資料2

感染症定期報告に関する今後の対応について

平成１６年度第５回
運営委員会確認事項
（平成１６年９月１７日）

１ 基本的な方針

運営委員会に報告する資料においては、

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

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

２ 具体的な方法

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

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

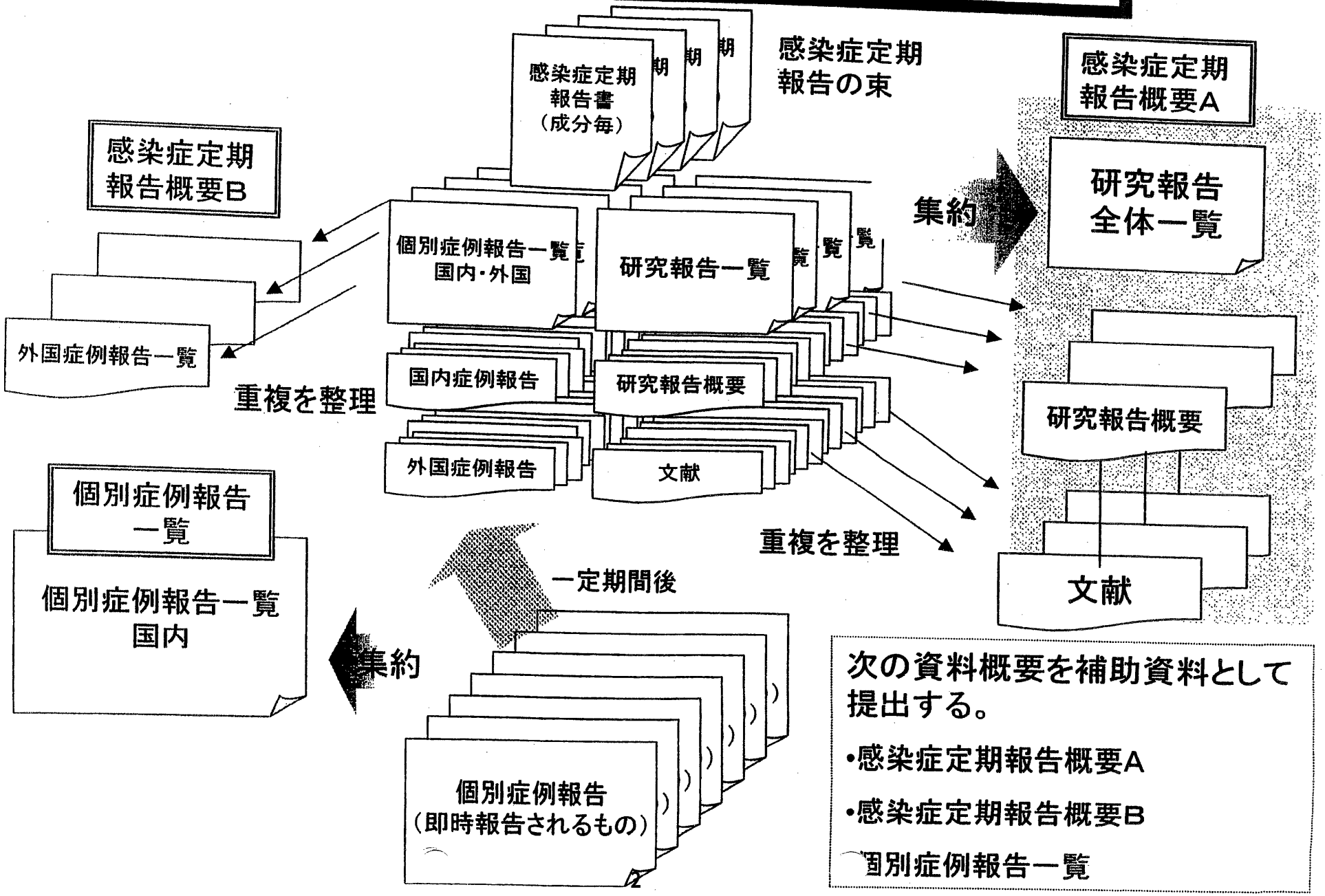
② 感染症発生症例報告のうち、発現国が「外国」の血漿分画製剤の使用による症例は、同一製品毎に報告期間を代表する感染症発生症例一覧（別紙様式第4）をまとめた**「資料概要B」**を事務局が作成し、送付する。

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

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

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

感染症定期報告・感染症個別症例報告の取り扱い



次の資料概要を補助資料として提出する。

- 感染症定期報告概要A
- 感染症定期報告概要B
- 個別症例報告一覧

感染症定期報告概要

（平成２３年２月１８日）

平成２２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２２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 (2010/9/1～2010/11/30)

血対ID	受理日	番号	感染症 (PT)	出典	概要	新出文献No.
100214	2010/9/29	100547	B型肝炎	J Infect Dis. 2010 Jul 15;202(2):192-201.	広範なB型肝炎ワクチン接種後の、米国におけるHBV感染の状況について傾向について検討された。1999-2006年と1988-1994年の2期間、米国健康･栄養調査において6歳以上を対象に、HBc抗体、HBs抗原及びHBs抗体の検査が実施された。罹患率の概算は加重及び年齢調整された。その結果、1999-2006年間の、年齢調整後のHBc抗体 (4.7%) とHBs抗原 (0.27%) の罹患率は、1988-1994年 (各5.4%及び0.38%) であり、統計学的に違いはなかった。2期間のHBc抗体の罹患率は、6-19歳 (1.9%から0.6%) 、及び20-49歳 (5.9%から4.6%) では減少したが、50歳以上では (7.2%及び7.7%) 変化がなかった。1999-2006年のHBc抗体の罹患率は、非ラテンアメリカ系白人 (2.8%) やメキシコ系アメリカ人 (2.9%) より、非ラテンアメリカ系黒人 (12.2%) と他の人種 (13.3%) で高く、また米国出生 (3.5%) より外国出生 (12.2%) の方が高かった。米国出生の6-19歳 (0.5%) では、人種や民族性による違いがなかった。米国出生と外国出生の子供では1988-1994年 (1.0%対12.8%) より、1999-2006年 (0.5%対2.0%) の方が小さかった。また、6-19歳では、56.7%がワクチンによる獲得免疫を持っていた。米国の子供におけるHBV罹患率の減少から、世界的及び国内のワクチン接種の効果が反映されているが、一方で、成人におけるHBV罹患率の状況はほとんど変わらず、およそ73万人 (95%信頼区間、55万-94万人) の米国在住者は慢性的に感染していると説明している。	1
100214	2010/9/29	100547	B型肝炎	Pediatr Infect Dis J. 2010 May;29(5):465-7.	慢性B型肝炎患児の唾液中のB型肝炎ウイルス (HBV) の水平感染が伝播手段となっている可能性を検討するために、慢性B型肝炎患児を対象に唾液中及び血漿中のHBV量の関連性が検討された。デンマークにおいて2006年5月から2008年11月間で、慢性B型肝炎患児 (0～16歳) 46人由来の唾液と血液中のHBV-DNAをTaqManPCR法 にて定量した (検出感度は50 IU/mL)。その結果、本研究中にHBe抗原が陽性から陰性になった2人と、HBe抗原の状態が分からない1人を調査対象外とした25人 (58%) がHBe抗原陽性で、18人 (42%) がHBe抗原陰性であった。HBe抗原陽性の唾液中のHBV-DNA濃度は、HBe抗原陰性の血漿中のHBV-DNA濃度より高かった (39倍) 。唾液がHBVの伝播手段になっていることが示唆された。	2
100214	2010/9/29	100547	B型肝炎	Transfusion. 2010 Jan;50(1):65-74. Epub 2009 Aug 26.	台湾において微量のB型肝炎ウイルス (HBV) DNAを検出目的とした個別検査とミニプール検査の有効性について報告された。台湾では、財政的な問題でルーチンの血液スクリーニングとしてNATの実施が制約されている。そこで、Ultrio分析 (HBV、HCV、HIV) を用いて、実施可能な検査として個別供血検査 (IDT)及び4本のミニプール (MP4)の実施成績を評価した。供血者10,290名 (IDT 4210名、MP4 6080名) を対象に潜在的HBV陽性供血者 (HBs抗原陰性/NAT陽性) を最高9ヵ月間、追跡調査した。Ultrio分析とHBs抗原検査結果が不一致の場合、さらにHBV抗体血清検査、代替NAT、HBV DNA定量検査ならびに塩基配列決定の解析を行った。その結果、再検査率は、IDT 0.55%とMP4 0.33%であった。HIVまたはHCV陽性症例は認められなかったが、潜在的HBV陽性例は12名 (IDT 9名、MP4 3名) であった。そのうちの11名は、genotypeがB2であることが判明した。そのうちの10名は、追跡調査のために再来院し、ほとんどが潜在的HBV感染症 (OBI) であると判明した。IDTの陽性率 9/4210 (0.21%) はMP4の3/6080 (0.05%) と比べ高いことから、台湾のようにOBIキャリアが多い地域においては、より高感度のNAT法で検査を実施することが有益であると説明している。	3

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
100214	2010/9/29	100547	B型肝炎	第46回日本肝臓学会総会; 2010 May 27-28; 山形	小児B型肝炎ウイルス(HBV)キャリア患者の感染経路･感染要因を解析し、現在のHBV感染予防対策の問題点について検討された。 施設1では32例、施設2では133例、施設3では22例の合計187例のHBVキャリアにおいて、男女比は1.43:1、診断時年齢は中央値2歳(0ヶ月～15歳)であった。1985年までに出生していた症例は102例で、母児感染59例(57.8%)、父子感染6例(5.9%)、輸血5例(4.9%)、水平感染31例(30.4%)、不明1例で母児感染が過半数を占めていた。一方、母児感染予防処置が導入された1986年以降に出生した症例は85例で、母児感染51例(60%)、父子感染13例(15.3%)、輸血2例(2.4%)、水平感染19例(22.4%)であった。母児感染の割合は1985年までに出生していた症例と変化なく、父子感染は増加した。母児感染のうち胎内感染が16例、予防処置実施中あるいは実施後にHBV感染が判明した症例が22例で、現在の予防法で防ぐことができなかった症例が合計38例(74.5%)であったが、予防処置の不完全施行や未施行によるものが8例(15.7%)存在した。父子感染や水平感染の症例でHBワクチンの投与症例はいなかった。HBV母児感染予防処置導入後も小児のHBVキャリアは発生している。母児感染のうち約15%は予防処置の不完全施行や未施行が原因であり、医療者の啓発を行うとともに、予防処置プロトコールを簡略な国際方式にすることにより完遂率が高まると思われる。また、父子感染･輸血を含めた水平感染例も4割を占めており、諸外国のように日本でも出生後早期にHBユニバーサルワクチンが導入されることが望まれる。胎内感染例については出生後の予防処置では防ぐことができず、HBVキャリア妊婦へのHBIGや抗ウイルス剤投与などを行うべきか、今後検討していく必要があると説明している。	4
100214	2010/9/29	100547	B型肝炎	第58回日本輸血･細胞治療学会総会; 2010 May 28-30; 愛知	2009年に全国の医療機関から報告された輸血関連感染症例(疑い例を含む)の解析結果と医療機関における「血液製剤等に係る遡及調査ガイドライン」(以下GL)に基づいた輸血前後の患者検体の検査実施状況等について報告された。2009年に医療機関より報告された症例を対象とし、献血者検体(献血者の保管検体等の個別NAT、当該製剤(使用済みバッグ)等の無菌試験等)と患者検体の調査により輸血との因果関係を評価した。また、医療機関における患者の輸血前後の検査の実施項目等を2007、2008年時と比較した。 その結果、10月末現在の報告数は82例(HBV 37例、HCV 21例、細菌 20例、パルボB19 2例、HEV 1例、CMV 1例)であり、輸血との因果関係が高いと評価した症例は、HBV 5例、HEV 1例、及び細菌 1例であった。医療機関でのGLに基づく輸血前後の患者検体の検査実施数(輸血前:HBs抗原/HBs抗体/HBc抗体、輸血後:HBV-DNA)はHBV症例で2007年6例(8%)、2008年12例(20%)、2009年9例(24%)であった。またHCV症例では(輸血前:HCV-RNA or HCVコア抗原/HCV抗体, 輸血後:HCV-RNA or HCVコア抗原)2007年12例(29%)、2008年5例(12%)、2009年5例(24%)であった。細菌症例での医療機関における患者血培の実施数は、2007年27例(90%)、2008年43例(94%)、2009年20例(100%)であった。また、医療機関からの使用済みバッグの提供が2007年17例(57%)、2008年35例(76%)、2009年17例(85%)であった。以上よりGLが医療機関に浸透していることが推察された。	5

