conceivable that the patient who underwent transfusion received blood from an HHV-8–infected donor who was in the so-called window period—that is, not yet HHV-8 seropositive but with newly acquired HHV-8 circulating in the blood. Alternatively, the seroconverters might have experienced community-acquired infections or nosocomial infections unrelated to transfusion.

The lack of evidence in this historical cohort suggests that the current risk of HHV-8 transmission via blood transfusion is very low. Even if we assume that the one seroconverter who received a blood transfusion was infected via the transfusion, current practices make it much less likely that such transmission would occur now compared with when the TTVS specimens were collected. Since the 1970s, blood banks have stricter donor-deferral guidelines [26], and tests that screen out blood positive for HIV, HBV, and HCV may also screen out blood positive for HHV-8, given that there are shared risk factors for infection among HHV-8 and these other viruses [5, 27]. Moreover, leukoreduction, which became commonplace in the mid-1990s, is likely to reduce the risk of HHV-8 transmission via transfusion, because HHV-8 is highly cell associated [7, 16, 28]. Similarly, the current increased use of red blood cell components, which are stored for up to 42 days at 4°C, is likely to reduce HHV-8 transmission because such storage conditions are known to decrease the infectivity of transfusion-transmissible herpesviruses, such as cytomegalovirus. However, it is worth noting that the seroprevalence of HHV-8 among TTVS blood donors is very similar to more recent estimates [3], suggesting that HHV-8 is endemic at low levels in the United States.

Our results are consistent with those from previous studies of HHV-8 transmission via blood transfusion in the United States—the risk to current transfusion recipients is very low, but rare transmission cannot be ruled out [6–8, 13]. For example, Pellett et al. [3] found that HHV-8 seroprevalence among blood donors was low (~3.5%), and HHV-8 DNA was not detected in the blood of seropositive donors. Although in another historical cohort we identified 2 possible transfusion-related HHV-8 seroconversions, that study was not able to show a linkage to seropositive donor blood [13]. Given the safety improvements created by current blood donation and transfusion practices, a cohort containing thousands of linked donor-recipient pairs, such as the NHLBI RADAR (REDS [Retrovirus Epidemiology Donor Study] Allogenic Donor and Recipient) repository [29], would be required to rule out rare transmission events.

In contrast with these US results, HHV-8 has been shown to be transmitted via blood transfusion in Uganda [14], with ~3% of HHV-8–seropositive units causing infection. If there were a comparable risk in the TTVS, we would have expected to see ~3.8 (3% of 128) infections resulting from blood transfusion, rather than the zero that we observed (for the difference between the observed vs. the expected, $P = .035$). The transfusion risk may be higher in Uganda because of a higher prevalence of immunosuppression, a higher risk of exposure and reinfection, and a higher frequency of viremia among HHV-8–seropositive individuals. In addition, donor-deferral guidelines in Uganda were less stringent, testing for HCV was not done, and leukoreduction was not performed. Furthermore, blood was often stored for short periods of time, perhaps allowing virus to remain viable.

The lack of evidence for HHV-8 transmission via blood transfusion is unlikely to be explained by assay deficiencies. We used an IFA and a dilution (1:80) that have been validated and used in previous studies [13, 14] and that have been shown to have high sensitivity and specificity. The assay detected HHV-8 in 96.3% of specimens from control patients with KS (specimens were randomly and blindly inserted among the TTVS specimens), including KS specimens that had been found to have relatively low levels of antibodies by other assays [30, 31]. Our low seroprevalence among blood donors (2.8%) was consistent with the findings of other studies [2, 3] and suggested high assay specificity. The higher seroprevalences among the transfusion recipients and the surgical control patients without transfusions (7.1% and 7.7%, respectively) were consistent with their older age and health status (i.e., surgical patients may be less healthy than the general population). Furthermore, our results for longitudinal follow-up specimens were highly coherent, with results remaining consistent throughout follow-up among postsurgery specimens for >95% of the presurgery specimens with a positive or

negative result (table 2). For the small number of patients with incoherent longitudinal reactivity patterns, a few explanations may pertain. First, a single positive serum specimen among a series of negative specimens (e.g., 2D, 2F, 4F, and 4H in figure 2) is likely the result of nonspecific reactivity or a specimen-labeling error. Second, up-and-down reactivity patterns (e.g., 2A–2C and 2E in figure 2) may be the result of periodic nonspecific reactivity or, more likely, low levels of HHV-8 antibody fluctuating above and below the lower limit of detection of the assay.

Screening of blood donors for HHV-8, if warranted, faces important technical challenges. Currently, there is no consensus on a standard HHV-8 assay that has known high sensitivity and specificity. The IFA used in the present study is time-consuming and could not be readily standardized across laboratories in the implementation of a screening program. Enzyme-linked immunosorbent assay formats, which might be more amenable to the high throughput demanded by a screening program, may be less sensitive. The main challenge is that the HHV-8 antibody response in healthy individuals is relatively weak, and most of the current assays have inadequate sensitivity and specificity.

In conclusion, the present study does not provide evidence of transmission of HHV-8 via blood transfusion in the United States. Rates of seroconversion in the transfusion and nontransfusion groups were not statistically different, and the historical nature of the cohort suggests that any current transfusion transmission is rare. However, much larger studies would be required to rule out rare transmission events. Nevertheless, if such transmission is shown to occur in the United States, universal screening of blood donors may not be warranted, because HHV-8 seldom causes disease in immunocompetent populations. If suitable assays become available, screening of blood for HHV-8 may be beneficial for immunosuppressed populations. However, the challenges associated with reliably detecting HHV-8 antibody or HHV-8 DNA in a healthy blood-donor population remain a substantial barrier, one that must be crossed before the costs and benefits of HHV-8 blood screening can be appropriately weighed.

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別紙様式第2-
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医薬品
医薬部外品　研究報告　調査報告書
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識別番号・報告回数			報告日	第一報入手日 2009年8月10日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	①②乾燥抗HBs人免疫グロブリン ③ポリエチレングリコール処理抗HBs人免疫グロブリン		研究報告の公表状況	Nature Medicine(online) 2009; 15(8): 871-872	公表国 カメルーン	
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研究報告の概要

ゴリラ起源の新型のヒト免疫不全ウイルス：
我々は、カメルーンの首都ヤウンデ近郊に住んでいた62歳の女性が、2004年に渡仏した際にHIV感染が発覚し、彼女から連続的に採取した血液分析により、HIV-1(SIVgor)に密接に関連した新型のヒト免疫不全ウイルスを同定した。
新型のヒト免疫不全ウイルスは、密接にゴリラ・サル免疫不全ウイルス（SIVgor）に関係があり、他のHIV-1系統で組換えの証拠を示さない。これまでに知られているチンパンジー由来のウイルス（種を超え交差伝播した(SIVcpzPtt)）とは異なり、最近ヒト感染に必要な生物学的特性の多くを持っているSIV（SIVgor）が野生のゴリラ（Gorilla gorilla gorilla）で発見されている。
発見された新型HIV-1変異株は現在確認されているHIVの3つの亜種（M、NおよびO）とは異なっている。我々はHIV-1グループPと称することを提案する。
Strain RBF168（subject number）は血清学的そして非特異的な分子試験で古典的なHIV-1の挙動を示すことより、気づかれずにカメルーンやその他の地域ですでに感染が広がっている可能性があることを示唆する。
結論として、我々の知見はゴリラがチンパンジーに加えて、HIV-1の有望な起源であることを示す。
この新しいHIV-1系統の発見は、特に西中央アフリカは全ての既存のHIV-1グループの起源であることより、新しいHIV変異株の出現を継続して見守る必要があることを強調する。

使用上の注意記載状況・その他参考事項等

代表としてヘプスブリンIH静注1000単位の記載を示す。
2. 重要な基本的注意
(1)本剤の原材料となる血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の抗HBs抗体を含有する血漿を原料として、Cohnの低温エタノール分画で得た画分からポリエチレングリコール4000処理、DEAEセファデックス処理等により抗HBs人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びびろ過膜処理（ナノフィルトレーション）を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見

新たに発見された亜型ウイルス(HIV-1 グループ P)は、カメルーンからパリに移住した62歳の女性の血液サンプルから発見されたという報告である。
HIV-1ウイルスは、レトロウイルス科レンチウイルス属に属し、成熟ウイルスの粒子直径約100nmのエンベロープを持つ一本鎖RNAウイルスである。HIV-1は塩基配列により3群に分類され、グループM（Major）、グループO（Outlier）、グループN（non-M/non-O）に分けられるが、世界的に分布しているウイルスの多くがグループMに属している。現在、原料血漿に実施されているスクリーニング(抗体検査、ミニプールNAT)によりこの新たなHIVが検出可能か否かは不明であるものの、もし原料血漿にHIV-1グループPが混入したとしても、HIV-1をモデルウイルスとしたウイルスバリデーション試験成績から、製造工程において十分に不活化・除去されると考えている。

今後の対応

本報告は本剤の安全性に影響を与えるものではないと考えるので、特段の措置はとらない。

8

nature medicine

BRIEF COMMUNICATION

BENESIS2009-1

A new human immunodeficiency virus derived from gorillas

Jean-Christophe Plantier[1], Marie Leoz[1], Jonathan E Dickerson[2], Fabienne De Oliveira[1], François Cordonnier[3], Véronique Lemée[1], Florence Damond[4], David L Robertson[2] & François Simon[5]

We have identified a new human immunodeficiency virus in a Cameroonian woman. It is closely related to gorilla simian immunodeficiency virus (SIVgor) and shows no evidence of recombination with other HIV-1 lineages. This new virus seems to be the prototype of a new HIV-1 lineage that is distinct from HIV-1 groups M, N and O. We propose to designate it HIV-1 group P.

HIV-1, the virus principally responsible for the AIDS pandemic, arose through cross-species transmission of a retrovirus (SIVcpzPtt) found in chimpanzees (*Pan troglodytes troglodytes* (*Ptt*))[1,2]. Another SIV (SIVgor), recently discovered in wild-living gorillas (*Gorilla gorilla gorilla*)[3], has many of the biological properties necessary for human infection[4]. We have now identified a new human immunodeficiency virus closely related to SIVgor in a Cameroonian woman. This new HIV-1 variant is distinct from the three established groups of HIV-1, namely M (major or main), N (non-M, non-O) and O (outlier)[5,6].