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100214	2010/9/29	100547	B型肝炎	第58回日本輸血･細胞治療学会総会; 2010 May 28-30; 愛知	スクリーニングNATのプール数の縮小効果について検討された。日本赤十字社では血液製剤等のHBV、HCV、HIVへの安全対策として1999年7月にプール検体(500本)によるスクリーニングNAT(AMP-NAT)を開始した。その後、プール検体数を50本、20本へと縮小し、2008年8月から検出感度向上を目的に新NATシステム(Taq-NAT)を導入した。2000年1月から2009年10月までの感染症報告症例のうち、輸血による感染を直接証明できた症例はHBV 91件、HCV 3件、HIV 1件であった。この原因となった輸血用血液の献血血液それぞれ87献血、3献血、1献血を対象にし、当該献血時のスクリーニングNATをプール検体数別･試薬別に分類した。その結果HBV･HCV･HIV別に、50本プール前は8･0･0、 50本プール/AMP-NAT(2000年2月-2004年7月:4.5年間)は46･2･1、 20本プール/AMP-NAT(2004年8月-2008年7月:4年間)は30･1･0、20本プール/Taq-NAT(2008年8月-2009年10月:1.25年間)は3･0･0 であった。ウイルス増殖スピードの遅いHBVについて、プール検体数の縮小･試薬の検出感度向上により、輸血感染HBVの減少傾向が認められた。一方、ウイルス増殖スピードの速いHCV、HIVはスクリーニングNAT導入後約10年が経過した中で輸血感染HCVが3件、輸血感染HIVが1件と、NATの導入自体に効果があったことが推測された。2008年8月から導入された新NATシステムにより、更なる安全性向上に努めているところである。	6
100214	2010/9/29	100547	A型肝炎	www.47news.jp/CN/201004	国立感染研究所により、A型肝炎の患者が平成22年3月以降に増加していることが報告された。A型肝炎ウイルスに汚染した水や食材の摂取によって感染する可能性を懸念して、魚介類の十分な加熱など、注意を呼びかけている。4月18日までの合計(速報値)は121人で昨年の報告数115人を超えている。11日までの5週間の81人について、年齢は20～88歳、2例が劇症化し、うち1例が死亡した。福岡県、広島県などが多く、報告医師が推定した原因食材は「カキ」が45%と最も多かった。	7
100209	2010/9/28	100530	E型肝炎	Journal of Medical Virology 2010;82(1):69-76	感染動態を調査するために、HEVに自然感染した2匹の国産妊娠ブタの各同産仔(A群及びB群)を生後6か月まで研究した。母子移行IgG及びIgA抗体はA群から検出されたが、B群からは検出されなかった。生後30-110日において、全群の糞便からHEVが検出され、17匹については、生後40-100日にウイルス血症が出現した。系統発生分析によって、全群にHEV遺伝子型3に非常に近い塩基配列であることが示された。特異的なIgG及びIgAの血清レベルは、IgAが糞便で検出されなかったが、全群で同様であった。ウイルス血症と抗体陽転の開始は、A群で有意に遅れていた。糞便に排出されたウイルスの動態は両群で同様であった。感染動態の違いから、母性抗体がウイルス血症と抗体陽転開始を遅延させることが示唆された。定量的リアルタイムPCR解析の結果、糞便中のHEV RNAは約10^6copies/gであり、最初の排泄から10日後にHEV RNAのコピー数はピークに達することが明らかとなった。生後200日で、HEV RNAは13匹中3匹の内臓から検出された。ブタでのHEV自然感染について時間的経過を追った当該研究結果は、ブタからヒトへ感染する際のHEVの動態を理解するのに役立つであろう。	8
100206	2010/9/28	100527	パルボウィルス	Journal of General Virology 2010;91(2);541-544	パルボウイルスPARV4は、ヒト宿主のパルボウイルス科の種類として最近報告されたウイルスである。B型肝炎、C型肝炎あるいはHIV感染患者等の様々な集団由来の血漿、血清及び全血を用いて、定量PCR法により血中のPARV4の検出率が検討された。その結果、8検体がPARV4陽性であり、うち1検体は高コピー数を示した。高力価の血清は約5×10^8genome equivalents/mLであった。間接免疫蛍光法によって、PARV4抗体陽性が同定された2患者の血清を用いて、血清中の天然(native)PARV4を免疫電子顕微鏡下で可視化したところ、1患者由来の血清においてPARV4粒子が観察された。天然(native)のPARV4の可視化は、初めてのことである。	9

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
100214	2010/9/29	100547	パルボウィルス	XXXIst International Congress of the ISBT;2010 Jun 26-July 1; Berlin,Germany	ヒトパルボウイルスB19(B19)DNA陽性血液製剤の感染性について検討された。2000年以降、ドイツのウルム研究所では、供血6～8週間後(血液製剤供給後)について、B19に対する供血者NATスクリーニングを実施している。レトロスペクティブな研究において、受血者を次の2群に分け(A群:B19ウイルス量≦10^5IU/mLの血液製剤受血者、B群:B19ウイルス量＞10^5IU/mLの血液製剤受血者)VP-1uゲノム領域の系統発生解析をB19DNA陽性供血者と受血者に対して行い、全ての試料に対して、IgM、IgG抗体を調べた。その結果、B19 DNAはB群の赤血球濃厚液受血者18名中9名に検出されたが、A群の受血者16名にはB19 DNAは検出されなかった。系統発生解析では、供血者と受血者間で同一ゲノム配列を示した。血液製剤によるB19伝播は、ウイルス濃度と中和抗体価に相関することが示唆されると説明している。	10
100214	2010/9/29	100547	ウイルス感染	Emerging Infectious Diseases 2010; 16 (5); 856-858 May 2010	2009年8月にテキサス州ダラスで採取した、ヒトスジシマカにおけるLa Crosseウイルス(LACV)について報告された。LACVは主にAedes triseriatusが媒介する、北アメリカでの小児脳炎の主要な原因である。しかし近年、LACV脳炎が南東部地域で増加し、南部でも報告されている。同時にアジアからの外来種であるヒトスジシマカが増加しているが、今までヒトスジシマカとLACV伝播の関連は不明であった。今回の調査で、テキサス州ダラスで採取したヒトスジシマカからLACVが検出され、これまで流行が確認されていた範囲外で、外来性の蚊に当該ウイルスが認められた。	11
100214	2010/9/29	100547	ウエストナイルウイルス	CDC/MMWR 2010 July 2	2009年の米国におけるウエストナイルウイルス(WNV)の流行状況について、米国疾病管理予防センター(CDC)が発表した。米国の38州の262郡と、コロンビア特別区から720症例のWNV感染症が報告された。そのうち386例(54%)が神経侵襲性疾患で、334例(46%)が非神経侵襲性疾患であった。WNV感染症での死亡者は全部で33人が報告され、そのうち32人が神経侵襲性疾患であった。神経侵襲性疾患のうち229例(59%)が脳炎、117例(30%)が髄膜炎、40例(10%)が急性弛緩性麻痺であった。急性弛緩性麻痺40例のうち、27例(68%)が脳炎または髄膜炎を併発した。WNVによる疾病を制御する上で、調査の継続、蚊の管理、蚊に対する防御用具、及び更に予防戦略を検討することが必要である。	12
100214	2010/9/29	100547	レトロウイルス(XMRV)	ABC Newsletter #15.2010 Apr 23;15	ニュージーランドの血液バンクでは慢性疲労症候群(CFS)の既往を持つ供血者の供血延期を開始し、オーストラリア当局は、供血ガイドラインの見直しを行っている。 ニュージーランドの決定は、前立腺癌と関連性があるXMRVが、健康集団と比較してCFS患者の血中に非常に多く認められたという調査を受けてなされた。他の科学者は、この結果を確認することができなかったが、米国保健当局は、CFSとXMRV間の関連の可能性について調査を行っており、カナダ血液サービスはすでにCFSの診断を受けた供血者からの供血を無期限延期としている。一方、オーストラリア赤十字血液サービスは、独自にリスク分析を行い、完全に回復するまでのCFS患者からの供血を延期することを現行のガイドラインで求めている。	13
100230	2010/10/26	100654	レトロウイルス(XMRV)	www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm223277.html	米国食品医薬品局生物製剤評価･研究センター及び米国国立衛生研究所臨床センターの研究者は、慢性疲労症候群(CFS)と診断された患者37例と健康血液ドナー44例由来の血液試料において、CFS患者由来の32例(87%)及び健康血液ドナー由来の3例(7%)に複数の異なるマウス白血病ウイルス(MLV)遺伝子配列を同定した。当該研究はMLV様ウイルスの遺伝的変異体であるXMRVがCFS患者の血液中に存在するとの過去の研究報告を支持し、CFSの診断と血液中のMLV様ウイルス遺伝子配列の存在との間に強い関連性があることを示している。さらにごく一部の健康血液ドナーにおいてMLV様ウイルス遺伝子配列が検出されている。CFSとの統計的な関連は強いものの、当該研究でレトロウイルスがCFSの原因であることが証明されたわけではない。	14

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
100214	2010/9/29	100547	リフトバレー熱	ProMED-mail 20100513.1557	2010年5月10日の時点で南アフリカ保健省は、18人の死者を含む186人のリフトバレー熱(RVF)症例を報告している。主要な感染経路は、感染した家畜の血液や組織に触れることであるが、蚊に刺されることも感染原因となる。世界保健機関(WHO)は、南アフリカへの旅行に対して規制の勧告は行っていないが、特に農場や動物保護区に行く者は、動物組織や血液との接触を避け、未殺菌、非加熱ミルクや生肉の摂取をしないことを勧めている。全旅行者に対し、長袖長ズボンの着用や防虫剤、蚊帳を使用するなどして、蚊や吸血昆虫に刺されないよう注意を呼びかけている。また、ドイツ保健当局は、南アフリカ旅行から帰国したドイツ人の予備的診断ではＲＶＦであったが、その後の追加検査により、この症例はRVFではなくリケッチア感染であったと報告した。	15
100236	2010/10/27	100663	Q熱	Clinical Infectious Diseases 50(11) 1433-1438 2010	2005年6月28日、イスラエル中央部の都市部で、全寮制高校の生徒及び職員の322名において多数の熱性疾患(発熱、頭痛、発汗など)症例が報告された。その後の調査で、その2週間前に大規模なQ熱アウトブレイクが発生していたことが分かった。Q熱疾患の危険因子特定するため、症例対照研究が実施された。2005年6月15日～7月13日の間に、303名中187名(62%)が体調不良の報告をしており、血清学的検査を実施した164名中144名(88%)に、*C.burnetii*感染が明らかとなった。Q熱感染の重大な危険因子は、学生であること、学校の食堂で定期的に食事をしたこと、6月の宗教上の休日期間並びにその前の週末に寮にいたことであった。PCR法により学食の空調から*C.burnetii*DNAが検出され、空調を介して病原体に空気感染したことが示唆された。	16
100236	2010/10/27	100663	アメリカ･トリパノソーマ症	J Infect Dis 201(9) 1308-1315 2010	Trypanosoma cruzi(T.cruzi)は媒介動物の糞便によって汚染された食物から経口感染する。アメリカ大陸での急性シャーガス病CDのアウトブレイク時において、ベネズエラでコホート疫学研究が実施された。曝露された1000名中103名に感染が確認され、そのうち75%に症状が認められ、20.3%が入院を必要とした。また59%は心電図異常を示し、44名(子供1名)に寄生虫血症が認められた。臨床的な特徴は媒介による感染で見られるものと異なっていた。子供は感染率が有意に高かった。疫学的な調査から、汚染した生グアバジュースが唯一の感染原因とされた。当該アウトブレイクは大都市部で主に若年齢を中心とした健康に問題のない集団における感染という、先例のない珍しいものであった。	17
100254	2010/10/28	100688	細菌感染	Agence France-Presse 2010/08/14	ベルギーにおいて、南アジア起源の薬剤耐性のsuperbugによる死亡1例が報告された。当該症例は、パキスタンを旅行中、交通事故にて脚を負傷し、パキスタンの病院で治療をうけ、ベルギーに帰国後死亡した。新規に同定されたNew Delhi metallo-β-lactamase 1(NDM-1)遺伝子を有する細菌に感染していた。2症例目はモンテネグロを旅行中に事故に遭い、入院後感染したが、ベルギーで治療をうけ回復した。	18
100202	2010/9/15	100453	細菌感染	The Lancet Infectious Diseases 10(9); 597-602; 2010 September	NDM-1(New Delhi metallo-β-lactamase 1)に起因するcarbapenem耐性腸内細菌(G(-))が問題となっており、インド、パキスタンおよび英国における多剤耐性腸内細菌におけるNDM-1の検出率を調査した。NDM-1が存在する分離株はChennaiで44、Haryanaで26、英国で37およびインドおよびパキスタンでは73株が分離された。NDM-1は大腸菌(36株)および肺炎桿菌(111株)で広く認められ、tigecyclineおよびcolistinを除くすべての抗生剤に強い耐性を示した。NDM-1陽性である英国人の多くは、一年以内にインドもしくはパキスタンに渡航歴があり、もしくは関連があった。	19
100202	2010/9/15	100453	細菌感染	毎日新聞 2010年8月17日	インド･パキスタンが発生源とみられ、ほとんどの抗生物質が効かない新種の細菌感染患者が欧州などで増えており、ベルギーでは2010年6月に最初とみられる死者が確認された。欧州メデイアによると、英･仏･ベルギー･オランダ･独･米･カナダ･豪で感染が確認され、更なる拡大の恐れがある。Lancetの最新号に、特定の抗生物質を分解する酵素「NDM1」を作り出す遺伝子を持ち、ほとんどすべての抗生物質に対して耐性を持つ細菌について報告がある。	20

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100236	2010/10/27	100663	真菌感染	PLoS Pathogens 6(4); e1000850; 2010 April	Cryptococcus gattiiは、従来、熱帯・亜熱帯性真菌と考えられていたが、1999年にカナダ、バンクーバー島で大流行し、現在においても隣接するカナダ本土ブリティッシュコロンビアや米国本土においてヒトや動物に感染し続けている。この大流行はVGII型、特にVGIIa/majorが原因であったが、加えて、オレゴンで新しい遺伝子型(VGIIc型)が出現した。MLST及びVNTR解析によって、新型VGIIc及びVGIIa/majorは、マクロファージやマウスに感染し、強毒性を示すことが分かった。	21
100263	2010/11/29	100734	クロイツフェルト・ヤコブ病	ANN NEUROL 2010;68:162-172	新規の弧発性プリオン蛋白質疾患の特性解析について報告された。プロテアーゼ感受性プリオン(PSPr)の新規の2遺伝子型、メチオニン同型接合(129MM)とメチオニン/バリン異型接合(129MV)が報告された。2008年に報告された新規のプリオン病の被験者11人はプリオン蛋白質(PrP)遺伝子のコドン129が全員バリン同型接合(129VV)であった。129MM、129MV、129VVの被験者15人について、罹患期間(22～45ヵ月)は129VVと129MVの被験者で有意に異なった。PrP電気泳動プロファイルと共に他のほとんどの機能は同様であったが、主な違いは疾患関連PrPのプロテアーゼ消化の感受性であり、129VVは感受性が高いが、129MVと129MMでは低いか、あるいは全くない。この違いにより可変プロテアーゼ感受性プリオン症(VPSPr)と呼ばれるようになった。被験者のPrP遺伝子コドン領域に変異はなかった。3つの129遺伝子型が全て関係し、区別でき、表現型として関係するので、VPSPrは2番目の弧発性プリオン蛋白質疾患になる。この特徴は1920年に報告したクロイツフェルトヤコブ病に似ていた。しかし、VPSPrは異常プリオン蛋白質の特性において典型的なプリオン病と異なり、恐らくゲルストマン・ストロイスラー・シャインカー疾患の亜型と類似している。	22
100206	2010/9/28	100527	異型クロイツフェルト・ヤコブ病	European Medicines Agency 2010/07/24	2003年2月に公表され、2004年6月に改訂されたクロイツフェルト・ヤコブ病と、血漿由来医薬品及び尿由来医薬品についてのCPMPの見解(EMEA/CPMP/BWP/2879/-02)の第2改訂版(案)であり、2010年9月30日まで意見を公募している。累積した疫学的エビデンスは、血液成分あるいは血漿由来製品による弧発性・家族性・医原性CJD感染を支持していない。ドナーの弧発性・家族性・医原性CJDが供血後に確認された場合、血漿由来製品の回収は妥当でないという以前からのCHMPの方針に変更はない。尿由来製品についてCJD、vCJDが感染したという疫学的なエビデンスはない。予防的措置として採血と同じドナーの選択基準を適用する。	23
100259	2010/11/25	100725	異型クロイツフェルト・ヤコブ病	Haemophilia 2010;16,305-315	英国の血液製剤による感染と遺伝性出血性疾患患者における英国の血液製剤による影響のリスクを低減する為の対策について報告された。vCJDの発生後、感染及び二次感染拡大のリスクを最小限に抑えるため、2004年に供血後にvCJDを発症したドナーから採取された血漿を含んでいるかどうかに関わらず、1980年から2001年までの間に英国でプールされた血液凝固因子製剤を投与された患者全員に予防措置が実施された。以降、英国におけるvCJDの新規症例は減少し、過去に関係する血液または血液製剤の投与を受けたvCJD患者は見つかっていない。しかし一般母集団における無症候性vCJD感染の有病率は不明であり、適切かつ有効なvCJDのスクリーニング試験はない。血友病患者において最近確認された1例目の無症候性のvCJD感染症例ならびにメチオニン/バリン異型接合患者におけるvCJD報告は、遺伝性出血性疾患患者を含む「リスクのある」集団において、継続調査が必要であることを示している。	24
100230	2010/10/26	100654	異型クロイツフェルト・ヤコブ病	Transfusion. 2010 May;50(5):1003-1006.	現在までに、後に変異型クロイツフェルト・ヤコブ病(vCJD)を発症した患者からの輸血によるvCJD感染例が4例報告されている。共通の供血者から輸血された可能性が示唆された症例は2例(症例A及びB)であった。症例Aは1989年に新生児特別治療室で4回の輸血歴があり、2006年、vCJDと診断されて6ヵ月後の18歳で死亡。症例Bは1993年6月と10月に2回の輸血歴があり、1998年にvCJDを発症し、41歳で死亡。合計103名の供血者の血液に曝露していた。症例Aと症例Bがいた両病院は同じ血液センターから供血血液の配給を受けていた。症例Bが曝露していた供血者103名中99名が症例Aへ輸血された後も、20年以上生存している。残りの4名はCJD以外の要因で死亡していた。vCJDを発症していない供血者から輸血を受けた症例AとBの2症例がvCJDを発症したことから、vCJD感染のパターンとして食事を通してBSEに感染した可能性も考えられる。	25

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 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		公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)		Wasley A, Kruszon-Moran D, Kuhnert W, Simard EP, Finelli L, McQuillan G, Bell B. J Infect Dis. 2010 Jul 15;202(2):192-201.	米国

研究報告の概要

○ワクチン接種世代の米国におけるB型肝炎ウイルス(HBV)感染の状況
目的:広範なB型肝炎ワクチン接種後の、米国におけるHBV感染の状況について傾向を評価すること。
方法:HBV感染と免疫の状況を調べるため、1999-2006年と1988-1994年の期間、米国健康・栄養調査の6歳以上の参加者で、HBc抗体、HBs抗原及びHBs抗体を検査した。罹患率の概算は加重及び年齢調整された。
結果:1999-2006年の期間中の、年齢調整後のHBc抗体(4.7%)とHBs抗原(0.27%)の保有率は、1988-1994年(それぞれ5.4%及び0.38%)と統計学的に違いはなかった。HBc抗体の保有率は、6-19歳(1.9%→0.6%;P<0.01)及び20-49歳(5.9%→4.6%;P<0.05)の間で減少したが、50歳以上(7.2%対7.7%)では変化がなかった。1999-2006年では、HBc抗体の保有率は、非ラテンアメリカ系白人(2.8%)やメキシコ系アメリカ人(2.9%)より、非ラテンアメリカ系黒人(12.2%)と他の人種(13.3%)で高く、そして、米国生まれ(3.5%)より外国生まれ(12.2%)の方が高かった。米国生まれの6-19歳の子供(0.5%)では、人種や民族性による違いがなかった。米国生まれと外国生まれの子供の相違は1988-1994年(1.0%対12.8%)より、1999-2006年(0.5%対2.0%)の方が小さかった。また、6-19歳では、56.7%がワクチンによる獲得免疫を持っていた。
結論:HBVの罹患率は米国の子供で減少した。それは世界的及び国内のワクチン接種の効果を反映している。しかし、成人の状況はほとんど変わらず、およそ730万人(95%信頼区間、550万-940万人)の米国在住者は慢性的に感染している。

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
広範なB型肝炎ワクチン接種後の米国におけるB型肝炎ウイルス罹患率を評価したところ、子供で罹患率が減少しており、ワクチン接種の効果を反映していることが分かったとの報告である。 これまで、本剤によるHBV感染の報告はない。また本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。さらに最終製品についてHBV-NAT陰性であることを確認しており、安全性は確保されていると考える。	これまでの使用実績やバリデーション成績に鑑み本製剤の安全性は確保されており、特別の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。なお、日本赤十字社では献血時のスクリーニング法としてより感度の高い化学発光酵素免疫測定法(CLEIA)および新NATシステムを導入した。

MAJOR ARTICLE

The Prevalence of Hepatitis B Virus Infection in the United States in the Era of Vaccination

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Background. Our objective was to assess trends in the prevalence of hepatitis B virus (HBV) infection in the United States after widespread hepatitis B vaccination.

Methods. The prevalence of HBV infection and immunity was determined in a representative sample of the US population for the periods 1999–2006 and 1988–1994. National Health and Nutrition Examination Surveys participants ≥6 years of age were tested for antibody to hepatitis B core antigen (anti-HBc), hepatitis B surface antigen (HBsAg), and antibody to hepatitis B surface antigen (anti-HBs). Prevalence estimates were weighted and age-adjusted.

Results. During the period 1999–2006, age-adjusted prevalences of anti-HBc (4.7%) and HBsAg (0.27%) were not statistically different from what they were during 1988–1994 (5.4% and 0.38%, respectively). The prevalence of anti-HBc decreased among persons 6–19 years of age (from 1.9% to 0.6%; $P<.01$) and 20–49 years of age (from 5.9% to 4.6%; $P<.05$) but not among persons ≥50 years of age (7.2% vs 7.7%). During 1999–2006, the prevalence of anti-HBc was higher among non-Hispanic blacks (12.2%) and persons of "Other" race (13.3%) than it was among non-Hispanic whites (2.8%) or Mexican Americans (2.9%), and it was higher among foreign-born participants (12.2%) than it was among US-born participants (3.5%). Prevalence among US-born children 6–19 years of age (0.5%) did not differ by race or ethnicity. Disparities between US-born and foreign-born children were smaller during 1999–1996 (0.5% vs 2.0%) than during 1988–1994 (1.0% vs 12.8%). Among children 6–19 years of age, 56.7% had markers of vaccine-induced immunity.

Conclusions. HBV prevalence decreased among US children, which reflected the impact of global and domestic vaccination, but it changed little among adults, and ~730,000 US residents (95% confidence interval, 550,000–940,000) are chronically infected.

Hepatitis B virus (HBV) is a bloodborne and sexually transmitted virus. Each year, ~600,000 HBV-related deaths occur worldwide [1, 2], most of which result from the chronic sequelae of HBV infection [3–5]. Approximately 25% of persons who become chronically infected during childhood and ~15% of those who become chronically infected after childhood die from cirrhosis or liver cancer [2]. In the United States, before hepatitis B vaccines were licensed in 1982, 200,000–300,000 persons each year became infected with HBV [6]. Hepatitis B vaccination is the most effective measure to prevent HBV infection and its consequences. However, for persons already infected with HBV, antiviral agents are available that may prevent the serious sequelae of chronic liver disease, which highlights the importance of identifying infected individuals [7].

Patterns of HBV infection vary worldwide. Approximately 45% of the world's population live in regions that are highly endemic for HBV infection, where most infections are acquired perinatally or during early childhood [2, 8]. Another 43% live in regions of intermediate endemicity, where multiple modes of transmission (ie, perinatal, household, sexual, injection drug use associated, and health care associated) are important. In

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countries of low endemicity, most infections occur among adolescents and adults and are attributable to sexual and injection drug use exposures. In 1992, the World Health Organization set a goal for all countries to integrate hepatitis B vaccine into their childhood vaccination programs by 1997 [9].

In the United States, a country of low endemicity, a strategy to eliminate HBV transmission [10] was initiated in 1991, which includes universal vaccination of infants; screening of all pregnant women for HBV, with postexposure prophylaxis provided to infants born to infected women; catch-up vaccination of adolescents; and vaccination of adults who are at increased risk of infection [11, 12]. To assess US trends in the burden of HBV and to provide the first nationally representative analysis of the impact of hepatitis B vaccination, we compared the prevalence of HBV infection among National Health and Nutrition Examination Survey (NHANES) participants during 1999–2006 to that during 1988–1994 and measured the prevalence of vaccine-induced immunity among participants during 1999–2006.

METHODS

Study populations and sample design. NHANES is a series of surveys conducted periodically to obtain representative data on the health status of the US population. Participants are chosen using a complex, stratified, multistage sampling design to obtain a representative sample of the civilian, noninstitutionalized population. Our analyses include data from 1999–2006 (NHANES 1999–2006) and 1988–1994 (NHANES 1988–1994). Further details on the design and implementation of these surveys are described elsewhere [13, 14].

During the years evaluated, all ages were eligible to participate. Participants were interviewed at home and then visited a mobile examination center for additional interviews and a physical examination. Blood samples were collected for participants aged ≥6 years in NHANES 1988–1994 and aged >2 years in NHANES 1999–2006. Informed consent was obtained. Efforts were made to ensure participation; respondents were nominally remunerated for their time and travel expenses.

Laboratory methods. Serum samples from participants aged ≥6 years were tested for antibody to hepatitis B core antigen (anti-HBc) (NHANES 1988–1994: Corab radioimmunoassay [Abbott Laboratories]; NHANES 1999–2006: Ortho HBc ELISA [Ortho Clinical Diagnostics]) and, if results were positive, were tested for hepatitis B surface antigen (HBsAg) (NHANES 1988–1994: Ausria II [Abbott Laboratories]; NHANES 1999–2006: Auszyme [Abbott Laboratories]). Starting with NHANES 1999–2006, serum samples from participants aged >2 years were tested for antibody to hepatitis B surface antigen (anti-HBs) (Ausab [Abbott Laboratories]).

Definitions. Past or present HBV infection was defined as the presence of anti-HBc. Chronic HBV infection was defined as the presence of anti-HBc and HBsAg. For NHANES 1999–2006, persons with test results positive for anti-HBs and negative for anti-HBc were considered to have vaccine-induced immunity.

In NHANES 1988–1994, 25,733 (83.2%) of the participants aged ≥6 years were interviewed, of whom 23,527 (91.4% of those interviewed) were examined and 21,260 (90.4% of those examined) were tested for anti-HBc and HBsAg. In NHANES 1999–2006, 34,338 (79.8%) were interviewed, 32,534 (94.7% of those interviewed) were examined, and 29,828 (91.7% of those examined) provided serum samples. Analysis of vaccine-induced immunity included NHANES 1999–2006 participants aged ≥2 years tested for anti-HBs. Samples for participants aged 2–5 years were collected starting in NHANES 1999; participation rates in this age group were low, with samples available for 55.8% of 3592 examined children. In NHANES, race and ethnicity is categorized as non-Hispanic white (hereafter "NH-white"), non-Hispanic black (hereafter "NH-black"), Mexican American, or Other (which includes all other racial and ethnic groups, including Asians and other Hispanics). Age groups were 6–11, 12–19, 20–29, 30–39, 40–49, 50–59, and ≥60 years of age.

Statistical analyses. Prevalence estimates were weighted to represent the US population and to account for oversampling and nonresponse to the household interview and physical examination. Standard errors were calculated in SUDANN Statistical Analysis Software (Research Triangle Institute). Prevalence estimates were age-adjusted by the direct method using the age groups listed above to the 2000 US census population for comparisons across subgroups and between surveys [15]. Prevalence of vaccine-induced immunity was compared between the periods 1999–2002 and 2003–2006. Prevalence estimates of HBV infection and chronic infection for some subgroups, where noted in the tables, are based on a small number of persons with positive results and may be unstable. Statistical comparisons were evaluated using a t test for linear contrast procedure in SUDAAN. No adjustments for multiple comparisons were made.

RESULTS

Overall prevalence of past and present HBV infection and markers of immunity. The prevalence of past and present infection during the period 1999–2006 was 4.8% (95% confidence interval [CI], 4.3%–5.3%). Prevalence of chronic HBV infection was 0.28% (95% CI, 0.21–0.36%), which represents ~730,000 infected persons (95% CI, 550,000–940,000). Prevalence of markers of vaccine-induced immunity was 22.2% (95% CI, 21.3%–23.1%).

Prevalence of HBV infection increased with age, from 0.6%

(95% CI, 0.2%–1.4%) among persons 6–11 years of age to 7.3% (95% CI, 6.2%–8.5%) among persons ⩾60 years of age (Figure 1). Prevalence of vaccine-induced immunity was negatively correlated with age, ranging from 53.5% (95% CI, 50.8%–56.3%) among persons aged 6–11 years to 5.1% (95% CI, 4.3%–6.0%) among persons ⩾60 years of age. Among the 2003 children 2–5 years of age who were tested, 57.3% (95% CI, 54.1%–60.4%) had test results that were positive for anti-HBs; the representativeness of that estimate is uncertain because of the low response rate in this age group.