Since 2001, a French network of reference laboratories has been monitoring HIV genetic diversity. Infection with an unusual variant is suspected when RNA viral load assays or molecular tests are negative in an individual with acquired immunodeficiency and of antiretroviral therapy. As part of these surveillance activities, we analyzed serial samples from a 62-year-old woman (subject number RBF168), who was found to be HIV seropositive in 2004, shortly after moving to Paris from Cameroon (Supplementary Methods). Several HIV-1 screening tests were all reactive, and western blot with HIV-1 group M proteins showed weak reactivity against the envelope glycoprotein 120 and no reactivity against Gag p18 protein (Supplementary Methods and Supplementary Fig. 1). She currently has no signs of AIDS, remains untreated and has a stable $CD4^+$ cell count of about 300 cells per mm^3 (Supplementary Fig. 2). Her viral load has been consistently high since diagnosis (4.4 to 5.3 log copies per ml) in nonspecific group M and O PCR commercial assays (HIV-1 HIV RNA Quantitative and RealTime HIV1, Abbott) and in an in-house real-time RT-PCR assay[7] (Supplementary Fig. 2). The virus replicates in cultured human donor peripheral blood mononuclear

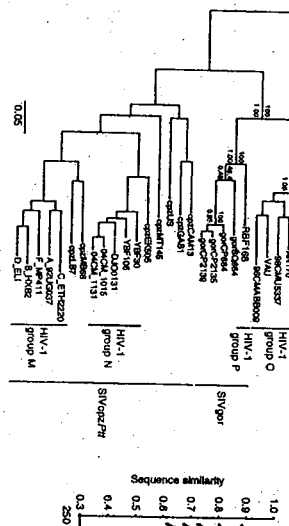

Figure 1 Evolutionary relationship of strain RBF168 to HIV-1, SIVcpz and SIVgor. (**a**) Maximum likelihood phylogeny inferred from concatenated amino acid alignments corresponding to the partial sequences available for SIVgorBQ564 (ref. 4), 1,052 amino acid positions remained after stripping gap-containing sites. The support values (indicated for key nodes only) in black above the branches are from 1,000 maximum likelihood bootstraps (shown as percentages), whereas posterior probabilities from amino acid Bayesian analysis are shown in blue below the branches (shown as proportions). (**b**) Average sequence similarity (250 amino acid windows, 100-amino-acid increments) of RBF168 with representative strains of HIV-1 groups M, N and O, SIVgor, SIVcpz from *Pan troglodytes schweinfurthii* (SIVcpzPts) and SIVcpzPtt across the concatenated translated gene sequence alignments. Similar results were obtained with the nucleotide sequence alignment (data not shown).

[1]Laboratoire associé au Centre National de Référence du Virus de l'Immunodéficience Humaine, Centre Hospitalier Universitaire de Rouen, Equipe d'Accueil EA2656, Faculté de Médecine-Pharmacie, Université de Rouen, France. [2]Faculty of Life Sciences, University of Manchester, U.K. [3]Hôpital Louis Mourier, Colombes, France. [4]Hôpital Bichat, Paris, France. [5]Hôpital Saint-Louis, Institut National de la Santé et de la Recherche Médicale U941, Faculté de Médecine, Université Paris-Diderot, Paris, France. Correspondence should be addressed to J.-C.P. (jean-christophe.plantier@univ-rouen.fr).

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cells and is easily isolated from both the subject's plasma and peripheral blood mononuclear cells (**Supplementary Methods**). Her viral load cannot, however, be quantified with a group M–specific commercial assay (Amplicor Monitor v1.5, Roche) or with an academic assay (Generic HIV charge virale, Biocentric[3]) (**Supplementary Fig. 2**). We did not obtain amplification with complementary group M–specific PCRs (**Supplementary Methods**). We initially suspected HIV-1 group O infection, endemic in western central Africa, especially in view of the subject's Cameroonian origin. However, amplification with our usual group O primers failed (**Supplementary Methods** and **Supplementary Table 1**), leading us to search for a divergent virus by using a nonspecific extra-long RT-PCR method. We successfully amplified the viral genome with this approach, allowing us to fully sequence it (**Supplementary Methods**, **Supplementary Fig. 5** and **Supplementary Table 2**).

Evolutionary analysis of the near-complete genome sequence (**Supplementary Methods**) shows that the RBF168 strain is most closely related to SIVgor (**Fig. 1a** and **Supplementary Fig. 3**), and similarity plotting confirms that this relationship is maintained in all regions of the genome (**Fig. 1b**). Before the discovery of strain RBF168, HIV-1 group O was the lineage most closely related to SIVgor, but it is too divergent to be directly derived from current SIVgor strains[4]. As strain RBF168 clusters significantly with SIVgor strains (see support values on tree, **Fig. 1a** and **Supplementary Fig. 3**), the most likely explanation for its emergence is gorilla-to-human transmission of SIVgor (**Supplementary Fig. 4a,b**). Similar to the proposed chimpanzee origin for the HIV-1 group O and SIVgor lineage[4], we cannot rule out the possibility that SIVcpz gave rise to strain RBF168, either indirectly by transmission to gorillas and then to humans (**Supplementary Fig. 4a,b**) or directly by transmission to humans and also to gorillas (**Supplementary Fig. 4c**). Detection of RBF168-like viruses in chimpanzees would be needed to confirm this possibility.

Strain RBF168 thus represents a new HIV-1 variant and is the prototype of a new human lineage that we designate as putative group P, pending the identification of further human cases, in keeping with nomenclature guidelines[6]. The human case described here does not seem to be an isolated incident, as before coming to Paris the subject had lived in the semiurban area of Yaoundé, the capital of Cameroon, and reported no contact with apes or bush meat (**Supplementary Methods**), and the variant's high level of replication *in vivo* and ready isolation in culture indicate that it is adapted to human cells. This efficient replication of RBF168 is rather unexpected, given the absence of an arginine (or lysine) at position 30 in the Gag protein, considered a signature of human-specific adaptation of HIV-1 (ref. 9). Contrary to most HIV-1 strains (apart from group M subtype C), but like SIVgor and all SIV*cpzPtt* strains[9], RBF168 has a methionine at this amino acid position.

The human prevalence of this new lineage remains to be determined. Strain RBF168 shows typical HIV-1 behavior in serological and nonspecific molecular tests, suggesting that it could be circulating unnoticed in Cameroon or elsewhere. HIV screening tests and molecular tools have improved markedly over the past two decades, enabling the distinct HIV types and groups to be detected. This increased sensitivity, however, may paradoxically mask the circulation of divergent strains. Indeed, new variant infections can now be detected only by monitoring discrepancies between immunological status and virological results in molecular assays. Currently, there is no simple detection algorithm based on existing serological and molecular tools, and, therefore, only nucleotide sequencing can identify further HIV-1 group P strains.

In conclusion, our findings indicate that gorillas, in addition to chimpanzees, are likely sources of HIV-1. The discovery of this novel HIV-1 lineage highlights the continuing need to watch closely for the emergence of new HIV variants, particularly in western central Africa, the origin of all existing HIV-1 groups.

Accession codes. The near-full-length sequence of strain RBF168 has been submitted to GenBank under accession number GQ328744.

Note: Supplementary information is available on the Nature Medicine website.

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AUTHOR CONTRIBUTIONS

J.-C.P., M.L. and F.D.O. conceived of and designed the experiments. M.L., F.D.O. and V.L. performed the molecular and serological experiments. J.E.D. and D.L.R. performed the computational analysis. P.C. managed the subject and collected epidemiological data. J.-C.P., V.L. and F.D. monitored the subject's virologic status. J.-C.P., M.L., J.E.D., F.D.O., D.L.R. and F.S. wrote the paper.

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No. 7

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一般的名称	人血清アルブミン		研究報告の公表状況	Gaur AH, Dominguez KL, Kalish ML, Rivera-Hernandez D, Donohoe M, Brooks JT, Mitchell CD. Pediatrics. 2009 Aug;124(2):658–66.	公表国 米国	
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研究報告の概要

○乳児への食物の噛み与え行為：HIV伝播のリスク要因の可能性

目的：一部の保護者は乳児に食物を噛んで与えているが、一般的に、当該行為と離乳期間におけるHIV伝播とは関連付けられていなかった。我々は、この行為に関連すると考えられる米国のHIV伝播3症例について述べる。

患者と方法：9、15、39ヵ月齢の小児においてHIV感染3症例が診断された。臨床症状の発症により検査を実施し、他の伝播経路を除外するため詳細な調査を行った。また、envのC2V3C3またはgp41領域とgag領域をコードするp17を用いて、症例および疑わしい感染源から得られたウイルスの系統発生学的比較を行った。

結果：2症例は、HIVに感染した母親から授乳は行われず、米国のHIV検査ガイドラインによってHIVの周産期伝播は否定されていた。第3の症例では、小児の世話を手伝った叔母がHIVに感染していたが、母親は感染していなかった。3例ともHIV感染者が世話をし、食物を噛んで与えていた。2例では、食物を噛み与えた大人に口腔内出血があったことが報告された。系統樹解析により、3例中2例において、世話をしていたHIV感染者からの噛み与えにより感染したという疫学的結論が支持された。

結論：この報告症例は、噛み与えとHIV感染とを関連づける有力な証拠を提供するものである。これは、重大な世界的影響を有する未報告の伝播ルートであり、これまで授乳によると考えられてきた乳児の生後HIV伝播報告の説明となり得る。噛み与えリスクおよび歯周病などの修飾因子についての理解が深まるまでは、HIV感染あるいはリスクのある保護者や出産を控えた親に対して、噛み与え行為について質問し、安全性が高く実行しやすい離乳食を指導するよう医療提供者に勧める。

報告企業の意見	今後の対応	使用上の注意記載状況・その他参考事項等
・HIVに感染した保護者が食物を噛み与えることによって乳児がHIVに感染したことが、系統樹解析により支持されたとの報告である。 ・これまで、本製剤によるHIV感染の報告はない。また本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。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製剤の安全性は確保されていると考える。	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。	赤十字アルブミン20 赤十字アルブミン25 赤十字アルブミン20%静注4g/20mL 赤十字アルブミン20%静注10g/50mL 赤十字アルブミン25%静注12.5g/50mL 血液を原料とすることに由来する感染症伝播等

(9)

Practice of Feeding Premasticated Food to Infants: A Potential Risk Factor for HIV Transmission

WHAT'S KNOWN ON THIS SUBJECT: Although some caregivers are known to premasticate food for infants, usually during the weaning period, HIV transmission has not been linked to this practice.