Age-adjusted estimates of the prevalence of past and present HBV infection. The overall age-adjusted prevalence of past and present infection in NHANES 1999–2006 (4.7%) was lower than but was not statistically different from the prevalence in NHANES 1988–1994 (5.4%) (Table 1). However, among children 6–19 years of age, prevalence decreased significantly, from 1.9% to 0.6% ($P<.01$). Among adults, prevalence decreased significantly among those 20–49 years of age, from 5.9% to 4.6% ($P<.05$) but was unchanged among those ⩾50 years of age.

In NHANES 1999–2006, age-adjusted prevalence of past and present infection was significantly higher among NH-blacks (12.2%; $P<.001$) and Others (13.3%; $P<.001$) than it was among NH-whites and Mexican Americans, and it was significantly higher among foreign-born persons (12.2%; $P<.001$) than it was among US-born persons (3.5%). Compared with NHANES 1988–1994, prevalence decreased significantly only among the Other (from 20.1% to 13.3%) and Mexican American (from 5.1% to 2.9%) race and ethnic groups. No significant change in sex-specific prevalence occurred; in NHANES 1999–2006, prevalence among male participants remained significantly ($P<.001$) higher than it was among female participants.

The age-adjusted prevalence of chronic HBV infection in NHANES 1999–2006 (0.27%) was lower but not statistically different than it was in NHANES 1988–1994 (0.38%) (Table 1). Among children 6–19 years of age, there was a 79% decrease in the age-adjusted prevalence of chronic infection, from 0.24% to 0.05%, which was not statistically significant. In NHANES 1999–2006, prevalence of chronic infection was lower among persons 6–19 years of age (0.05%) ($P<.001$) than it was among those 20–49 years of age (0.30%) or ⩾50 years of age (0.38%), and it was lower among female participants (0.19%) ($P<.05$) than it was among male participants (0.35%). Chronic infection was more common among persons classified as Other (0.98%; $P<.001$) or NH-black (0.89%; $P<.001$) than it was among NH-whites (0.09%) and Mexican Americans (0.07%). Chronic infection among foreign-born participants (0.89%) decreased significantly ($P<.05$), compared with NHANES 1988–1994 (1.75%), but remained >5-fold higher than it was among US-born participants (0.16%; $P<.001$). The number of chronically infected persons identified in NHANES was small; estimates for some sparsely populated strata, where noted in the tables, have large confidence intervals and may be unstable.

Trends among children in past and present HBV infection. Among children, the age-adjusted prevalence of past and present infection among NH-blacks ($P<.05$) and Others ($P<.01$) decreased significantly across surveys. The decreases in these groups, which both had significantly ($P<.01$) higher prevalence than did NH-whites and Mexican Americans in NHANES 1988–1994, resulted in a narrowing of racial and ethnic disparities in NHANES 1999–2006, although the difference between the highest (NH-black) and lowest 2 groups (Mexican Americans and Other) remained significant ($P<.01$ and $P<.05$ respectively) (Table 2). Differences in prevalence between

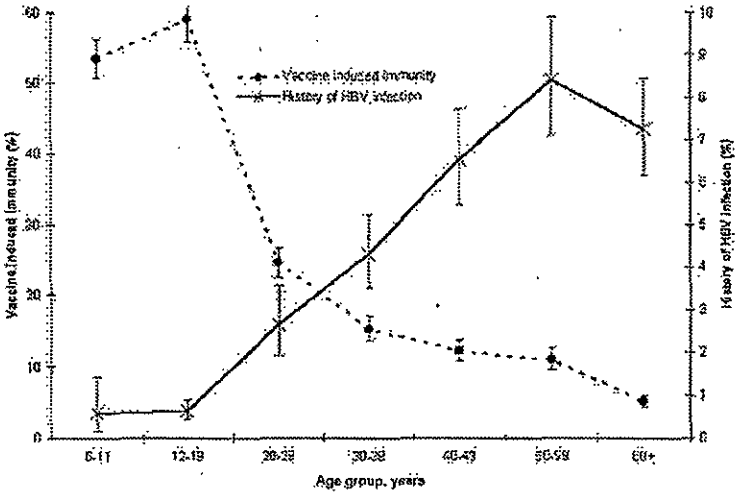

Figure 1. Crude prevalence of markers of hepatitis B virus (HBV) infection and vaccine-induced immunity by age, 1999–2006.

Table 1. Age Adjusted Prevalence of Hepatitis B Virus (HBV) Infection, by Selected Demographic Characteristics

	Past or present HBV infection					Chronic HBV infection		
	NHANES III (1988–1994)		NHANES 1999–2006			NHANES III (1988–1994): Prevalence, % (95% CI)	NHANES 1999–2006: Prevalence, % (95% CI)	P^b
Variable	Sample size[a]	Prevalence, % (95% CI)	Sample size[a]	Prevalence, % (95% CI)	P^b			
Overall	21,260	5.4 (4.8–6.1)	29,828	4.7 (4.2–5.2)	NS	0.38 (0.29–0.49)	0.27 (0.20–0.35)	NS
Age, years								
6–19	5679	1.9 (1.2–2.7)	12,004	0.6 (0.4–0.9)	<.01	0.24 (0.07–0.56)[c]	0.05 (0.02–0.11)[c,d]	NS
20–49	8857	5.9 (5.1–6.9)	9465	4.6 (3.9–5.3)	<.05	0.39 (0.25–0.60)	0.30 (0.21–0.42)	NS
≥50	6724	7.2 (6.2–8.3)	8359	7.7 (6.8–8.7)	NS	0.45 (0.21–0.84)	0.38 (0.25–0.55)	NS
Race/ethnicity								
White, non-Hispanic	7963	3.0 (2.6–3.5)	12,075	2.8 (2.5–3.1)	NS	0.21 (0.09–0.41)[c]	0.09 (0.05–0.14)	NS
Black, non-Hispanic	6133	13.8 (12.4–15.3)	7302	12.2 (11.1–13.5)	NS	0.83 (0.59–1.14)	0.89 (0.57–1.33)	NS
Mexican American	6275	5.1 (3.8–6.6)	8094	2.9 (2.4–3.5)	<.01	0.15 (0.05–0.37)[c,d]	0.07 (0.01–0.25)[c,d]	NS
Other	889	20.1 (15.4–25.5)	2357	13.3 (10.9–16.0)	<.05	1.51 (0.83–2.51)	0.98 (0.57–1.56)	NS
Country of birth								
United States	17,301	3.9 (3.5–4.4)	24,291	3.5 (3.1–3.9)	NS	0.20 (0.12–0.30)	0.16 (0.11–0.23)	NS
Foreign born	3901	16.2 (12.8–19.9)	5528	12.2 (10.7–13.9)	<.05	1.75 (1.26–2.36)	0.89 (0.55–1.35)	<.05
Sex								
Male	10,088	6.4 (5.5–7.3)	14,523	5.6 (4.9–6.3)	NS	0.52 (0.35–0.74)	0.35 (0.25–0.48)	NS
Female	11,172	4.5 (3.8–5.4)	15,305	3.8 (3.2–4.4)	NS	0.23 (0.14–0.36)	0.19 (0.11–0.30)	NS

NOTE. CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; NS, not significant.

[a] Stratum-specific sample sizes may not sum to total because of missing data.

[b] Determined by *t* test evaluating change across surveys.

[c] Estimate is small relative to its standard error (relative standard error >30%) and therefore may be unstable.

[d] Estimate based on <10 individuals with positive samples.

US and foreign-born children diminished as a result of greater decreases in prevalence among foreign-born children. The prevalence among foreign-born children (12.8%) in NHANES 1988–1994, which was almost 13-fold higher than that among US-born children (1.0%; $P < .01$), decreased to 2.0% in NHANES 1999–2006, compared with 0.5% ($P < .01$) among US-born children. Most notable was a >90% decrease among foreign-born Other children ($P < .001$).

Among US-born children, racial and ethnic disparities were reduced. In NHANES 1988–1994, prevalence was significantly higher among US-born NH-black children (2.1%; $P < .05$), compared with NH-whites (0.7%) and Mexican Americans (0.5%). In comparison, in NHANES 1999–2006, prevalence was similar among US-born children by race and ethnicity, ranging from 0.1% (Other) to 0.6% (NH-white). Race-specific estimates for some subgroups, as noted in Table 2, are based on <10 positive samples and may be unstable.

Trends among adults. The significant decrease in prevalence across surveys among persons 20–49 years of age ($P < .05$) reflected decreases among US-born and foreign-born participants, although only the decrease among US-born participants was statistically significant ($P < .05$). Prevalence remained significantly higher among foreign-born participants (10.3%) in NHANES 1999–2006 than among US-born participants (3.4%; $P < .001$) (Table 3). Among US-born adults, a pattern of decreasing prevalence was noted in all racial and ethnic groups, but only the decrease in prevalence among NH-blacks was statistically significant ($P < .05$). In NHANES 1999–2006, prevalence among US-born non-Hispanic NH-blacks (9.6%) remained higher ($P < .001$) than the prevalence among NH-whites and Mexican Americans. In contrast, prevalence among US-born Others no longer differed from that among US-born NH-whites or Mexican Americans. The decrease among foreign-born participants 20–49 years of age ($P < .05$) was seen among several racial and ethnic groups but was statistically significant only among Mexicans Americans ($P < .05$). The prevalence was ~3-fold higher among foreign-born Others (16.1%) than it was among US-born Others (5.6%; $P < .001$), a gap that appeared to widen, compared with NHANES 1988–1994, when prevalences among foreign-born and US-born Others were 21.3% and 17.4%, respectively.

In contrast to the trends among younger adults, the prevalence among persons ≥50 years of age in NHANES 1999–2006 (7.7%; 95% CI, 6.8%–8.7%) did not differ from that in NHANES 1988–1994 (7.2%; 95% CI, 6.2%–8.3%). Disparities by race and country of birth that were present in NHANES 1988–1994 (data not shown) remained unchanged in NHANES 1999–2006. In particular, prevalence remained unchanged and significantly higher among NH-blacks (21.7%; 95% CI, 19.2%–24.3%; $P < .001$) and Others (25.5%; 95% CI, 19.6%–32.1%;

Table 2. Age-Adjusted Prevalence of Past and Present Hepatitis B Virus Infection among Children 6–19 Years of Age, by Selected Demographic Characteristics

Variable	NHANES III (1988–1994)			NHANES 1999–2006			
	Sample size[a]	No. of children with positive results	Prevalence, % (95% CI)	Sample size[a]	No. of children with positive results	Prevalence, % (95% CI)	P[b]
Overall	5679	77	1.9 (1.2–2.7)	12,004	81	0.6 (0.4–0.9)	<.01
Race and ethnicity							
White, non-Hispanic	1478	13	0.7 (0.4–1.9)[c]	3058	15	0.6 (0.3–1.2)[c]	NS
Black, non-Hispanic	1921	35	2.2 (1.4–3.3)	3830	44	1.0 (0.7–1.4)	<.05
Mexican American	2011	6	0.5 (0.1–1.3)[c]	4148	17	0.4 (0.2–0.7)[c]	NS
Other	269	23	10.3 (5.2–17.7)	968	5	0.4 (0.1–1.1)[c]	<.01
US born							
All	5022	50	1.0 (0.6–1.4)	10,474	44	0.5 (0.2–0.8)	<.05
White, non-Hispanic	1448	13	0.7 (0.4–1.3)	2963	13	0.6 (0.2–1.2)[c]	NS
Black, non-Hispanic	1840	31	2.1 (1.2–3.2)	3644	18	0.5 (0.3–0.7)	<.01
Mexican American	1581	4	0.5 (0.1–1.8)[c]	3079	12	0.4 (0.1–0.7)[c]	NS
Other	153	2	0.9 (0.0–5.8)[c]	788	1	0.1 (0.0–0.6)[c]	NS
Foreign born							
All	639	27	12.8 (6.7–21.4)	1529	37	2.0 (1.2–3.2)	<.01
White, non-Hispanic	28	0	0.0 (0.0–97.5)[c]	95	2	1.8 (0.3–5.9)[c]	NS
Black, non-Hispanic	74	4	5.3 (0.9–16.0)[c]	185	26	11.8 (5.9–20.3)	NS
Mexican American	421	2	0.5 (0.1–2.1)[c]	1069	5	0.3 (0.1–0.8)[c]	NS
Other	116	21	22.9 (12.6–36.3)	180	4	1.4 (0.3–3.9)[c]	<.001

NOTES. CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; NS, not significant.

[a] Stratum-specific sample sizes may not sum to total because of missing data.

[b] Determined by t test evaluating change across surveys.

[c] Estimate is small relative to its standard error (relative standard error >30%) and therefore may be unstable.

$P<.001$), compared with NH-whites (4.7%; 95% CI, 3.9%–5.5%) and Mexican Americans (mean value, 6.0%; 95% CI, 5.0%–7.2%), and was significantly higher among foreign-born persons (22.8%; 95% CI, 19.4%–26.5%), compared with US-born persons (5.9%; 95% CI, 5.0%–6.9%; $P<.001$).

Age-adjusted prevalence of vaccine-induced immunity in NHANES 1999–2006. The age-adjusted prevalence of markers of vaccine-induced immunity in NHANES 1999–2006 was 22.9% (95% CI, 21.9%–24.0%), ranging from 56.7% (95% CI, 54.0%–59.3%) among children 6–19 years of age to 17.0% (95% CI, 15.8%–18.2%) among those 20–49 years of age to 7.5% (95% CI, 6.7%–8.3%) among persons ⩾50 years of age (Table 4). Prevalence of vaccine-induced immunity increased significantly, from 20.5% during 1999–2002 to 25.2% during 2003–2006 ($P<.001$). This reflected significant increases in all age and racial and ethnic groups and among foreign-born and US-born participants. Comparing data from 1999–2002 with that from 2003–2006, the age-adjusted prevalence of vaccine-induced immunity increased from 52.7% to 60.5% among those 6–19 years of age, from 14.3% to 19.6% among those 20–49 years of age, and from 6.6% to 8.2% among those ⩾50 years of age.