WHAT THIS STUDY ADDS: The reported cases provide compelling evidence linking premastication to HIV infection, a route of transmission not previously reported that has important global implications including being a possible explanation for some of the reported cases of "late" HIV transmission in infants, so far attributed to breastfeeding.

ABSTRACT

OBJECTIVES: Although some caregivers are known to premasticate food for infants, usually during the weaning period, HIV transmission has not been linked to this practice. We describe 3 cases of HIV transmission in the United States possibly related to this practice.

PATIENTS AND METHODS: Three cases of HIV infection were diagnosed in children at ages 9, 15, and 39 months; clinical symptomatology prompted the testing. A thorough investigation to rule out alternative modes of transmission was conducted. In addition, phylogenetic comparisons of virus from cases and suspected sources were performed by using the C2V3C3 or gp41 region of *env* and the p17 coding region of *gag*.

RESULTS: In 2 cases, the mothers were known to be infected with HIV, had not breastfed their children, and perinatal transmission of HIV had previously been ruled out following US HIV testing guidelines. In the third case, a great aunt who helped care for the child was infected with HIV, but the child's mother was not. All 3 children were fed food on multiple occasions that had been premasticated by a care provider infected with HIV; in 2 cases concurrent oral bleeding in the premasticating adult was described. Phylogenetic analyses supported the epidemiologic conclusion that the children were infected through exposure to premasticated food from a caregiver infected with HIV in 2 of the 3 cases.

CONCLUSIONS: The reported cases provide compelling evidence linking premastication to HIV infection, a route of transmission not previously reported that has important global implications including being a possible explanation for some of the reported cases of "late" HIV transmission in infants, so far attributed to breastfeeding. Until the risk of premastication and modifying factors (eg, periodontal disease) are better understood, we recommend that health care providers routinely query children's caregivers and expecting parents who are infected with HIV or at risk of HIV infection about this feeding practice and direct them to safer, locally available, feeding options. *Pediatrics* 2009; 124:658–666

CONTRIBUTORS: Aditya H. Gaur, MD,[a] Kenneth L. Dominguez, MD, MPH,[b] Marcia L. Kalish, PhD,[c] Delia Rivera-Hernandez, MD,[d] Marion Donohoe, CPNP,[a] John T. Brooks, MD,[b] and Charles D. Mitchell, MD[a]

[a]Department of Infectious Diseases, St Jude Children's Research Hospital, Memphis, Tennessee; Divisions of [b]HIV/AIDS Prevention and [c]AIDS, STD, and TB Laboratory Research, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; and [d]Miller School of Medicine, University of Miami, Miami, Florida

KEY WORDS
HIV, feeding, premastication, prechewed, child

ABBREVIATIONS
MTCT—mother-to-child transmission
CDC—Centers for Disease Control and Prevention
PCR—polymerase chain reaction
EIA—enzyme immunoassay
EBV—Epstein-Barr virus

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Address correspondence to Aditya H. Gaur, MD, St Jude Children's Research Hospital, Department of Infectious Diseases, MS 600, 262 Danny Thomas Place, Memphis, TN 38105-3678. E-mail: aditya.gaur@stjude.org

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The availability of antiretroviral medications, the appropriate use of cesarean delivery, and the avoidance of breastfeeding have dramatically reduced the incidence of mother-to-child transmission (MTCT) of HIV in the United States and other developed nations. Every diagnosis of HIV infection in a child, especially in the developed world, should prompt us to identify missed opportunities for diagnosis and intervention to prevent MTCT.[1,2] Although the practice of premasticating food for children, usually during the weaning period, has been described in various parts of the world,[3–8] including the United States, HIV transmission has not been linked to this practice. We report 3 cases of pediatric HIV infection that are likely to have resulted from a child, who was not infected with HIV, receiving premasticated (prechewed) food from an adult who was infected with HIV.

PATIENTS AND METHODS

Local health departments investigated the 3 cases through interviews with the available involved adults and through review of medical charts. Blood specimens from the children, available family caregivers, and the sexual partner of a deceased caregiver were sent to the Centers for Disease Control and Prevention (CDC) for HIV nucleic acid extraction, polymerase chain reaction (PCR) amplification, and genetic sequencing of the C2V3C3 or gp41 coding regions of *env* and the p17 coding region of *gag*.[9] These regions are commonly used for phylogenetic comparison of HIV sequences to determine relatedness between strains when transmission is suspected. Phylogenetic analysis has been widely used in transmission cases, both epidemiologic and forensic, and both person-to-person and transmission chains.[9] In brief, sequences were edited with Sequencher 3.1 software (Gene Codes, Madison, WI) and aligned with the SE-AI 1.0 sequence alignment editor.[10] The Modeltest 3.04 program[11] was used with each alignment to test for a statistically justified model of DNA substitution for use in the phylogenetic tree-building program by using neighbor-joining methodology implemented in *PAUP**.[12] Because of the epidemiologic focus of this report, phylogenetic analysis has been used to either support or fail to support the conclusions of the epidemiologic investigations. Available family caregivers consented to specimen collection and participation in the investigation. In addition, consent to report deidentified case details was obtained from the mothers of the children in cases 1 and 3. Case 1, who is now an adolescent, provided his assent as well. Unfortunately, Case 2 and his mother, as well as the great-aunt of case 1, have died.

RESULTS

Case 1 (Miami, FL)

In 1993, a previously healthy 15-month-old black boy was seen by a pediatrician for recurrent diarrhea and otitis media. The results of a first-generation HIV-1 antibody test (enzyme immunoassays [EIAs]) (Bio-Rad Laboratories, Hercules, CA) and Western blots performed on specimens from the child at 15, 16, and 19 months of age were positive. PCR-based tests for HIV were not available for clinical care at that time. The results of EIAs performed on specimens from the mother (21 years old) at these same 3 intervals were negative.

The mother reported that when the child was aged 9 to 14 months, she and the infant had lived with a maternal great-aunt (33 years old) infected with HIV. During this time, the great-aunt helped care for the child and fed him food that she had premasticated. The mother noted that on more than 1 occasion, the great-aunt's gingiva were bleeding when she premasticated the child's food, and the mother saw blood mixed with the prechewed food; however, at that time, the mother was unaware of the great-aunt's HIV diagnosis. The great-aunt died of sepsis and pneumonia related to *Streptococcus pneumoniae* when the child was ~14 months of age (~1 month before the child's first positive EIA test result). She was not reported to be on antiretroviral medications and had an absolute CD4 count of ~270 cells per μL on more than 1 occasion during the 6 months before her death.

The great-aunt had been in a 12-year sexual relationship with a male intravenous drug user who was HIV-infected. The mother stated that he did not use intravenous drugs in the house while she and the child resided there. She did not recall seeing needles in the house (and thus did not believe that the child could ever have been stuck by one) and did not believe that the child had ever been sexually abused by her great-aunt's sexual partner. In addition, there was no history of him ever feeding the child premasticated food.

HIV phylogenetic analysis was performed on the HIV-1 sequences of the great-aunt's sexual partner because clinical specimens from the great-aunt had not been banked before her death. Phylogenetic analysis of the HIV-1 sequences from the child and the great-aunt's sexual partner showed no phylogenetic clustering, suggesting that these 2 viral strains were not epidemiologically linked (Fig 1). However, the history of premastication in the absence of known risk factors for HIV transmission and the possibility that the great-aunt's HIV strain was from a source other than her sexual partner suggested that the great-aunt was the possible source of the child's HIV infection.

Case 2 (Miami, FL)

A black child born to a mother (36 years old) infected with HIV was followed up in the University of Miami

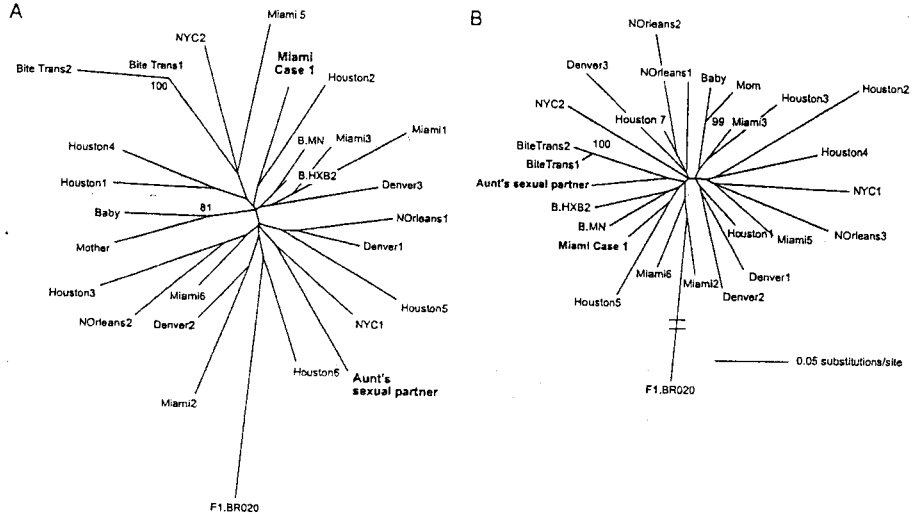

FIGURE 1

Case 1 (Miami). A, Phylogenetic relationship of the HIV sequences derived from case 1 and the great-aunt's sexual partner, 5 unrelated subtype B strains from Miami (Miami 1–3, 5, and 6), 15 unrelated subtype B strains from US cities other than Miami (Denver 1–3, Houston 1–6; New Orleans 1 and 2; New York City 1 and 2, B.MN, and B.HXB2), 1 subtype F strain (F1.BR020), and 2 epidemiologically related transmission pairs (bite transmission 1 and 2; infant and mother). Shown is a neighbor-joining tree of the gp17 region of *gag*; only bootstrap values of >70% are indicated. B, Phylogenetic relationship of the HIV sequences derived from case 1 and the great aunt's sexual partner, 4 unrelated subtype B strains from Miami (Miami 2, 3, 5, and 6), 16 unrelated subtype B strains from US cities other than Miami (Denver 1–3, Houston 1–5 and 7, New Orleans 1–3, New York City 1 and 2, B.MN, and B.HXB2), 1 subtype F strain (F1.BR020), and 2 epidemiologically related transmission pairs (bite transmission 1 and 2; infant and mother). Shown is a neighbor-joining tree of the C2V3C3 region of *env*; only bootstrap values of >70% are indicated. In A and B, US subtype B sequence strains were used as references along with subtype F as an outgroup. Sequences from 2 epidemiologically related transmission pairs were also included (bite transmission 1 and 2; infant and mother). Phylogenetic analysis shows no clustering or epidemiological relatedness between the virus from case 1 (Miami) and the virus from the great aunt's sexual partner.