The prevalence of vaccine-induced immunity during 1999–2006 among children 6–19 years of age varied little by race and ethnicity, ranging from 53.6% (95% CI, 49.7%–57.6%) among NH-blacks to 59.7% (95% CI, 54.2%–65.0%) among Others and did not differ by sex. A significantly higher proportion of foreign-born children (63.7%; 95% CI, 59.3%–67.9.0%; $P<.01$) had evidence of vaccine-induced immunity, compared with US-born children (56.3%; 95% CI, 53.5%–59.1%), although the lowest prevalence in this age group occurred among foreign-born NH-blacks (51.2%; 95% CI, 41.7%–60.6%) (data not shown).

Among adults 20–49 years of age, prevalence was significantly higher among US-born persons (17.9%; 95% CI, 16.5%–19.4%; $P<.001$) than foreign-born persons (12.7%; 95% CI, 10.9%–14.6%) and higher among women (20.1%; 95% CI, 18.2%–22.0%; $P<.001$) than among men (13.8%; 95% CI, 12.6%–15.0%). Among adults ⩾50 years of age, the age-adjusted prevalence of vaccine-induced immunity (7.5%; 95% CI, 6.7%–8.3%) did not differ by race and ethnicity or country of birth (data not shown) but was significantly higher among women (8.7%; 95% CI, 7.6%–9.9%; $P<.001$) than among men (6.1%; 95% CI, 5.2%–7.0%).

DISCUSSION

In this analysis of the most recent NHANES, conducted a decade after universal vaccination of US children against hepatitis

Table 3. Age-Adjusted Prevalence of Past and Present Hepatitis B Virus Infection among Persons 20–49 Years of Age by Selected Demographic Characteristics

Variable	NHANES III (1988–1994) Sample size[a]	NHANES III (1988–1994) Prevalence, % (95% CI)	NHANES 1999–2006 Sample size[a]	NHANES 1999–2006 Prevalence, % (95% CI)	P[b]
Overall	8857	5.9 (5.1–6.9)	9465	4.6 (3.9–5.3)	<.05
Race/ethnicity					
White, non-Hispanic	2724	3.3 (2.6–4.2)	4176	2.6 (2.2–3.1)	NS
Black, non-Hispanic	2825	13.8 (12.2–15.5)	2018	11.5 (9.6–13.6)	NS
Mexican American	2929	4.2 (3.1–5.6)	2398	2.2 (1.5–3.1)	<.01
Other	379	20.0 (14.4–26.7)	873	11.5 (8.8–14.8)	<.05
US born					
All	6564	4.5 (3.8–5.3)	6935	3.4 (2.9–4.0)	<.05
White, non-Hispanic	2604	3.2 (2.4–4.1)	3941	2.3 (1.9–2.8)	NS
Black, non-Hispanic	2601	12.5 (10.8–14.5)	1804	9.6 (8.0–11.4)	<.05
Mexican American	1283	4.3 (2.8–6.1)	826	2.3 (1.2–3.9)	NS
Other	76	17.4 (6.7–34.1)[c,d]	364	5.6 (2.6–10.2)[d]	NS
Foreign born					
All	2269	14.4 (11.0–18.3)	2530	10.3 (8.2–12.6)	NS
White, non-Hispanic	118	7.5 (3.4–14.1)[c]	236	8.1 (4.8–12.6)	NS
Black, non-Hispanic	207	28.1 (20.4–36.9)	214	25.9 (19.2–33.5)	NS
Mexican American	1645	4.3 (2.7–6.5)	1572	2.2 (1.4–3.3)	<.05
Other	299	21.3 (14.4–29.7)	509	16.1 (12.2–20.6)	NS

NOTE. CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; NS, not significant.

[a] Stratum-specific sample sizes may not sum to total because of missing data.

[b] Determined by t test evaluating change across surveys.

[c] Estimate is small relative to its standard error (relative standard error >30%) and therefore may be unstable.

[d] Estimate based on <10 individuals with positive samples.

B began in 1991, we demonstrate a significant reduction of 68% in HBV infection prevalence among children, including those born in the United States and elsewhere. In addition, a 79% decrease in the prevalence of chronic infection in this age group, although based on a small number of children and not statistically significant, further suggests that substantial progress has been made in reducing the disease burden among children. NHANES, the only source of nationally representative information on the seroprevalence of hepatitis virus infections in the United States, has been critical to describing the burden of HBV infection and, for the first time with this report, determining how it is changing after implementation of a comprehensive national strategy to eliminate HBV transmission in the United States. Keeping in mind the limitations of estimates that are based on small numbers, extrapolation from these data suggests that the number of chronically infected children during 1999–2006 was ~29,000 (95% CI, 11,000–63,000), compared with ~122,000 (95% CI, 36,000–290,000) during 1988–1994. These decreases among children are likely due, in large part, to the incorporation of hepatitis B vaccination into domestic and global routine infant and childhood vaccination programs. A smaller yet significant decrease in the prevalence of HBV infection occurred among US-born adults 20–49 years of age. Among US-born and foreign-born adults aged ≥50 years, HBV infection prevalence changed little over the decade. An estimated 730,000 US residents, mostly adults, had chronic HBV infection, which demonstrates the ongoing burden of HBV-associated disease.

The decrease in the prevalence of infection among children, which was primarily the result of large decreases among US-born NH-black and Other children and among foreign-born Other children, resulted in the elimination or narrowing of many disparities. Among US-born children, prevalence of HBV infection was uniformly low. Although the prevalence among foreign-born children continued to be higher than that among US-born children, it decreased by 84%, compared with data from the previous survey. Most strikingly, there was a >90% decrease among the foreign-born Other group, and the disparity between US-born and foreign-born children was reduced from 13-fold to 4-fold. These data provide a sense of the impact of vaccination here and abroad on preventing HBV infections among children living in the United States.

In the United States, the first recommendations for universal vaccination of children against hepatitis B were made in 1991 [10]. To prevent perinatal transmission of HBV, screening of pregnant women for HBsAg was recommended with the follow-up of infants born to infected women to ensure that they receive postexposure prophylaxis. "Catchup" vaccination of unvacci-

Table 4. Age-Adjusted Prevalence of Vaccine-Induced Immunity to Hepatitis B Virus (HBV) Infection by Selected Demographic Characteristics, 1999–2006

Variable	NHANES 1999–2006		NHANES 1999–2002		NHANES 2003–2006		
	Sample size[a]	Prevalence, % (95% CI)	Sample size[a]	Prevalence, % (95% CI)	Sample size[a]	Prevalence, % (95% CI)	P^b
Overall	29,828	22.9 (21.9–24.0)	15,051	20.5 (18.7–22.4)	14,777	25.2 (24.2–26.3)	<.001
Sex							
Male	14,523	20.8 (19.8–21.8)	7290	18.8 (17.2–20.5)	7233	22.7 (21.7–23.8)	<.001
Female	15,305	25.0 (23.6–26.3)	7761	22.2 (20.0–24.5)	7544	27.6 (26.2–29.1)	<.001
Age, years							
6–19	12,004	56.7 (54.0–59.3)	6202	52.7 (48.1–57.3)	5802	60.5 (57.9–63.0)	<.01
20–49	9465	17.0 (15.8–18.2)	4701	14.3 (12.5–16.2)	4764	19.6 (18.1–21.2)	<.001
≥50	8359	7.5 (6.7–8.3)	4148	6.6 (5.5–7.9)	4211	8.2 (7.3–9.3)	<.05
Race and ethnicity							
White, non-Hispanic, by age in years							
Overall	12,075	23.5 (22.2–24.8)	5910	21.0 (18.9–23.3)	6165	25.7 (24.4–27.0)	<.001
6–19	3058	56.7 (53.4–59.8)	1556	53.6 (48.5–58.7)	1502	59.3 (55.6–62.9)	NS
20–49	4176	18.0 (16.5–19.6)	2020	15.0 (12.8–17.4)	2156	20.9 (18.9–23.0)	<.001
≥50	4841	7.7 (6.8–8.6)	2334	6.6 (5.3–8.2)	2507	8.5 (7.4–9.8)	<.05
Black, non-Hispanic, by age in years							
Overall	7302	21.4 (20.0–22.8)	3461	18.5 (16.5–20.6)	3841	24.0 (22.4–25.7)	<.001
6–19	3830	53.6 (49.7–57.6)	1849	46.5 (40.7–52.4)	1981	60.3 (56.6–64.0)	<.001
20–49	2018	15.5 (13.7–17.5)	934	13.1 (10.6–16.0)	1084	17.5 (15.1–20.2)	<.05
≥50	1454	6.9 (5.6–8.5)	678	6.3 (4.5–8.5)	776	7.4 (5.5–9.8)	NS
Mexican American, by age in years							
Overall	8094	19.8 (18.3–21.3)	4408	17.9 (16.0–20.0)	3686	21.5 (19.5–23.6)	<.05
6–19	4148	57.0 (53.2–60.6)	2275	49.9 (44.5–55.3)	1873	63.5 (59.3–67.6)	<.001
20–49	2398	11.3 (9.6–13.3)	1291	10.7 (8.7–13.1)	1107	11.9 (9.3–14.9)	NS
≥50	1548	5.8 (4.2–7.7)	842	5.7 (4.0–7.8)	706	5.8 (3.5–9.1)	NS
Other, by age in years							
Overall	2357	24.1 (21.9–26.4)	1272	21.9 (18.6–25.4)	1085	27.0 (24.5–29.7)	<.05
6–19	968	59.7 (54.2–65.0)	522	57.8 (49.1–66.2)	446	63.3 (57.7–68.6)	<.001
20–49	873	18.2 (15.0–21.6)	456	14.2 (10.1–19.3)	417	22.7 (18.7–27.1)	<.01
≥50	516	7.4 (5.4–9.8)	294	7.5 (5.4–10.1)	222	7.1 (4.0–11.6)	NS
Country of birth							
US born	24,291	23.3 (22.1–24.6)	12,103	20.9 (18.8–23.1)	12,188	25.7 (24.6–26.8)	<.001
Foreign born	5528	22.1 (20.7–23.6)	2941	19.5 (17.6–21.5)	2587	24.8 (22.7–27.1)	<.001

NOTES. CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; NS, not significant.

[a] Stratum-specific sample sizes may not sum to total because of missing data.

[b] Determined by *t* test evaluating change from 1999–2002 to 2003–2006.

nated adolescents was recommended in 1995 [16]. Vaccine coverage data indicate that, between 1993 and 2006, the percentage of children 19–35 months of age who received hepatitis B vaccine increased from 16% to 93% [17]. Coverage rates among adolescents 13–17 years of age have also increased substantially, to 81% in 2006 [18].

Considerable progress also has been made in implementing hepatitis B vaccination programs for children in other countries. As of December 2006, 164 (85%) of 193 World Health Organization member countries had introduced hepatitis B vaccination into their infant immunization schedules [19]. Of the 27 countries in the western Pacific, where HBV infection is endemic, 55% introduced infant hepatitis B vaccination by 1992 and, to date, 96% have integrated hepatitis B vaccine into their childhood immunization programs. Studies from Asian countries have documented the impact of these programs, including decreases in the prevalence of chronic infection and the incidence of hepatocellular carcinoma among children [20–22]. Of the 29 countries that have not yet integrated hepatitis B vaccination, 12 (41%) are in Africa, where endemicity remains high. The prevalence patterns among foreign-born children in NHANES appear to correlate with these global patterns of vaccination implementation, with dramatic decreases among the Other group, which includes those born in Asia.

Although patterns of markers of vaccine-induced immunity in NHANES 1999–2006 reflect the implementation of domestic and international vaccination programs, the results undoubtedly underestimate the true prevalence of vaccine-induced immunity, particularly that among children. Among persons who were vaccinated as infants or young children and responded to vaccination, 15%–45% have low or undetectable concentrations of anti-HBs 5–22 years after vaccination [8, 23–26]. However, evidence indicates that immunocompetent persons who respond to the vaccine remain protected against HBV even as anti-HBs levels become undetectable [27, 28]. Thus, prevalence of anti-HBs in NHANES underestimates the population level of vaccine-induced immunity by misclassifying participants who lost detectable anti-HBs as susceptible to HBV. Results from the National Immunization Survey and other surveys, which indicate high coverage among 19–35-month-old children and adolescents, provide a more complete reflection of coverage and immunity among US-born children [17].

The decreases in prevalence among younger US-born adults likely reflect the impact of several factors. Over the 18 years spanned by these NHANES surveys, the risk of HBV transmission has decreased, as evidenced by an 80% reduction in the incidence of acute hepatitis B cases since 1990[29]. This likely reflects the implementation of prevention strategies, such as improvements in infection control and screening of the blood supply, modified risk taking practices among high-risk groups, and the impact of targeted vaccination of adults at risk because of occupational or behavioral factors [30–32]. This decrease may also reflect the impact of programs to vaccinate adolescents [16]. This effect recently was documented among US military recruits, among whom anti-HBs prevalence ranged from 62% among those born during 1987–1988 to 27% among those born before 1982 [33].

Although substantial progress has been made in preventing HBV infection among children and young adults, NHANES indicates that the burden of chronic hepatitis B among adults remains large. Many disparities persist that reflect infections acquired over the participants' lifetimes. Among US-born adults, prevalence increased with age and was higher among NH-black and Other races and ethnicities. Of interest, prevalence decreased among young US-born adult Others, which could reflect an impact of vaccination programs targeting Asians of all ages [34–36]. As in previous surveys, HBV infection prevalence was significantly higher among foreign-born adults than it was among US-born adults, which reflected the level of endemicity in participants' countries or regions of origin. Foreign-born persons accounted for ~14% of the NHANES 1999–2006 population, which is similar to estimates from the US Census [37] that indicated that 12% of the US population was foreign-born. In NHANES 1999–2006, this group accounted for 43% of all chronic infections or ~317,000 (95% CI, 202,000–479,000) infections among foreign-born persons in the United States in 1999–2006.

The large burden of chronic HBV infection among adults demonstrated by NHANES highlights the need to improve screening programs and other efforts to identify chronically infected persons, most of whom remain asymptomatic until cirrhosis or end-stage liver disease develops. Limited data indicate that many persons with chronic infection are unaware of their infection status [38–40]. Screening and counseling programs are important to educate and medically manage infected patients to prevent liver disease progression and to identify and vaccinate susceptible contacts to interrupt further transmission [7].

There are limitations to the use of NHANES data to assess HBV prevalence. In NHANES, participants classify themselves with regard to race and ethnicity, but because the numbers of persons belonging to specific racial and ethnic groups other than non-Hispanic white, non-Hispanic black, or Mexican-American are not large enough to make stable prevalence estimates, the National Center for Health Statistics (NCHS), which oversees NHANES, groups these persons into a category of Other nonspecified race and does not release self-reported race data. Thus, the calculation of specific estimates for subgroups, such as Asians and Native Americans, is not possible. It is likely that prevalence among Asians is considerably higher than that reflected by the overall Other category, which includes populations which have lower prevalence of disease. Nevertheless, these groups are sampled in the NHANES population, and overall NHANES estimates reflect and are greatly influenced by the prevalence in these subgroups. A summary analysis provided by NCHS of unedited data, not publicly released, of participants' self-reported race and country of origin suggests that persons likely to be Asian represent ~3.3% (95% CI, 2.8%–3.8%) of the overall NHANES weighted sample and that ~71% of that group are foreign-born. These results may be subject to some error because of misclassification of Asian ethnicity based on unedited data but appear similar to US Census estimates [37], which characterize 4.4% of the US population as Asian, with 68% of this Asian population being born overseas. In addition, although composition of the Other category is not specified and varies somewhat across surveys, an estimated 30% of the group were classified as Asian based on the analysis of raw ethnicity and country of origin data, and the trends and patterns expected among the Asian population appear to be discernible in the results for the Other race and ethnic group.

Another limitation of NHANES is that it samples only from the noninstitutionalized civilian population of the United States. Thus, the overall estimate does not reflect infections among populations that include incarcerated persons, among whom HBV prevalence is known to be high. The prevalence of chronic HBV infection among the estimated 2.2 million

persons in US jails and prisons is ~2.0% [41], resulting in an estimated 44,000 persons with HBV infection in these settings and increasing the estimated number of chronically infected persons in the United States by 6%, to 774,000. Homeless persons, who also may have increased prevalence of infection, are also not included in NHANES [7].

In summary, this analysis of unique population-based data provides new evidence of the impact of domestic and global childhood hepatitis B vaccination programs on preventing HBV infections, while illustrating the remaining large burden of chronic HBV infection in the United States, which consists of ~730,0000 persons. These results are relevant to public health policy makers and highlight the importance of ongoing hepatitis B vaccination programs and of programs to identify persons with chronic HBV infection.

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
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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	Heiberg IL, Hoegh M, Ladelund S, Niesters HG, Hogh B. Pediatr Infect Dis J. 2010 May;29(5):465-7.	公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)			デンマーク

研究報告の概要

○慢性B型肝炎患児の唾液中のB型肝炎ウイルス(HBV)DNA:唾液がHBV水平感染の伝播手段となっている可能性
目的:小児におけるHBVの水平感染の機序を検討するため、慢性B型肝炎患児46人の唾液中HBV量と血漿中HBV量を定量し、関連性を調べた。
対象および方法:デンマークにおいてB型肝炎は2000年から届出疾患となっている。2006年5月から2008年11月までに0～16歳までの慢性B型肝炎患児(HBs抗原陽性)180人に手紙を送り、両親から同意が得られた46人について、6ヶ月あるいは12ヶ月ごとに唾液と血液を得た。HBV-DNAはTaqMan Assayにて定量した(検出感度は50 IU/mL)。
結果:本研究中にHBe抗原が陽性から陰性になった2人と、HBe抗原の状態が分からない1人を調査対象外とした。25人(58%)がHBe抗原陽性で、18人(42%)がHBe抗原陰性であった。HBe抗原陽性の子供の唾液に含まれるHBV-DNA濃度は、HBe抗原陰性の子供の血漿中より39倍高かった。
考察:唾液がHBVの伝播手段になっている。子供において血漿中のHBV量と唾液への分泌量は相関する。ユニバーサルワクチン接種が、児童間のB型肝炎の唾液による感染への懸念を軽減できる可能性がある。

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	今後の対応
小児におけるHBVの水平感染の機序を検討するため、慢性B型肝炎患児の唾液中と血漿中のHBV量の関連性を調べたところ、HBe抗原陽性患児の唾液中に高値HBV-DNAを認め、児童間での唾液によるHBV水平感染の可能性が示唆されたとの報告である。これまで、本剤によるHBV感染の報告はない。また本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。さらに最終製品についてHBV-NAT陰性であることを確認しており、安全性は確保されていると考える。	これまでの使用実績やバリデーション成績に鑑み本製剤の安全性は確保されており、特別の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。なお、日本赤十字社では献血時のスクリーニング法としてより感度の高い化学発光酵素免疫測定法(CLEIA)および新NATシステムを導入した。

(2)

HEPATITIS B VIRUS DNA IN SALIVA FROM CHILDREN WITH CHRONIC HEPATITIS B INFECTION

IMPLICATIONS FOR SALIVA AS A POTENTIAL MODE OF HORIZONTAL TRANSMISSION

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Abstract: To explore the mechanism of horizontal transmission of hepatitis B virus (HBV) among children, we investigated the quantitative relationship between HBV in saliva and blood from 46 children with chronic hepatitis B.

We found high levels of HBV DNA in saliva of HBeAg (+) children, suggesting saliva as a vehicle for horizontal transmission of HBV among children.

Key Words: chronic hepatitis B, children, HBV DNA, saliva, horizontal transmission

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Hepatitis B virus (HBV) infection is a major global health problem and more than 350 million people worldwide are chronically infected. The course of hepatitis B infection is dependent on age at the time of infection. When infected perinatally, 90% of children become chronic carriers and 25% develop liver cirrhosis and are at risk for hepatocellular carcinoma. During childhood the HBV infected children are in a prolonged immune tolerance phase, and they constitute a silent infectious reservoir that may further maintain and spread HBV to susceptible individuals.

The most common routes of acquiring hepatitis B infection in adults are sexual contact and sharing injecting equipment. In childhood, perinatal and horizontal child-to-child transmission are the most common modes of transmission, but the mechanism of viral spread in horizontal transmission remains to be elucidated.[1–3]

Since 1992, WHO has recommended global vaccination against HBV, and by the end of 2006, 168 countries had implemented or were planning to implement a universal HBV immunization program for newborns, infants, and/or adolescents. Only 7 countries in Northern Europe have not yet implemented such a policy—Denmark, Finland, Iceland, the Netherlands, Norway, Sweden, and the United Kingdom.[4] These countries have adopted an at-risk strategy offering vaccination to individuals at high risk of infection.[5] The selective immunization strategy in Denmark includes immunization of staff and children at day-care centers before an HBsAg positive child is admitted. The Medical Officer of Health informs staff and parents before the vaccinations are given, and knowledge about the individual child with chronic hepatitis B infection is confidential. However, despite professional information, this strategy can cause social discrimination of the family and the child with chronic hepatitis B infection. The selective strategy in Denmark does not include hepatitis B vaccination before school entry, and parents are not obliged to inform the school that their child has chronic hepatitis B infection. For the parents of a child with chronic hepatitis B infection, this policy leads to fear of transmission of HBV from their child to unvaccinated children at school. The potential importance of saliva as a vehicle of spread is often a major concern, although transmission from saliva has not been documented except through percutaneous exposure (eg, a bite that breaks the skin).[6] Recent studies have shown that HBV DNA is present in saliva from infected adults and that there is a quantitative correlation between viral load in saliva and serum.[7,8]

The aim of this study was to explore the potential significance of saliva as a vehicle of transmission, and the quantitative relationship between HBV DNA in saliva and in plasma of children was determined.

MATERIALS AND METHODS

In Denmark, chronic hepatitis B infection has been a notifiable disease since the year 2000. All children nationwide, aged 0 to 16 years, notified with chronic hepatitis B (n = 180) were invited by letter to participate in the study during the period May 2006 to November 2008. The families of 46 children responded positively, and after written informed consent from the parents, 46 children were included in the study. Blood and saliva samples were obtained at the children's clinical visits every sixth or 12th month. The saliva samples were obtained using the saliva collection kit Oracol (Malvern Medical Developments, Worcester, United Kingdom). Blood was collected in EDTA tubes, spun, and separated into cells and plasma fractions. Purification of HBV DNA from plasma and saliva was performed using the MagNa Pure LC Instrument (Roche Applied Science, Penzberg, Germany). HBV DNA in plasma and saliva was quantitatively measured using the HBV TaqMan Assay as previously described.[9] The lower detection limit was 50 IU/mL. To monitor both loss and inhibition of the samples, a universal internal control consisting of a known number of Phocid herpesvirus type-1 particles was added to the samples, as previously described.[10] Corrections in viral load assessments were made if necessary. Data on the serological status (HBsAg, HBeAg, anti-HBeAg) were obtained from the children's clinical records. Statistical analyses were performed using mixed models with random intercepts with the statistical environment R-2.8.1 using the NLME package, taking into account repeated measurements on several of the patients. All HBV DNA values were log transformed by the natural logarithm prior to analysis, to ensure normality of standardized residuals.

RESULTS

A total of 46 HBsAg positive children were included in the study. Two children were excluded from the analyses as they converted from HBeAg (+) to HBeAg (−) during the study period, and one child was excluded due to unknown HBeAg status. Of those, 25 (58%) of the children were HBeAg (+) and 18 (42%) were HBeAg (−). Mean age at sample date was 10.2 years (SD ± 3.9 years). The number of samples collected ranged from 1 to 7 from each child. In total, we collected 117 plasma samples and 124 saliva samples from 43 children; 116 plasma and saliva samples were paired.

The geometric mean for HBV DNA in plasma from HBeAg (+) children was 41.9×10^6 IU/mL and 33.9×10^3 IU/mL in

TABLE 1. HBV DNA in Saliva and Plasma From Children With Chronic Hepatitis B Infection According to HBeAg Status

Subjects/Specimens	Log HBV DNA IU/mL	95% CI	*P*	Geometric Mean HBV DNA IU/mL	95% CI
HBeAg (+)					
Plasma	17.6	16.6–18.5		41.9×10^6	16.7×10^6 to 105.0×10^6
Saliva	10.4	9.5–11.4		33.9×10^3	13.0×10^3 to 88.4×10^3
HBeAg (−)					
Plasma	6.8	5.9–7.6		880	380–2038
Saliva	NA*			NA*	NA*
HBeAg (+) vs. HBeAg (−) in plasma	10.6	9.2–12.0	<0.001		
HBeAg (+) saliva vs. HBeAg (−) plasma	3.7	2.4–4.9	<0.001		

*All values below lower detection limit.

saliva, compared with 880 IU/mL in plasma from HBeAg (−) children. This showed a 39 times higher levels of HBV DNA in saliva from the HBeAg (+) children than in plasma from the HBeAg (−) children ($P < 0.001$). HBV DNA was undetectable in saliva from the HBeAg (−) children (lower detection limit 50 IU/mL). Results are shown in Table 1.

In 60% (50/84) of samples from HBeAg (+) children, HBV DNA levels in saliva were above 10^4 IU/mL, and in 33% (28/84) HBV DNA levels were above 10^5 IU/mL.

When analyzing the paired measurements of quantitative HBV DNA in plasma and saliva samples, we found a linear relationship between log HBV DNA in plasma and saliva of the HBeAg (+) children described by the equation:

log HBV DNA in saliva = − 6.63

+ 0.92 times (log HBV DNA in plasma)

The relationship is presented graphically online in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/A417.

DISCUSSION

Saliva has been considered a potential source of HBV transmission, and HBV DNA has been detected in saliva from adults.[7,8] We studied paired saliva and plasma samples from 43 children with chronic hepatitis B and known HBeAg status. We found a high level of HBV DNA in saliva from the HBeAg (+) children. Of note, the levels of HBV DNA were 39 times higher in saliva from the HBeAg (+) children than it was in plasma from the HBeAg (−) children.

Our findings show that saliva is a source of HBV DNA. Assuming that HBV DNA levels reflect the number of infectious particles, saliva is a potential vehicle of spread of HBV. However, studies of the infectivity of HBV DNA in saliva are limited due to lack of available animal models and cell lines that support HBV infection. It is known that HBV can survive for at least 7 days outside the body, and that infection through close interpersonal contact within households is a common mode of transmission of HBV during early childhood in high endemic countries.[2,3] It is presumed that in these settings transmission occurs from skin lesions or by sharing blood contaminated objects, although a specific pathway of transdermal exposure is rarely identified.

A significant concern for children with chronic hepatitis B infection and their parents, is the risk of infecting unvaccinated children. Older children might experience anxiousness when sharing drinks and food with friends. Because not all countries routinely vaccinate children against hepatitis B, it is a dilemma affecting families in those countries.

In samples from the HBeAg (−) children, HBV DNA was not detectable in saliva (lower detection limit 50 IU/mL) and the levels of HBV DNA were low in plasma in this group (880 IU/mL). This confirms our knowledge that HBeAg (−) children are much less infectious than HBeAg (+) children. It is shown in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/A417, that HBV DNA becomes detectable in saliva at a level where log HBV DNA in plasma is around 11, corresponding to a viral load in plasma of about 60×10^3 IU/mL. It has been discussed at what levels HBV DNA of a chronic carrier should be considered to be infectious. Various guidelines are used in the European countries for when health care workers are allowed to work with exposure prone procedures, based on knowledge of HBV DNA levels at which HBV transmission has occurred. In the United Kingdom and Ireland, a cut-off limit of 10^3 HBV DNA copies/mL (=185 IU/mL) is used; in the Netherlands it is 10^5 copies/mL (=18.5×10^3 IU/mL) and a European consensus group decided in 2003 for a cut-off level at 10^4 HBV DNA copies/mL (=1.9×10^3 IU/mL).[11,12]

The mean viral load in saliva from HBeAg (+) children in our study was 33.9×10^3 IU/mL and 33% of these children had HBV DNA levels more than 10^5 IU/mL. Provided that the saliva is contagious, these children should be considered as highly infectious.