Pediatric HIV Screening Clinic until 1993, when HIV-1 infection was ruled out on the basis of negative results from first-generation HIV-1 antibody test (EIAs) (Bio-Rad Laboratories) performed when the child was aged 20 and 21 months. PCR-based tests for HIV were not available for clinical care at that time. The child had normal immunoglobulin levels and a normal CD4 count (absolute count: 1700 cells per μL) at the time of the negative EIA results. Neither the mother nor child received perinatal antiretroviral prophylaxis. In 1995, at age 39 months, the child was seen by a pediatrician for anemia and recurrent submandibular lymphadenitis with abscess caused by *Mycobacterium fortuitum*. The mother's history of AIDS and intranasal cocaine abuse without intravenous drug abuse, combined with the child's clinical presentation, prompted the pediatrician to order an HIV-1 EIA (Bio-Rad Laboratories), a confirmatory Western blot, and p24 antigen testing for the child; all results were positive. A concurrent CD4 count of 24 cells per μL (1%) indicated severe immunosuppression.

The mother reported feeding the child premasticated table food but could not recall details regarding the child's age or her own oral health during the time she prechewed the child's food.

Phylogenetic analysis of the mother's and the child's HIV-1 sequences supported the epidemiologic conclusion that the mother was the source of the child's HIV-1 infection (Fig 2).

Case 3 (Memphis, TN)

In 2004, a 9-month-old black girl was seen in an emergency department because of fever, jaundice, nosebleed, oral thrush, and failure to thrive. HIV-1 infection was diagnosed based on an ultrasensitive HIV-1 RNA PCR of >100 000 copies per mL (Cobas Amplicor HIV-1 Monitor 1.5 test [Roche Molecular Systems, Inc, Branchburg, NJ]; dynamic range of detection: 50–100 000 copies per mL). Given the mother's history of chronic HIV infection since 1995, this child had previously been screened for perinatal infection. Three

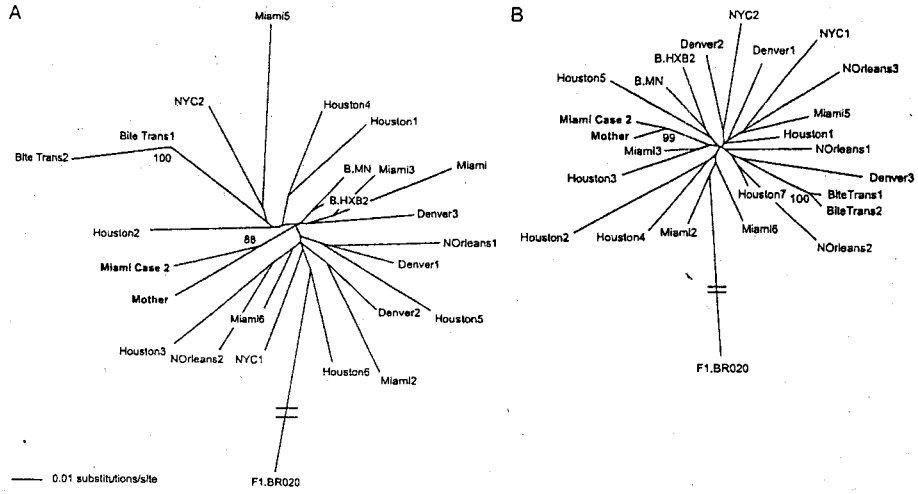

FIGURE 2

Case 2 (Miami). A, Phylogenetic relationship of the HIV sequences derived from the mother-infant pair of case 2, 5 unrelated subtype B strains from Miami (Miami 1–4 and 6), 15 unrelated subtype B strains from US cities other than Miami (Denver 1–3, Houston 1–6, New Orleans 1 and 2; New York City 1 and 2, B.MN, and B.HXB2), 1 subtype F strain (F1.BR020), and 1 epidemiologically related human bite-transmission pair (bite transmission 1 and 2). Shown is a neighbor-joining tree of the gp17 region of *gag*; only bootstrap values of >70% are indicated. In A and B, US subtype B sequences were used as reference strains along with a subtype F as an outgroup. Sequences from an epidemiologically related transmission pair were also included (bite transmission 1 and 2). Phylogenetic analysis shows strong clustering, with an 88% bootstrap support for the epidemiological relatedness between the virus from case 2 (Miami) and the child's mother. B, Phylogenetic relationship of the HIV sequences derived from the mother-infant pair of case 2 from Miami, 4 unrelated subtype B strains from Miami (Miami 2, 3, 5, and 6), 16 unrelated subtype B strains from US cities other than Miami (Denver 1–3, Houston 1–5 and 7, New Orleans 1–3, New York City 1 and 2, B.MN, and B.HXB2), 1 subtype F strain (F1.BR020), and 1 epidemiologically related human bite-transmission pair (bite transmission 1 and 2). Shown is a neighbor-joining tree of the C2V3C3 region of *env*; only bootstrap values of >70% are indicated. Phylogenetic analysis shows strong clustering with a 99% bootstrap support for the relatedness between the virus from case 2 (Miami) and the child's mother.

standard quantitative HIV RNA viral loads (Cobas Amplicor HIV-1 Monitor 1.5 test; dynamic range of detection: 400–750 000 copies per mL) were performed at 41, 60, and 118 days of life. Results of all 3 tests were negative (no copies of HIV RNA detected).

The mother (31 years old) had not adhered to highly active antiretroviral therapy during pregnancy. During pregnancy, she was started on nevirapine, stavudine, and lamivudine and was later switched to once-a-day ritonavir-boosted atazanavir and tenofovir because of poor compliance. Her viral load on the day before delivery was 35 100 copies per mL. The child was delivered at 35 weeks' gestation via cesarean delivery because of the mother's high blood pressure and edema. The mother received intravenous zidovudine before her cesarean delivery. The mother reported that she gave the infant oral zidovudine during the first 6 weeks of life and that the infant did not breastfeed.

At ~8 months of age, the child was seen for low-grade fever and was diagnosed with oral candidiasis and a nonspecific viral infection. In the following week, a red blotchy rash developed on the child's face, arms, and legs; the pediatrician ascribed the rash to allergic dermatitis.

A clinician who routinely queried caregivers about infant care feeding practices, including premastication, determined that the mother had intermittently offered the child prechewed meats from ~120 days of life until the child's current illness. The mother reported that during the period that she prechewed the child's food, she had intermittently bleeding gums and mouth sores that later resolved spontaneously or with medications for oral thrush. During this same period, the mother's adherence to highly active antiretroviral therapy was poor, her HIV viral load was 499 000 copies per mL, and her CD4 count was 100 cells per μL (6%).

Phylogenetic analysis of the mother's and the child's HIV-1 sequences sup-

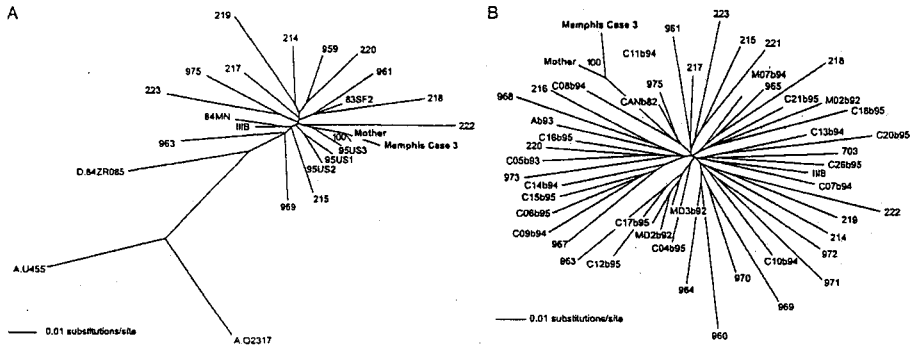

FIGURE 3

Case 3 (Memphis). A, Phylogenetic relationship of the HIV sequences derived from the mother-infant pair of case 3 and unrelated subtype strains from the United States (19 subtype B, 2 subtype A, and 1 subtype D). Shown is a neighbor-joining tree of the gp17 region of *gag*; US subtype B sequences and 1 subtype D sequence were used as reference strains in the tree, and 2 subtype A sequences were used as an outgroup. Only bootstrap values of >70% are indicated for the subtype B branching order. This phylogenetic analysis shows strong clustering, with a 100% bootstrap support for the epidemiological relatedness of the virus from case 3 (Memphis) and the child's mother. B, Phylogenetic relationship of the HIV sequences derived from the mother-infant pair of case 3 from Memphis and 49 unrelated subtype B strains from the United States. Shown is a neighbor-joining tree of the gp41 region of *env*, only bootstrap values of >70% are indicated. US subtype B sequences were used as reference strains in this unrooted tree. Phylogenetic analysis shows strong clustering with a 100% bootstrap support for the relatedness between the virus from case 3 (Memphis) and the child's mother.

ported the epidemiologic conclusion that the mother was the source of HIV-1 infection in the child (Fig 3).

In all 3 cases, additional follow-up interviews with caregivers and physical examinations of the children did not reveal other modes of potential HIV transmission (eg, percutaneous injuries, transfusion or receipt of transplanted tissues, other parenteral exposures or other high-risk contacts [including sexual abuse] with persons infected with HIV in the household).

DISCUSSION

The cases described suggest that HIV may be transmitted through consumption of food that has been premasticated by a person infected with HIV. To our knowledge, this route of HIV transmission has not been reported previously. Bleeding in the oral cavity of the adult infected with HIV, who prechewed the food as documented in cases 1 and 3, was likely the primary source of HIV. The caregivers' lack of access to or lack of adherence to perinatal HIV prophylaxis or antiretroviral therapy probably decreased the suppression of their HIV-1 viral loads. This factor in addition to the children's compromised oral mucosa because of teething or intercurrent oral illness such as candidiasis (reported in case 1) likely facilitated HIV transmission. In addition, tonsillar epithelial factors[13] may have facilitated HIV infection because the tonsils come into contact with blood-tinged food and saliva.