We found a clear association between HBV viral load in plasma and saliva. Similar results have been shown in adults.[8] As discussed, we do not know whether the HBV DNA in saliva is infectious, but it has previously been demonstrated that inoculation of chimpanzees and gibbons with saliva from hepatitis B infected individuals caused an acute infection.[13,14] Today contact tracing of the transmission of HBV using epidemiological and molecular data can identify possible sources of infection.[15]

Infection with HBV in childhood has serious consequences, as most children become chronic carriers and are at increased risk of developing liver cirrhosis and hepatocellular carcinoma. We have an ethical duty on both individual and country level to protect children from an oncogenic virus when we have the means to do so. Universal immunization can be implemented during infancy and adolescence; vaccination of adolescents provides immunization at a time of increased high-risk behavior. However, vaccination of infants is preferable because immunization of this age group is better established, and children infected at this age are at high risk of acquiring chronic infection. Universal vaccination might alleviate the fear of saliva as a potential vehicle of trans-

mission among children, and it is the only logical strategy to protect against HBV infection.

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SEQUENCE TYPES AND ANTIMICROBIAL SUSCEPTIBILITY OF INVASIVE *STREPTOCOCCUS PNEUMONIAE* ISOLATES FROM A REGION WITH HIGH ANTIBIOTIC SELECTIVE PRESSURE AND SUBOPTIMAL VACCINE COVERAGE

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Abstract: Multilocus sequence typing was carried out on 95 invasive pneumococcal isolates belonging to the most common 7 serotypes currently circulating in Taiwan. The study confirmed continued prevalence in Taiwan of a few global clones and sequence types (STs) since the mid-1990s and identified the recent emergence of ST320 (19A) and ST902 (6A). Antimicrobial nonsusceptibility was common in the predominant STs of serotypes 14, 19A, 19F, and 23F.

Key Words: sequence type, serotype, *Streptococcus pneumoniae*, antimicrobial susceptibility, pneumococcal conjugate vaccine, Taiwan

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Dissemination of multiple antibiotic resistant clones of *Streptococcus pneumoniae* across regions and countries is well documented.[1–5] Global clones and their variants, which have spread in Taiwan, include Spain^{6B}-2, England^{14}-9, Taiwan^{19F}-14, Colombia^{23F}-26, Spain^{23F}-1, and Taiwan^{23F}-15.[5,6] Recently, Hsieh et al, reported the emergence of invasive serotype 19A isolates in Taiwan among the 2007 invasive pneumococcal isolates.[3] To prevent pneumococcal infections, 7-valent pneumococcal conjugate vaccine (PCV7) is being widely used.[1,7] PCV7 has significantly reduced invasive pneumococcal diseases (IPD) caused by vaccine serotypes, but serotype 19A has dramatically increased in some countries, but not in others.[1,8] In Taiwan PCV7 was not available until October 2005.[3] The vaccine is now being used in the private sector, with a low penetration in the pediatric population.[3] The aim of this study was to determine the sequence types (STs) of common serotypes that caused IPD in Taiwan after the introduction of PCV7. We also analyzed antimicrobial susceptibility patterns of these isolates.

METHODS

The 95 IPD isolates were selected for sequence typing and antimicrobial susceptibility testing because their serotype distribution covered the most common 7 serotypes currently circulating in Taiwan.[3] All these pneumococcal isolates were identified as described previously by Hsieh et al.[6] An IPD isolate was from a positive blood culture or pleural fluid culture from a child with a consolidation pattern upon chest x-ray. IPD also included primary bacteremia without focus defined as a positive blood culture from a child with fever but without a focal lesion. These isolates were collected from Chang Gung Children's Hospital (CGCH) during 2005–2007. The age range of children was from 1 to 9 years, with a median of 4.5 years. Prior to all experiments, the *S. pneumoniae* isolates were cultivated in trypticase soy agar with 5% sheep blood (in CO_2 incubator). Antimicrobial susceptibility to penicillin, ceftriaxone, erythromycin and imipenem was assayed by E-test (AB Biodisk, Solna, Sweden) and interpretation was based on Clinical and Laboratory Standards Institute standards.[9] The susceptible, intermediately resistant, and resistant MIC interpretative breakpoints for penicillin (nonmeningitis criteria) were ≤2 μg/mL, 4 μg/mL, and ≥8 μg/mL, respectively.[9] Serotyping was performed by latex agglutination and confirmed by Quellung reaction (Statens Serum Institute, Copenhagen, Denmark). All the serotypes were double checked by a PCR method described earlier.[10] The nucleotide sequences of 450-bp internal regions

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研究報告の概要

○台湾における微量のB型肝炎ウイルス(HBV)DNAを検出するための個別検査とミニプール検査の有効性

背景:財政的な制約は、現在も台湾の、ルーチンの血液スクリーニングとしてのNAT実施において、主要な問題となっている。実現可能な解決策を講じるため、TIGRISシステム(Novartis Diagnostics)のPROCLEIX ULTRIO(Ultrio)分析を用いて、個別供血検査(IDT)と4本のミニプール法(MP4)双方の実施成績を評価した。

試験デザインおよび方法:分析感度はWHO国際標準品により決定した。供血者10,290名(IDT 4210名、MP4 6080名)に検査を行った。潜在的HBV陽性供血者(HBs抗原陰性/NAT陽性)を最高9ヵ月間、追跡調査した。Ultrio分析とHBs抗原検査結果が不一致の場合、さらにHBV抗体血清検査、代替NAT、HBV DNA定量検査ならびに塩基配列決定の解析を行った。

結果:検出の95%検出限界(IU/mL)(95%信頼区間)は以下のとおり:

ヒト免疫不全ウイルスType 1(HIV-1)18(12～34)、C型肝炎ウイルス(HCV)4.4(2.8～8.9)、HBV6.3(4.4～11)。再検査率は、IDT 0.55%とMP4 0.33%であった。HIVまたはHCV陽性症例は認められなかったが、潜在的HBV陽性例は12名(IDT 9名、MP4 3名)であった。そのうちの11名は、genotypeがB2であることが判明した。そのうちの10名は、追跡調査のために再来院し、ほとんどがオカルトHBV感染症(OBI)であると判明した。IDTの陽性率 9/4210(0.21%)はMP4の3/6080(0.05%)と比べ4倍高かった(p < 0.05)。

結論:MP4と比較したIDTの高い陽性率は、OBIキャリアが顕著である台湾のような地域で、高感度NAT法を実施する有益性を示している。

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
微量のB型肝炎ウイルス(HBV)DNAを検出するための個別NATとミニプールNATの有効性の評価を行い、オカルトHBVキャリアが多い台湾で、高感度NATの有益性が示されたとの報告である。 これまで、本剤によるHBV感染の報告はない。また本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。さらに最終製品についてHBV-NAT陰性であることを確認しており、安全性は確保されていると考える。	これまでの使用実績やバリデーション成績に鑑み本製剤の安全性は確保されており、特別の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。なお、日本赤十字社では献血時のスクリーニング法としてより感度の高い化学発光酵素免疫測定法(CLEIA)および新NATシステムを導入した。

The efficacy of individual-donation and minipool testing to detect low-level hepatitis B virus DNA in Taiwan

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BACKGROUND: Financial constraints are the main concern in implementing nucleic acid testing (NAT) as routine blood screening in Taiwan. The PROCLEIX ULTRIO assay (Ultrio) on the TIGRIS System (Novartis Diagnostics) was evaluated for its operational performance both for individual-donation testing (IDT) and in minipools of 4 (MP4) to develop a feasible solution.

STUDY DESIGN AND METHODS: Analytical sensitivity was determined by testing WHO international standards. We tested 10,290 blood donors, 4210 in IDT and 6080 in MP4. Potential hepatitis B virus (HBV) yield donors (hepatitis B surface antigen [HBsAg] negative/NAT reactive) were evaluated for up to 9 months' follow-up. Discordant results between the Ultrio assay and the HBsAg tests were further analyzed by HBV antibody serology, alternative NATs, HBV DNA quantification, and sequencing.

RESULTS: The 95% limits of detection in IU/mL (95% confidence interval) were as follows: human immunodeficiency virus Type 1 (HIV-1), 18 (12-34); hepatitis C virus (HCV), 4.4 (2.8-8.9); and HBV, 6.3 (4.4-11). The retest rates were 0.55% for IDT and 0.33% for MP4. No HIV or HCV yield cases were found, while there were 12 potential HBV yield cases, nine from IDT and three from MP4 testing. Eleven of them were successfully genotyped as B2. Ten of them returned for follow-up and mostly were determined as occult HBV infection (OBI). The IDT yield rate of 9 in 4210 (0.21%) was fourfold greater than the MP4 yield rate of 3 in 6080 (0.05%; $p < 0.05$).

CONCLUSION: The higher yield rate for IDT versus MP4 demonstrates the benefit to implement a more sensitive NAT strategy in regions having significant OBI carriers such as Taiwan.

Introduction of nucleic acid amplification testing (NAT) has been shown to result in the improvement of blood safety in many countries around the world.[1] NAT markedly reduces the window period (WP) defined as the time between infection and first detectable viral marker, compared to serologic assays. NAT can detect not only WP infections for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV), but also occult HBV infection (OBI), which are missed by even the most sensitive hepatitis B surface antigen (HBsAg) tests. NAT has been introduced in North America, many European countries, Australia, New Zealand, and parts of Asia including Japan, Hong Kong, and Singapore. However, at the time of this study, it has not been implemented in Taiwan. While NAT screening for HIV-1 and HCV is more widespread than for HBV, the recent advancement of automated or semiautomated systems with multiplex tests has facilitated the

ABBREVIATIONS: d = discriminatory (HBV, HCV, HIV-1 assay); IDT = individual donor testing; LOD(s) = limit(s) of detection; MP4 = minipool of 4; OBI(s) = occult hepatitis B virus infection(s); qPCR = quantitative polymerase chain reaction; S/CO = signal-to-cutoff; TTIBV = transfusion-transmitted HBV; WP = window period.

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simultaneous screening of all three viruses. The two assays currently commercially available are the Chiron PROCLEIX ULTRIO assay (Novartis Diagnostics, Emeryville, CA) and the Roche cobas MPX assay (Roche Molecular Systems, Pleasanton, CA).

Taiwan is an endemic area for HBV infection, with an HBsAg seroprevalence of 17.3% compared to 4.4% for HCV[2] and 0.012% for HIV.[3] Adoption of anti-hepatitis B core antigen (HBc) screening that correlates with HBV exposure, in many low-prevalence countries, resulted in the deferral of only a small number of donors. However, adding this safety measure in Taiwan, where anti-HBc seropositivity is reported to be 16% to 90% in the general population,[4,5] would defer far too many otherwise acceptable donors.

Taiwan has implemented widespread HBV vaccination since 1985 and adopted third-generation HBsAg blood screening tests to limit HBV infections. Nonetheless, one study[6] reported that at least 3% of the population carried occult HBV and hence transfusion-transmitted HBV (TTHBV) infections still occur underscoring the need for additional blood safety measures. Wang and coworkers[7] estimated that approximately 0.02% of donated blood in Taiwan could transmit HBV and predicted the HBV NAT yield to be 20-fold higher in Taiwan than in low-prevalent regions such as the United States. A more recent study[6] showed the rate of transfusion transmission of HBV in Taiwan to be 7- to 40-fold higher than that observed in low-prevalence countries with approximately 0.1% of the transfused recipients acquiring TTHBV. The same study showed that even some vaccinated children with low levels of anti-HBs developed HBV viremia posttransfusion, highlighting the continued threat of TTHBV despite the use of sensitive HBsAg blood screening and more than 20 years of HBV vaccination.[6]

While many recent evaluations of NAT systems in Asian populations have demonstrated their clinical utility, especially for HBV,[8-13] each country undertook evaluations of NAT, given the complexity and cost of NAT, in its own setting and determined which multiplex test is best suited to their circumstances. A recent pilot study[13] of minipool NAT screening of Taiwanese blood donors with an alternative technology showed yield rates 0.10 and 0.01% for HBV and HCV, respectively, that were higher than those observed in Hong Kong.[8]

The objective of this study was to evaluate both the performance of the Ultrio assay on the automated TIGRIS System under standard operational conditions and its ability to identify infectious units in seronegative Taiwanese blood donations (yield). A secondary objective was to determine which configuration of the Ultrio assay, individual donor testing (IDT) or minipool of 4 (MP4) testing, would provide the optimal combination of operational efficiency and blood safety in Taiwan.

MATERIALS AND METHODS

PROCLEIX ULTRIO assay

The Ultrio assay is an in vitro NAT utilizing transcription-mediated amplification for the qualitative detection of HIV-1 RNA, HCV RNA, and HBV DNA simultaneously in human plasma. The technology has been previously described.[14-16]

Analytical sensitivity

To verify the analytical sensitivity for detecting HIV-1, HCV, and HBV, diluted panels of World Health Organization (WHO) international standards (HIV-1 RNA International Standard 97/656, HCV RNA International Standard 96/798, and HBV DNA International Standard 97/746) were tested. The WHO international standards were obtained from the National Institute for Biological Standards and Control (NIBSC, Hertfordshire, UK) and panels were prepared at Acrometrix (Benicia, CA), by serially diluting the respective standard with nonreactive human plasma and storing aliquots at –80°C. Four sets of each WHO standard panel were prepared and tested, each set consisting of eight concentrations, with eight replicates of 1.5-mL aliquots for each concentration. The analytical ranges for each WHO standard were as follows: 0.23 to 30 IU/mL for HCV, 0.78 to 100 IU/mL for HIV-1, and 0.31 to 40 IU/mL for HBV. Aliquots were stored frozen at –20°C until testing. Eight replicates of each concentration were tested on each of three different days, to give a total of 24 replicates for each dilution of each virus. An additional eight replicates of all concentrations were tested with the PROCLEIX HIV-1, HCV, and HBV discriminatory assays (dHIV-1, dHCV, dHBV) on a fourth day. A Probit statistical model[17] was applied to the analytical sensitivity data and the 95% limit of detection (LOD) was calculated for the Ultrio assay and the discriminatory assays.

Operational performance

System reliability was assessed by computing the total sample invalid rate, the failed run rate for both IDT and MP4 testing, and the non–repeatable-reactive rate. A total of two reagent master lots were used in 64 test runs over 11 weeks by three operators.