In reviewing the cases, it is important to understand why the first 2 cases were not reported earlier. In cases 1 and 2, the clinicians first contacted the local health department soon after each child's HIV diagnosis. The local and state health departments collaborated with the CDC to conduct an epidemiological investigation. These 2 cases were not reported immediately to the general public for several reasons. Only one of the two possible transmission events was supported by phylogenetic data. Prechewing as a mode of HIV transmission had not been described, and ample data at the time indicated that routine household contact and kissing were not associated with a significantly increased risk of oral HIV transmission. In case 1, transmission through child sexual abuse, a known mode of pediatric HIV transmission that is difficult to establish, and needle-stick exposures were denied but could not be absolutely ruled out. The report of a third possible case, supported by laboratory data, provided the impetus for this report.

Although the practice of premasticating food for children has been described in various parts of the world,[5–8,14–16] including the United States, the extent of this practice is not well known. In the late 1980s, a first-year medical student's observation of this practice prompted a survey of black patients at a primary care pediatrics clinic at the University of Nebraska Medical Center.[7] Although the reports of several infant-feeding surveys conducted at about this time did not mention the practice of premastication, 45 (65%) of 68 adult caregivers in the Nebraska survey acknowledged prechewing food for their infants, and 90% reported knowledge of this practice.[7] More recently, a study of oral health in a random sample of Alaska Native children (aged 12–36 months) and their caregivers documented that 86.2% of caregivers were currently prechewing or had prechewed food for their infants.[8]

From October 2005 to May 2007, the US Food and Drug Administration, in conjunction with the CDC and other federal agencies, conducted the Infant Feeding Practices Study II,[17] which collected data from responses to questionnaires mailed to a sample of US women who had given birth to term or near-term infants. After learning about the cases reported here and because of the lack of information about the prevalence of this behavior in the United States, researchers added the question, "In the past 2 weeks, have you chewed up food and then given it to your infant, so the food was already chewed up before you fed it to your infant?" Separate questionnaires were mailed to parents when the infants were aged 4, 5, 6, 7, 9, 10.5, and 12 months.

Unpublished data from the Infant Feeding Practices Study II[17] indicate that the prevalence of premastication rose from 0.77% (17 of 2203 respondents) at 4 months of age to 10.5% (189 of 1794 respondents) at 10 months of age (Sara Fein, PhD, and Laurence Grummer-Strawn, PhD, written personal communication, 2007). Among the subset of black respondents, the prevalence of premastication was higher than that among other racial and ethnic subgroups and increased as children aged: 5 (6%) of 87 respondents premasticated food for children aged 4 months; 33 (50%) of 66 respondents premasticated food for children aged 10 months. Although the sample was skewed toward white respondents with more education and higher income, the findings suggest a much higher prevalence of premastication than expected and the need for clinical care providers in the United States to be cognizant of this practice.

In a study of complementary infant-feeding practices in China, 62.5% of 104 respondents in various cities reported ever having prechewed food for their children.[16] Among those respondents practicing premastication, 21.5% did so often or very often. They started prechewing food when the child was a median of 8 months old (range: 1–24 months) and stopped at a median of 24 months (range: 5–48 months). Prechewing was also more common when someone other than the parent was involved in feeding the infant.

The association between prechewing food and the transmission of infectious organisms has been documented or hypothesized. The transmission of group A streptococci[18] and hepatitis B virus[15] through premasticated food has been documented; however, both organisms are considerably more infectious than HIV, and as noted, multiple reports have indicated that the risk of oral HIV transmission under ordinary circumstances, such as kissing or sharing household items, is extremely low.[19,20] The feeding of premasticated foods by mothers to infants has been associated with increased risk of *Helicobacter pylori* infection in infants in Burkina Faso[21] and with dental caries in children in southern Asia.[22] Similar transmissions of human herpesvirus 8 in rural Tanzania[23] and Epstein-Barr virus (EBV) in Uganda[24] have been hypothesized. In EBV-endemic regions, some authors have suggested that prechewing food may foster viral transmission to toddlers and may explain, in part, local elevations in the incidence of EBV-associated Burkitt lymphoma in children.[25]

Eating prechewed food, however, may provide health benefits. The premastication of food was protective in univariable but not multivariable analysis against respiratory syncytial virus infection for Alaska Native children aged <6 months.[26] It has also been hypothesized that the feeding of premasticated iron-rich foods may prevent iron deficiency during the first 6 to 12 months of life in resource-limited countries where other sources of iron supplementation are not available during the breastfeeding period.[16] Although the prechewing of food increased bacterial counts in the weaning foods given to infants in northern Thailand, it was suggested that the mother's immunoglobulin A in saliva mixed with the food may reduce the infectivity of these bacteria.[4]

Although our evidence argues in favor of premastication-related HIV transmission facilitated by blood in the mouth of the caregiver and compromised oral mucosa in the child, we acknowledge some limitations. In case 1, phylogenetic evidence linking infection in the child and infection in the premasticating caregiver was lacking because no blood sample was available for the latter. However, the history of premastication and the absence of other modes of transmission are compelling. The possibility of late perinatal seroconversion, for cases 2 and 3 whose mothers were infected with HIV, is extremely unlikely because the results of sequentially performed highly specific tests were negative: in case 3, HIV RNA PCR was performed thrice in the first 6 to 18 weeks of life,[27,28] and in the child of case 2, HIV enzyme-linked immunosorbent assays were performed twice after 18 months of age.[29] HIV-1 RNA testing is reliable for early diagnosis of HIV in infants.[30] Finally, in light of the findings of the Infant Feeding Practices Study II, which indicate that prechewing is common, one might question why, in >10 years, only 3 cases in the United States have been linked to this practice and why no

cases have been reported in resource-limited settings such as Africa, where premastication may be more common than in the United States. A possible explanation is that transmission through breastfeeding makes it difficult to detect premastication-related HIV transmission in resource-limited countries such as Africa; the absence of breastfeeding transmission has allowed us to detect premastication-related transmission in the United States. Premastication-related HIV transmissions are probably rare, requiring a convergence of risk factors affecting both the caregiver and the child. In addition, health care providers are unaware of the practice and have not considered it a potential cause of "late" HIV infection in infants. To our knowledge, no HIV-related MTCT studies with breastfeeding populations have specifically queried caregivers about premastication.[31] The 3 reported cases raise the question as to whether some cases of late pediatric HIV infection reported in MTCT studies and attributed to breastfeeding might have been due in part to the coexisting practice of premastication. Eliciting a history of premastication requires that health care providers be aware that premastication exists and that they are culturally sensitive in asking questions about it. It is crucial to educate caregivers who are infected with HIV about prechewing, because they may be unaware of its potential health risks and may perceive it as a routine, safe, and culturally acceptable practice.

CONCLUSIONS

We hope that our results will prompt additional investigation and the reporting of other potential cases of premastication-related perinatal HIV transmission. Until the risk of prechewing and modifying factors (eg, periodontal disease) are better understood, we recommend that health care providers routinely query children's caregivers and expecting parents who are infected with HIV or at high risk of HIV infection about the practice of premasticating food, that they advise against premastication and that they direct parents and other caregivers to safer, locally available, and accessible feeding options. Translating these recommendations into practice will require cognizance of culturally sensitive issues and potential nutritional consequences linked to premastication. Health care providers should identify the extent to which premastication is practiced in their communities and should notify public health authorities of cases of HIV infection that are potentially linked to premastication. In the United States, such cases should be reported to local health departments according to state surveillance guidelines for HIV/AIDS reporting.

We recognize the potential global implications of our findings. Because infants are fed prechewed food worldwide, we understand that a recommendation against premastication by caregivers infected with HIV should not be made lightly, especially in areas where alternative methods of food preparation are limited and sociocultural beliefs may favor this practice. For example, even in developed nations, providing alternative means for preparing infant food safely, such as blenders, may not eliminate premastication if it has traditional or cultural roots. In resource-limited settings, a risk/benefit analysis will be needed and should take into account the availability of safe feeding practices. Finally, it will be important to determine not only the prevalence of premastication but its contribution to HIV infection in children worldwide in the context of other well-described prenatal, intrapartum, and postnatal risk factors, including breastfeeding.

ACKNOWLEDGMENTS

We appreciate the contributions of the children and their families, who provided essential information; the health departments of Miami-Dade (Florida) and Jackson (Tennessee) and the states of Florida and Tennessee for helping conduct the epidemiological investigation of all 3 cases; Ruby Booth (CDC) for coordinating the HIV surveillance–related investigation of these cases with the local health departments; John Guidi, referring physician for case 3, for the information he provided on the child and the mother; Lee Lam, Kenneth E. Robbins, and Tom Spira, CDC laboratory staff who assisted with the HIV-sequence generation and phylogenetic analysis; Laurence Grummer-Strawn (CDC) and Sara Fein (Food and Drug Administration) for including a question about prechewing food for infants in the Infant Feeding Practices Survey II; Julie Groff (St Jude) for assistance in enhancing the phylogenetic figures; Donald D. Samulack (St Jude) and Marie Morgan (CDC) for the scientific editing of this article; and finally Tom Folks, Sal Butera, Dawn Smith, Linda Valleroy, Terrence Chorba, Nathan Shaffer (CDC), and Patricia M. Flynn (St Jude) for their detailed and helpful review of this article.

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別紙様式第2-1

No. 8

医薬品 研究報告 調査報告書

識別番号・報告回数				第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 7. 21	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	伊部史, 横幕能行, 服部純子, 間宮均人, 杉浦亙. 第83回日本感染症学会総会学術講演会; 2009 Apr 23-24; 東京.	公表国 日本	
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○東海地域におけるHIV-2感染疑い症例の遺伝子学的解析

【目的】HIV-2は西アフリカを中心に感染者数の多い疾患である。HIV-1のように世界的規模で感染は拡大しておらず、本邦では、これまで数例が報告されているのみである。今回、我々は名古屋医療センターにおいて新たにHIV-2の感染が疑われた4例を対象に遺伝子学的診断と分子疫学的解析を実施した。

【方法】血清学的にHIV抗体陽性かつ血中HIV-1 RNAコピー数が検出限度以下を示した4例を対象とした。4例のプロファイルは、外国籍の男性が3例、日本国籍の女性が1例であった。患者末梢血白血球より抽出したDNAを鋳型にnested PCRによりgag (778 bps)およびenv (496 bps)領域の遺伝子増幅を試みた。標的遺伝子の増幅に成功した症例についてはダイレクトシークエンス法で塩基配列を決定したのち、リファレンス株と共に系統樹解析を実施した。

【結果】4例中3例で標的遺伝子の増幅に成功し、遺伝子配列よりHIV-2であることが確認された。これら3例は、全て外国籍の男性症例であり、日本国籍の女性では、いずれの領域も増幅産物を得ることができず確定診断には至らなかった。HIV-2は遺伝子学的にサブタイプAからHの8種類のサブタイプに分類されるが、解析に成功した3例のうち1例はgag、env領域ともにリファレンス株のサブタイプA株と同じ枝に分岐し、サブタイプA株と判定し得た。残り2例は、gag領域ではサブタイプBの近傍への分岐を示し、env領域の解析でも独立した系統群を形成し、両遺伝子領域のみではサブタイプ判定には至らなかった。

【結論】活発化する国際交流は感染症の拡大における地理的な障壁の閾値を低下させている。東海地域において見出されたHIV-2感染症例3例について報告したが、これは我が国においてもHIV-2のスクリーニングを強化しなければならないことを示唆している。

使用上の注意記載状況・その他参考事項等

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

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
東海地域においてHIV抗体陽性かつ血中HIV-1 RNAコピー数が検出限度以下を示し、HIV-2感染が疑われた症例4例を分析したところ、3例でウイルス遺伝子の増幅に成功し、HIV-2感染が確認されたとの報告である。 これまで、本製剤によるHIV感染の報告はない。また本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。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製剤の安全性は確保されていると考える。	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。

(10)

P-101　血液培養より *Histoplasma capsulatum* を分離したHIV感染症の1例―細菌学的所見を中心に―

東邦大学医療センター大森病院臨床検査部[1]，
東邦大学医療センター大森病院感染管理部[2]，
東邦大学医学部微生物学・感染症学講座[3]，
東邦大学医療センター大森病院呼吸器内科[4]，
東邦大学医療センター大森病院病院病理部[5]，
千葉大学真菌医学研究センター[6]
○村上日奈子[1]，吉澤定子[2]，舘田一博[1,3]，岩田基秀[4]，
渋谷和俊[5]，佐野文子[6]，亀井克彦[6]，山口恵三[1,2,3]

【目的】ヒストプラズマ症は輸入真菌症のひとつであり，培養陽性率が低いとされている．今回，血液培養より *Histoplasma capsulatum* を分離したHIV感染症の1例を経験したため報告する．

【症例】39歳，タイ人男性．主訴は発熱，発疹，歯肉出血．15年前にタイより来日．4週間前より39～40℃台の発熱が出現，1週間前から歯茎より出血を認め，3日前から出血傾向が増悪したため当院救急外来を受診．精査加療目的にて入院となった．

【入院後経過】HIV抗体陽性．BALFから *Candida albicans* が検出され，β-Dグルカン値の上昇もみられた．IPM，CPFX，FLCZにより治療が開始されたが全身状態は増悪．第6病日に骨髄生検を施行し，病理学的所見で細胞質内に小型類円形の構造物が多数認められ，ヒストプラスマ症が強く疑われた．第8病日よりAMPHにより治療開始したがDICとなり，第25病日，消化管出血のため死亡された．

【血液培養検査】入院時に2セットのボトルが提出された．血培装置で1週間培養を行ったが陰性であったため，ボトルより抽出した培養液沈渣のサブカルチャーを試みた．培養17日目にサブロー寒天に集落の発育を認め真菌陽性との報告をした．同定は27℃と35℃の温度差で二形性を示すこと，集落の形態よりヒストプラズマ属を推定し，血培採取後50日目に報告した．最終的に千葉大学真菌医学研究センターに依頼し，*H. capsulatum* と同定された．一方，ボトルは血培装置で計3週間培養を行ったが陰性であった．

【考察】本症例は臨床側からヒストプラズマ症疑いの情報があったため執拗に培養を行ったことから分離に成功したと思われる．ヒストプラズマ属の培養は27℃で4週間まで観察することが推奨されているが，一般細菌用の血培ボトルは5～7日しか培養を行わないため本菌をはじめとする培養に時間を要する真菌を疑うときは繰り返し血培装置に充填するか，培養液沈渣を用いてサブカルチャーを行う必要があると考えられた．

P-102　東海地域におけるHIV-2感染疑い症例の遺伝子学的解析

名古屋医療センター臨床研究センター感染免疫研究部
○伊部史朗，横幕能行，服部純子，間宮均人，
杉浦　亙

【目的】HIV-2は西アフリカを中心に感染者数の多い疾患である．HIV-1のように世界的規模で感染は拡大しておらず，本邦では，これまで数例が報告されているのみである．今回，我々は名古屋医療センターにおいて新たにHIV-2の感染が疑われた4例を対象に遺伝子学的診断と分子疫学的解析を実施した．

【方法】血清学的にHIV抗体陽性かつ血中HIV-1 RNAコピー数が検出限度以下を示した4例を対象とした．4例のプロファイルは，外国籍の男性が3例，日本国籍の女性が1例であった．患者末梢血白血球より抽出したDNAを鋳型にnested PCRによりgag（778 bps）およびenv（496 bps）領域の遺伝子増幅を試みた．標的遺伝子の増幅に成功した症例についてはダイレクトシークエンス法で塩基配列を決定したのち，リファレンス株と共に系統樹解析を実施した．

【結果】4例中3例で標的遺伝子の増幅に成功し，遺伝子配列よりHIV-2であることが確認された．これら3例は，全て外国籍の男性症例であり，日本国籍の女性では，いずれの領域も増幅産物を得ることができず確定診断には至らなかった．HIV-2は遺伝子学的にサブタイプAからHの8種類のサブタイプに分類されるが，解析に成功した3例のうち1例はgag，env領域ともにリファレンス株のサブタイプA株と同じ枝に分岐し，サブタイプA株と判定し得た．残り2例は，gag領域ではサブタイプBの近傍への分岐を示し，env領域の解析でも独立した系統群を形成し，両遺伝子領域のみではサブタイプ判定には至らなかった．

【結論】活発化する国際交流は感染症の拡大における地理的な障壁の閾値を低下させている．東海地域において見出されたHIV-2感染症例3例について報告したが，これは我が国においてもHIV-2のスクリーニングを強化しなければならないことを示唆している．

No. 19

：別紙様式第2-1

医薬品　研究報告　調査報告書

識別番号・報告回数		報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
			2009. 7. 9	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	47 news. Available from: http://www.47news.jp/CN/20090906/CN2009062701000591.html.	公表国 日本	
販売名（企業名）	赤十字アルブミン20（日本赤十字社） 赤十字アルブミン25（日本赤十字社） 赤十字アルブミン20%静注4g/20mL（日本赤十字社） 赤十字アルブミン20%静注10g/50mL（日本赤十字社） 赤十字アルブミン25%静注12.5g/50mL（日本赤十字社）				使用上の注意記載状況・その他参考事項等 赤十字アルブミン20 赤十字アルブミン25 赤十字アルブミン20%静注4g/20mL 赤十字アルブミン20%静注10g/50mL 赤十字アルブミン25%静注12.5g/50mL 血液を原料とすることに由来する感染症伝播等

研究報告の概要

○白血病ウイルス感染者108万人（推計）：大都市圏で割合増
母乳を通じて母子感染し、白血病などを引き起こす可能性がある成人T細胞白血病ウイルス（HTLV-1）について厚生労働省研究班が約20年ぶりに実施した調査で、感染者の地域別割合がもともと高かった九州で減少し、関東や中部、近畿の大都市圏で増加したことが27日、分かった。国内の感染者数は約108万人と推計。旧厚生省研究班が1988～90年度にまとめた調査の約120万人と比べ大きな変化はなかった。これまで全国的な対策は取られておらず、子供への感染を防ぐ取り組みが急務となりそうだ。
研究班班長の山口一成国立感染症研究所客員研究員は大都市圏での割合増加について、感染者が多い九州からの人の移動が背景にあると指摘。「妊婦への抗体検査や授乳指導を実施している自治体は一部に限られ、感染者総数もあまり減少していない」と話した。
HTLV-1はATLと呼ばれるタイプの白血病や、歩行障害などが出る脊髄症（HAM）の原因となる。ATLの発症率は3～5%。根本的な治療法はなく、年間約千人が亡くなっている。
今回の調査は、2006～07年に初めて献血した全国の約119万人を対象に実施、3787人の感染が確認された。感染者の地域別割合は、九州が前回調査の50.9%から41.4%に減少。一方、関東は17.3%（前回10.8%）、中部8.2%（同4.8%）、近畿20.3%（同17.0%）で、いずれも前回より増加した。

報告企業の意見

2006～07年に初めて献血した人を対象に行った調査の結果、全国の成人T細胞白血病ウイルスの感染者数は約108万人と推計され、感染者の地域別割合はもともと高かった九州で減少し、関東や中部、近畿の大都市圏で増加したことが分かったとの報告である。
これまで、本製剤によるHTLV-1感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。本製剤の安全性は確保されていると考える。

今後の対応

今後も引き続き、新たなウイルス等による感染症の発生状況等に関する情報の収集に努める。

(11)

白血病ウイルス感染者108万人　大都市圏で割合増

母乳を通じて母子感染し、白血病などを引き起こす可能性がある成人T細胞白血病ウイルス（HTLV1）について厚生労働省研究班が約20年ぶりに実施した調査で、感染者の地域別割合がもともと高かった九州で減少し、関東や中部、近畿の大都市圏で増加したことが27日、分かった。

国内の感染者数は約108万人と推計。旧厚生省研究班が1988～90年度にまとめた調査の約120万人と比べ大きな変化はなかった。これまで全国的な対策は取られておらず、子供への感染を防ぐ取り組みが急務となりそうだ。

研究班班長の山口一成国立感染症研究所客員研究員は大都市圏での割合増加について、感染者が多い九州からの人の移動が背景にあると指摘。「妊婦への抗体検査や授乳指導を実施している自治体は一部に限られ、感染者総数もあまり減少していない」と話した。

HTLV1はATLと呼ばれるタイプの白血病や、歩行障害などが出る脊髄症（HAM）の原因となる。ATLの発症率は3～5%。根本的な治療法はなく、年間約千人が亡くなっている。

今回の調査は、2006～07年に初めて献血した全国の約119万人を対象に実施、3787人の感染が確認された。

感染者の地域別割合は、九州が前回調査の50・9%から41・4%に減少。一方、関東は17・3%（前回10・8%）、中部8・2%（同4・8%）、近畿20・3%（同17・0%）で、いずれも前回より増加した。

2009/08/27 18:03 【共同通信】

ホーム 共同ニュース

最47ニュース アクセスランキング一覧へ

別紙様式第2-1

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 8. 18	該当なし	
一般的名称	新鮮凍結人血漿				公表国	
販売名（企業名）	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血（日本赤十字社）	研究報告の公表状況	Euro Surveill. 2009 May 14;14(19).		オランダ	

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
○オランダ南部におけるQ熱の持続的集中的伝播、2009年 オランダは、2007年と2008年のアウトブレイク後再びQ熱報告の急増に直面している。もっとも影響が大きいのは大規模なヤギ農場が集中しているNoord Brabant県であり、流産の増加している農場が発生源と疑われる。複数の専門分野にわたる大規模な調査研究により、疾患の伝播や予防手段に関する知見が得られることが期待される。 Q熱症例数は2009年4月以降急増し、1月1日から5月11日までの間に345例(可能性例13例を含む)が報告された。11例は2008年、1例は2007年に発症していたため、2009年に発症した症例は合計333例という結果となった。男女比は約1.7:1で、年齢の中央値は49才(38-61才)であった。過去の2年と比べて4-5月に患者数が急増しており、流行の規模は2008年と同程度以上になることが示唆されている。ほとんどの患者が、2007年、2008年と同様Noord Brabant県民であったが、感染区域に拡大傾向が見られている。 主な症状は肺炎で、2008年に報告された患者では、545名が肺炎、33名が肝炎、115名が他の発熱性疾患を発症した。2009年の症例のうち、データの得られた226例中59例(26%)が入院した。これは2008年度と同程度の割合だが、2007年(49%)よりは少なかった。 Noord Brabant県を中心に、少なくとも10件の独立した流行クラスターがあることが明らかになってきた。一部のクラスターでは、家畜のQ熱が発生し流産が増加している小型反芻動物農場との明確な疫学的関連性があった。動物のワクチン接種キャンペーンが始まっており、2010年には効果を発揮する見込みである。	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	新鮮凍結血漿「日赤」 新鮮凍結血漿-LR「日赤」 新鮮凍結血漿-LR「日赤」成分採血
報告企業の意見	**今後の対応**	
オランダ南部においてQ熱の患者が急増しており、一部では家畜のQ熱が発生している農場との疫学的関連性があったとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。	

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Rapid communications

Sustained intensive transmission of Q fever in the south of the Netherlands, 2009

B Schimmer (barbara.schimmer@rivm.nl)[1], F Dijkstra[1], P Vellema[2], P M Schneeberger[3], V Hackert[4], R ter Schegget[5], C Wijkmans[6], Y van Duynhoven[1], W van der Hoek[1]

1. Centre for Infectious Disease Control, (CIb), National Institute for Public Health and the Environment, RIVM, Bilthoven, the Netherlands
2. Animal Health Service (GD), Deventer, the Netherlands
3. Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands
4. Municipal Health Service South Limburg, Sittard-Geleen, the Netherlands
5. Municipal Health Service Brabant-Southeast, Helmond, the Netherlands
6. Municipal Health Service "Hart voor Brabant", 's Hertogenbosch, the Netherlands

The Netherlands is again facing a sharp increase in Q fever notifications, after the unprecedented outbreaks of 2007 and 2008. The most affected province of Noord Brabant has a high density of large dairy goat farms, and farms with abortion waves have been incriminated. Mandatory vaccination of small ruminants has started and should have an effect in 2010. A large multidisciplinary research portfolio is expected to generate better knowledge about transmission and additional control measures.

Introduction

Q fever is a zoonosis caused by the obligate intracellular bacterium *Coxiella burnetii*. Cattle, sheep and goats are the primary animal reservoir, but the causative agent has also been noted in many other animal species. Infected goats and sheep may abort, mainly in late pregnancy. The bacterium is shed in urine, faeces, milk and in especially high concentrations in placentas and birth fluids of infected animals. Bacteria are transmitted to humans mainly through the aerosol route, resulting in subclinical infection, a flu-like syndrome with abrupt onset of fever, pneumonia or hepatitis, after an incubation period of two to three weeks [1]. People with underlying conditions, especially heart valve lesions, are more susceptible to developing chronic Q fever. Endocarditis, the most common form of chronic Q fever is estimated to occur in about 1% of acute Q fever cases.

Since 1978, when Q fever in humans became a notifiable disease in the Netherlands, until 2006, the number of notifications had ranged between 1 and 32 cases annually, with an average of 17 cases per year [2]. However, in 2007, Q fever emerged as an important human and veterinary public health challenge with large epidemics in the southern part of the Netherlands [3]. In 2007, 168 human cases were notified and in 2008 exactly 1,000 human cases were registered (Figure 1). Notification criteria for acute Q fever are a clinical presentation with at least fever, or pneumonia, or hepatitis and confirmation of the diagnosis in the laboratory. Currently, the laboratory criteria are a fourfold rise in IgG antibody titre against *C. burnetii* in paired sera or the presence of IgM-antibodies against phase II antigen. Identification of *C. burnetii* in patient material with a PCR test will soon be added to the notification criteria. Notification of probable cases, defined as clinical signs with a single high antibody titre is voluntary.

Current situation

From April 2009, a sharp increase in Q fever was observed again, and a total of 345 cases (including 13 probable) were notified between 1 January and 11 May 2009 (Figure 1). For 11 cases, the date of illness onset was in 2008 and one case fell ill in 2007, resulting in a total of 333 cases with confirmed or presumed illness onset in 2009. The overall male-to-female ratio for these 333 cases was 1.7:1 with a median age of 49 years (IQR 38-61 years).

The epidemic curve for 2009 shows an even steeper increase in case numbers in April-May, than in the previous two years, suggesting that an epidemic of at least the same magnitude as the one in 2008 is imminent. While most cases reside in the same region in the province of Noord-Brabant as the cases reported in 2007 and 2008 (see map in reference 3), the geographic area seems to be expanding (Figure 2).

Clinical features and diagnostics

Pneumonia is the predominant clinical presentation of the Q fever cases in the Netherlands. For those patients notified in 2008 for whom clinical details were available, 545 presented with pneumonia, 33 with hepatitis, and 115 with other febrile illness (data not yet analysed in detail). Of the 226 cases in 2009 where data regarding hospitalisation were available, 59 (26%) had been admitted to a hospital, a percentage comparable to figures in 2008, but lower than the proportion of patients hospitalised in 2007 (49%). Clinical follow-up of patients that were diagnosed with acute Q fever in 2007, shows that Q fever is not always a mild disease of short duration, as many cases still suffered from persisting fatigue several months after disease onset [4]. We have no clear information about the occurrence of other chronic sequelae, such as endocarditis at this stage.

The medical microbiology laboratories in the affected region have jointly formulated diagnostic recommendations. Cases are currently diagnosed with immunofluorescence assays (Focus Diagnostics), in-house complement fixation tests or ELISA. Real-time polymerase chain reaction (PCR) tests were developed by eight medical microbiology laboratories and the most sensitive (98%) PCR has been selected and has proven a valuable additional tool for early diagnosis of acute Q fever in the time window before seroconversion.

Increased alertness of general practitioners together with easy availability of diagnostic services certainly has an impact on the number of notifications. The current epidemic curve based on week of notification reflects a more real time situation than in previous years, as the interval between date of illness onset and date of diagnosis has decreased from a median of 77 days in 2007 (IQR 40-121) and 29 days (IQR 19-45) in 2008 to 17 days in 2009 (IQR 12-24 days).

Separate clusters with multiple sources

It is becoming increasingly clear that the overall outbreak consists of at least 10 separate clusters with multiple sources, mainly in the province of Noord Brabant. For some clusters a clear epidemiological link could be established to small ruminant farms with clinical Q fever cases in animals presented as abortion waves. For other clusters such a link was less obvious. An example of the latter is a medium sized city (87,000 inhabitants) that experienced a second Q fever outbreak in 2009 similar to the one in 2008. In 2008, a dairy goat farm with abortions due to Q fever was suspected as the source, but in 2009 there were no veterinary notifications from the area. The 73 notified human cases residing in the city were clustered in the same part of the city as the cases that were notified in 2008. It remains unclear whether the same source is involved, whether the bacteria have persisted and survived in the local environment, whether the primary source in 2008 has resulted in secondary sources in 2009, or whether there is increased awareness among health professionals in this part of the city based on the 2008 experience.

In March 2009, the Animal Health Service reported a Q fever-positive farm in the province of Limburg with more than a thousand goats. The place also serves as a care farm for young people with mental disabilities who work there as part-time farmhands. Prompted by this notification, the municipal health service (MHS) South Limburg performed active laboratory screening by ELISA of the individuals affiliated to this goat farm. The screening, which involved a total of 96 people, has resulted in 28 notified symptomatic cases to date.

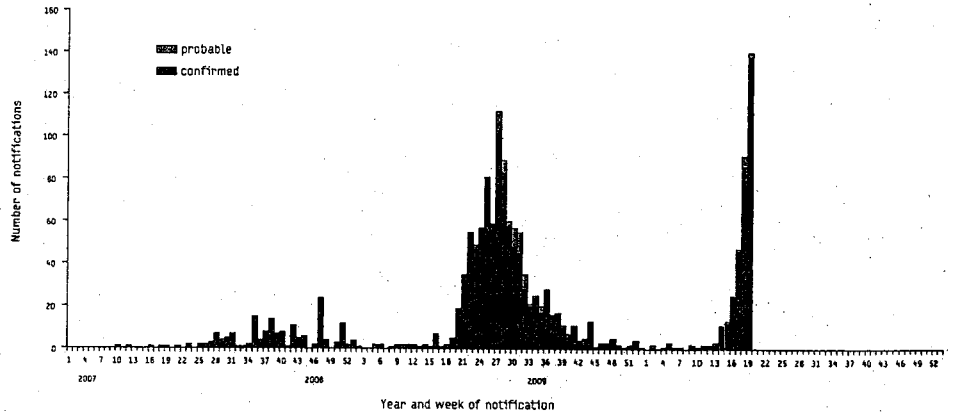
Veterinary situation

The total number of registered small ruminant farms in the Netherlands is 52,000, of which 350 are professional dairy goat farms with more than 200 adult goats and 40 are professional dairy sheep farms. In 2005, Q fever was diagnosed for the first time as a cause of abortion at a dairy goat farm, using immunohistochemistry on sections of placenta [5]. A second case was diagnosed later in 2005. In 2006, 2007 and 2008, six, seven and seven new cases at dairy goat farms were confirmed, respectively, mainly in the same area where human cases occurred. In the same period, two cases of abortion caused by *C. burnetii* were confirmed at dairy sheep farms, one in the southern and one in the northern part of the country but these two cases do not seem to be related to human cases. Analyses of abortion outbreaks showed that the average number of goats per farm was 900 of which 20% aborted, ranging from 10-60%. The average number of sheep on both infected sheep farms was 400 and the abortion rate was 5%.

Abortion outbreaks before June 2008 were reported on a voluntary basis to the Animal Health Service and also confirmed by immunohistochemistry. Since June 2008, notification of Q fever in goats and sheep is mandatory in the Netherlands. There is a legal requirement for farmers and their private veterinary surgeons to notify the occurrence of abortion in small ruminants held in deep litter houses. For large farms (>100 animals) the notification

FIGURE 1

Q fever notifications by week of notification, 1 January 2007 - 11 May 2009, the Netherlands (2007: n=168, 2008: n=1000, 2009 [week 1-week 19]: n=345)



criterion is an abortion wave defined as an abortion percentage higher than 5% among pregnant animals. For smaller holdings, a criterion of three or more abortions in a 30-day period is used.

From January to April 2009, this new regulation has led to notification of three dairy goat farms with clinical cases of Q fever. One farm is located in the province of Overijssel (notified in February), one in the south of the province of Limburg (notified in March), and one in the province of Noord-Brabant (notified in April).

This veterinary notification can potentially facilitate the detection of related human cases or clusters. Veterinarians, physicians and the public are informed through targeted mailings, publications and the media. The exact location of animal farms with clinical Q fever is now reported to the municipal health service. In February 2009, a nationwide stringent hygiene protocol became mandatory for all professional dairy goat and sheep farms, independent of Q fever status.

Vaccination campaigns

In the fall of 2008, a voluntary vaccination campaign was implemented in the province of Noord Brabant. In total, about 36,000 small ruminants were vaccinated in an area with a radius of 45 kilometer around Uden, a small town in the centre of the high-risk area.

Another, mandatory vaccination campaign led by the Animal Health Service (GD) started on 21 April 2009. From April to October 2009, 200,000 small ruminants will be vaccinated in an area which includes the province of Noord-Brabant and parts of the provinces of Gelderland, Utrecht and Limburg.

Ongoing research

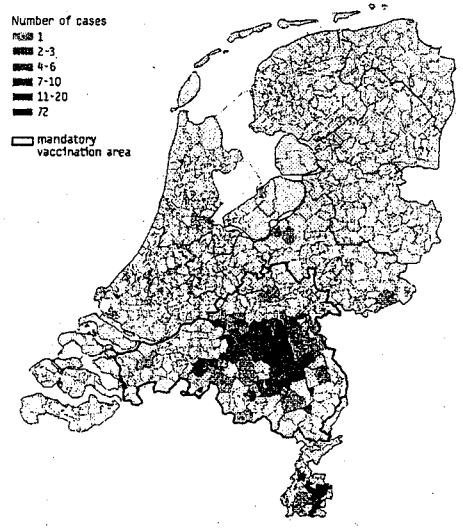
Ongoing studies address the factors involved in the 2008 epidemic at a national, regional and local level, the efficacy of the 2008 voluntary vaccination campaign in small ruminants and the nationwide occurrence of *C. burnetii* antibodies in the community and in small ruminants. From the human epidemiological perspective, a case control study is currently underway in the two main affected MHS regions of 2009, 'Hart voor Brabant' and Brabant-Southeast. Routinely collected sera of pregnant women from the affected regions over the period June 2007 to July 2008 are retrospectively screened for Q fever to study the effect of infection on pregnancy outcome (registered in a national database). An integrated human-veterinary study was started, in which small ruminant farmers and their animals will be screened for presence of *C. burnetii* antibodies. In addition, environmental samples will be obtained from a subset of these farms and the role of particulate matter in relation to *C. burnetii* transmission will be further investigated.

Conclusion

For the third consecutive year the Netherlands is facing a large outbreak of Q fever. The new upsurge in Q fever cases in 2009 is alarming. The mandatory vaccination campaign among small ruminants that was started in April 2009, if effective, is expected to reduce the occurrence of abortion waves and excretion of *Coxiella* in the lambing season 2010. There is a large portfolio of ongoing multidisciplinary research, but it will take some time before results become available that eventually will lead to the implementation of extended and improved control measures.

FIGURE 2

Notified cases of acute Q fever in the Netherlands by three-digit postal code area, 1 January – 11 May 2009 (n=344*). The black line indicates the mandatory vaccination area covering the province of Noord Brabant and parts of the provinces of Gelderland, Utrecht, and Limburg.



Source: OSIRIS notification system. Map compiled by Ben Bom, Expertise Centre for Methodology and Information Services, RIVM
* For one case the information on postal code is missing

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別紙様式第 2-1
番号 15

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6月29日	新医薬品等の区分	厚生労働省処理欄
一般的名称	①②③④人血清アルブミン ⑤乾燥濃縮人血液凝固第Ⅷ因子 ⑥⑦乾燥濃縮人血液凝固第Ⅸ因子				
販売名（企業名）	①献血アルブミン 25%静注 5g/20mL「ベネシス」（ベネシス） ②献血アルブミン 25%静注 12.5g/50mL「ベネシス」（ベネシス） ③献血アルブミン 5%静注 5g/100mL「ベネシス」（ベネシス） ④献血アルブミン 5%静注 12.5g/250mL「ベネシス」（ベネシス） ⑤コンコエイト-HT（ベネシス） ⑥クリスマシン M 静注用 400 単位（ベネシス） ⑦クリスマシン M 静注用 1000 単位（ベネシス）	研究報告の公表状況	FDA (Vaccines, Blood & Biologics)/2009/06/12	公表国 アメリカ	
研究報告の概要	FDAは、全血および成分血の製造施設、ヒト細胞・組織・それら由来製剤（HCT/Ps）のドナーの適性判定施設において、Trypanosoma cruzi（T. cruzi）抗体を検出するための酵素免疫反応試験（EIA）の承認申請（BAL）がFDAにより承認されたことを通知する。この検査は輸血に使用される全血および成分血、およびHCT/Pドナー（生体および死後（心停止））を含む個別ドナー血漿およびの血清サンプルにおけるT. cruzi抗体検出により、T. cruziの伝播リスクを低減させることを目的とする。このガイダンス文書は、分画製剤用原料血漿の採集には適用されない。FDAはこのガイダンスの最終版発行後1年以内にこのガイダンスに記載の推奨事項を実施するよう推奨する。 1989年9月のBlood Products Advisory Committee（BPAC）の会合で、委員会は適当な検査が利用可能になったとき、全血および成分血のドナーにシャーガス病の検査をすることを勧めた。2006年12月、FDAは血液及びHCT/Ps ドナーにおけるT. cruzi抗体の検出のためのELISA検査システムを製造業者1社に許可した。2007年1月の末以来、米国血液センターの多くは、この許可された測定法を使用してドナーを検査した。2009年2月、FDAは死んだ（心停止）HCT/Ps ドナーにおける、T. cruzi抗体の検出のためにこのELISA検査システムを認可した。 1990年代半ばの米国の血液ドナーの血清陽性率は1/5400～1/25000であった。しかし、最近の研究ではこれより増加していることを示唆している。例えば、Los Angeles大都市圏で最近では1/2000であることがわかった。 伝播経路として垂直感染、経口感染、粘膜感染、粘盤感染があり、適切なスクリーニング及び/又は検査を実施する有用性について報告をすることが記載されている。				
	報告企業の意見		今後の対応		
	米国における全血、血液成分及びHCT/Psにおけるトリパノソーマ症感染伝播のリスク低減のためのドナースクリーニングについての業者向けガイダンス（案）である。 血漿分画製剤からのトリパノソーマ原虫伝播の事例は報告されていない。また、万一原料血漿にTrypanosoma cruziが混入したとしても、除菌ろ過等の製造工程において十分に除去されると考えている。		本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。		
	使用上の注意記載状況・その他参考事項等				
	代表として献血アルブミン 25%静注 5g/20mL「ベネシス」の記載を示す。 2. 重要な基本的注意 (1) 本剤の原材料となる献血者の血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体、抗HTLV-1抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohnの低温エタノール分画で得た画分から人アルブミンを精製し、アルブミン濃度 25w/v%に調整した製剤であり、ウイルス不活化を目的として、製造工程において 60℃、10時間の液状加熱処理を施しているが、投与に際しては、次の点に十分注意すること。		

(13)

Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is for comment purposes only.

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

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

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

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Guidance for Industry

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

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I. INTRODUCTION

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

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

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

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

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

II. BACKGROUND

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1. Risk of Transmission

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

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

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

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

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

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

2. Severity of Effect

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

3. Availability of Appropriate Screening and/or Testing Measures

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

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

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

A. Blood Donor Testing and Management

1. Donor Testing

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

2. Donor Deferral

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

3. Confirmatory Testing and Donor Reentry

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

4. Donor Counseling and Physician Referral

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

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

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

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

B. Product Management

1. Index Donations

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

2. Lookback (Product Retrieval and Recipient Notification)

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

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

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

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

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

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

Retrospective Review of Records

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

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

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

3. Autologous Donations

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

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

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

4. Circular of Information

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

5. Biological Product Deviation Report and Fatality Report

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

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

C. Reporting the Test Implementation

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

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

IV. RECOMMENDATIONS FOR DONORS OF HCT/Ps

A. Donor Screening—Risk Factors or Conditions

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

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

B. Donor Testing

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

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

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

V. REFERENCES

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