Assay reproducibility

Signal-to-cutoff (S/CO) ratio results, including the means, standard deviations, and coefficients of variation (CV), from both assay controls and viral calibrators, were used to assess assay reproducibility. Data were taken from the routine testing runs only and did not include proficiency runs or runs of the WHO standards. Data were separately collected for the two master lots used in the study and the

three operators who performed the assays. Results from the operator who performed the fewest tests were combined with those of another operator for purposes of analysis.

Blood donor testing

A total of 10,290 different and consecutive blood donor specimens were collected at the Taipei Blood Center from August 13 to October 4, 2007. These blood donors had met the routine blood donation criteria established by Taiwan Health Authority and had consented to NAT screening of their blood. The study was conducted according to the regulatory guidelines in Taiwan and followed the Good Clinical Practice and Good Laboratory Practice Guidelines consistent with the principles originating in the Declaration of Helsinki. A separate BD VACUTAINER PPT plasma preparation tube (Becton Dickinson and Company, Franklin Lakes, NJ) was collected exclusively for NAT assay.

Routine serologic testing of donor specimens for HBsAg (Murex HBsAg v3.0, Abbott Diagnostics, Dartford, UK), anti-HCV (Murex anti-HCV v4.0, Abbott Diagnostics, Kyalami, South Africa), and anti-HIV-1 and -2 (Murex HIV 1.2.0, Abbott Diagnostics) was performed according to Taipei Blood Center's established standard operating procedures. Study specimens were linked to donors to permit follow-up evaluations.

Of the 10,290 specimens, 4210 were tested in IDT format and 6080 were tested in 1520 pools of MP4 format. MP4 testing was performed by pooling equal aliquots of plasma from four donation specimens. If a pool was reactive in the Ultrio assay, each specimen from the reactive pool was individually tested to identify the reactive specimen(s).

All Ultrio assay–reactive specimens, whether identified through IDT or MP4, were further tested with the discriminatory assays to determine specific viral activity. When the Ultrio assay was nonreactive and the donor specimen was seronegative, the testing was considered complete.

Supplemental serologic and alternative NAT

Donor specimens with discordant results between the Ultrio assay and the serologic tests of record were retested using specimens taken directly from the plasma unit. Supplemental serologic tests for HBV, HCV, and HIV were the HBsAg neutralization test (Quest Diagnostics, San Juan Capistrano, CA), anti-HCV recombinant immunoblot assay (Novartis Diagnostics, Emeryville, CA), and anti-HIV-1/2 Western blot (MP Diagnostics, Singapore), respectively. Additional supplemental serologic tests included anti-HBs (AxSYM, Abbott Diagnostics, Wiesbaden, Germany), anti-HBc Total and IgM (Quest Diagnostics), and anti-HCV (AxSYM, Abbott Diagnostics). Alternative NAT comprised two assays: the NGI HBV UltraQual assay (NGI, Los Angeles, CA), a polymerase chain reaction (PCR) assay with a 95% LOD of 0.9 IU/mL, and Cambridge University Laboratories quantitative (q)PCR assay (Cambridge, UK), with a 95% LOD of 20 IU/mL.[18]

For HIV, HCV, and HBV, the confirmed presence of viral genome without detectable viral antigen or specific antibody was identified as WP infection when follow-up samples confirmed seroconversion. For HBV, samples with the presence of DNA associated with anti-HBc and/or anti-HBs were defined as OBI.[19]

HBV nucleic acid sequencing and genotyping

Viral DNA was quantified from 500 µL of plasma.[20,21] In addition, after ultracentrifugation of 5 to 8 mL of plasma depending on the volume available, full-length HBV genome minus 50 bp in the precore region (approx. 3150 bp), pre-S/S region (approx. 1190 bp), and 300 bp in the basic core promoter/precore region were amplified using nested PCR. Amplified products were directly sequenced and those with sequences of greater than 1000 bp were phylogenetically analyzed.[20,21] Deduced amino acid sequences were compared to sequences of HBV strains of Genotypes B and C published in the GenBank database.

RESULTS

Analytical sensitivity

The 95% LOD for HIV-1, HCV, and HBV of the Ultrio assay and the corresponding discriminatory assays, as determined by Probit analysis, are shown in Table 1.

Assay reproducibility

For both reagent master lots used in the study the percent CVs for the reactive calibrators was less than 5%. There was 100% agreement between the expected and observed S/CO ratio results for the Ultrio assay controls. The three

TABLE 1. 95% LODs for Ultrio and discriminatory assays as determined by WHO panel tested by IDT

WHO panel	Assay tested	Estimated 95% LOD, IU/mL (95% CI)
HIV RNA 97/656	Ultrio*	18 (12-34)
	dHIV†	14 (8.1-48)
HCV RNA 96/798	Ultrio	4.4 (2.8-8.9)
	dHCV	8.5 (3.8-63)
HBV DNA 97/746	Ultrio	6.3 (4.4-11)
	dHBV	12 (5.6-69.1)

* Performed on 3 separate days with eight replicates per day, for a total of 24 replicates.
† Performed on 1 day with a total of eight replicates.

operators gave consistent and reproducible results (with no significant differences) for the reactive control specimens (data not shown).

Operational performance

A total of 4210 donations in IDT and 6080 donations in 1520 pools of MP4 were tested with the Ultrio assay on the TIGRIS platform. A summary of the testing data is shown in Tables 2 and 3. The non–repeat-reactive rates were 0.07% for IDT and 0.13% for MP4. There were 23 invalid results among 4210 specimens tested IDT (0.55%) and 5 invalid results among the 1520 pools tested (0.33%). All invalid results were valid when the tests were repeated. The retest specimen rate of 0.27% was mostly a result of assay processing errors.

Seronegative donor specimens tested in IDT and MP4

Testing results for 10,290 donor specimens by serology and by Ultrio assay in IDT (4210) and in MP4 (6080) are shown in Fig. 1A. None of the NAT-only-reactive samples were discriminated as either HIV or HCV. Among the 4179 seronegative specimens tested in IDT, 10 were Ultrio assay reactive. Six of these were discriminated as HBV, while four were nonreactive in discriminatory testing. These 10 specimens were further analyzed; 9 of 10 were found to be positive for HBV by alternative PCR, viral load, or genotyping and were regarded as potential yield cases. The results are summarized in Table 4. For donor IDT-A9, it was considered an indeterminate result. IDT-A9 was initially Ultrio assay reactive but no HBV, HCV, or HIV nucleic acid detectable (data not shown). Among the 6044 seronegative specimens in MP4, three were reactive in the Ultrio assay and were all discriminated as HBV and were also reactive in the NGI HBV UltraQual assay. These three specimens were further studied as potential yield cases as summarized in Table 4. In total, there were 12 potential yields cases, nine from IDT and three from MP4. They were between ages of 30 and 63, with equal male-to-female ratio.

Follow-up study of potential yield cases

Among the 12 potential yield cases, 10 donors joined in the follow-up study; results of the samples are listed in Table 4. All index samples and follow-up samples were anti-HBc positive, except the index sample of donor MP4-A3. Donors IDT-A1 and IDT-A3 became HBV DNA negative a few months after the index donations.

The combination of molecular and serologic marker data allows further definition of the diagnostic phase of HBV infection (Table 4). The presence of anti-HBc in all but one index sample excluded preseroconversion WP infection and in four cases anti-HBs were also detected indicating resolved infection. In IDT-A9 where molecular confirmation was doubtful, the presence of anti-HBc did not particularly help the diagnostic process because 16% to 90% in the Taiwanese general population[4,5] carry this marker. The potential yield cases were genotyped as B2, except donor IDT-A10. This sample could not be amplified in any of the four different regions targeted although the viral load tested by qPCR provided a positive result.

Finally, in 10 donors, at least one follow-up sample was obtained and this

TABLE 2. Summary of IDT and MP4 run results on Ultrio TIGRIS

Variable	IDT	MP4	Total
Number of individual donor samples	4,210	6,080	10,290
Total number of pools tested	4,210	1,520	5,730
Number of initially reactive pools	32	23	55
Initial reactive rate	0.76	1.51	0.96
Number of resolved pools	NA	21	21
Number of reactive donation(s) on discrimination assay	28	21	49
Non–repeat-reactive IDT/pools (%)	4 (0.09)	2 (0.13)	6 (0.1)
Total number of batches	21	24	45
Total invalid batch (%)	1* (4.76)	0 (0)	1 (2.22)
Total retested donor samples† (%)	23 (0.55)	5 (0.33)	28 (0.27)
Assay processing error	22	5	27
Internal control invalid	1	0	1

* Caused by negative control and HIV-1–positive control volume error.
† The retested donor samples resulted from invalid tests or invalid batch.
NA = not available.

TABLE 3. Summary of serology and Ultrio results observed

	IDT				MP4			
Result	HIV-1	HCV	HBV	Total	HIV-1	HCV	HBV	Total
Seropositive/Ultrio nonreactive	4	1	4	9	7	0	9	16
Seropositive/Ultrio reactive and discriminated	0	2	20	22	0	4	16	20
Seronegative/Ultrio reactive	0	0	6	6	0	0	3	3
Seronegative/Ultrio reactive and nondiscriminated				4*				0
Seronegative/Ultrio nonreactive				4169				6041

* Three confirmed reactive; one indeterminate result by alternative NAT (see Table 4).

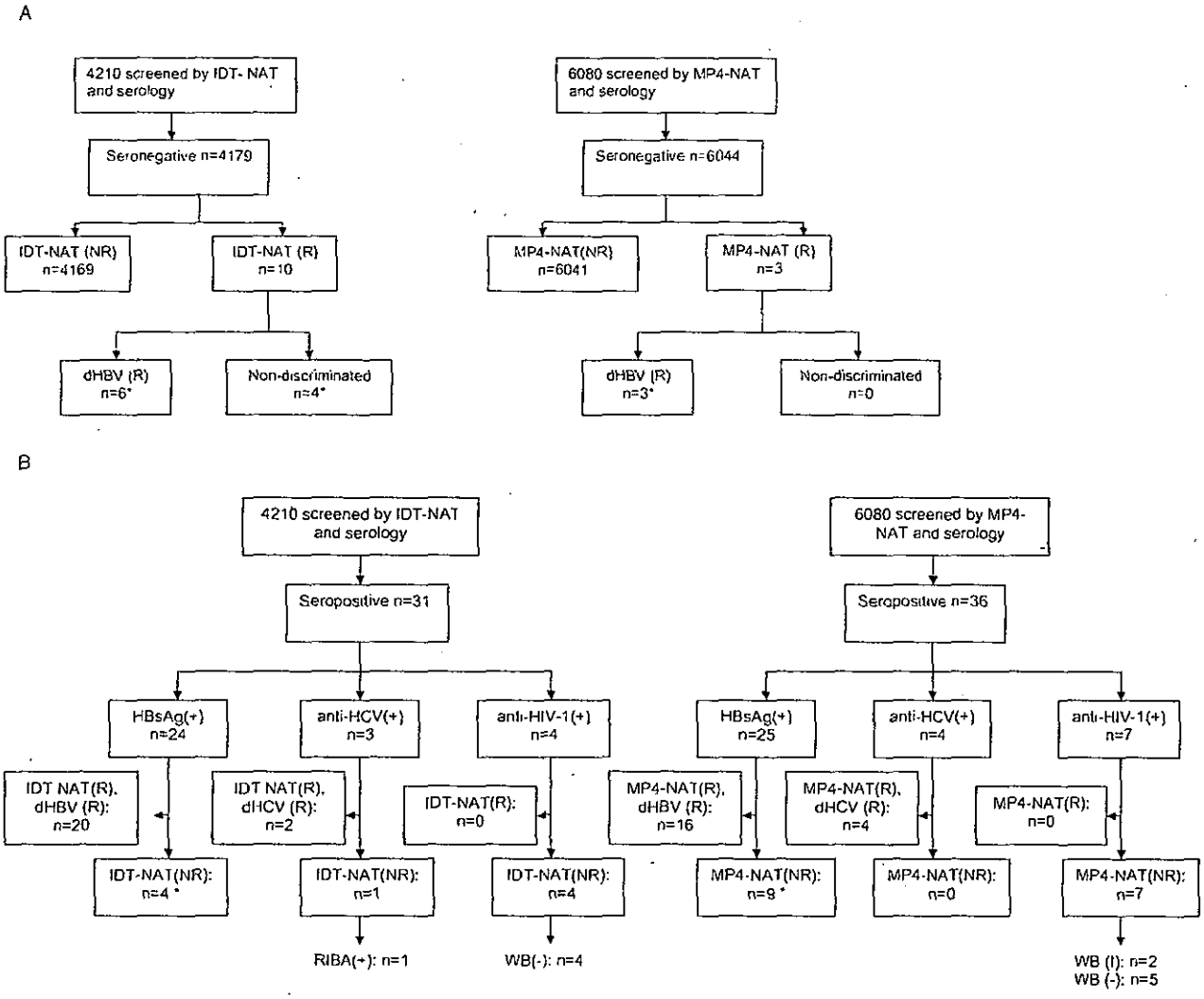

Fig. 1. (A) Results of seronegative donations screened by IDT and MP4 and serology. NR = nonreactive; R = reactive. *All these samples are discussed in Table 4. (B) Results of seropositive donations screened by IDT and MP4 and serology. NR = nonreactive; R = reactive. I = indeterminate; RIBA = recombinant immunoblot assay; WB = Western blot. *All these samples are discussed in Table 5.

refined the preliminary classification obtained on the basis of molecular and serologic results. In eight cases, the results obtained in the index samples were reproduced in the follow-up samples available confirming the diagnosis of OBI. In two cases, IDT-A3 and IDT-A6, a low level of anti-HBs was found in follow-up samples indicating cases of resolved infections with fluctuating levels of anti-HBs. In IDT-A5 HBsAg was detected in the follow-up sample together with the persistence of anti-HBc already present in the index sample. This profile suggested a chronic HBV infection with fluctuating, low-level, HBsAg. In MP4-A3, the follow-up sample became anti-HBc positive, while it was negative in the index donation. And the presence of HBV DNA in index donation of MP4-A3 suggested that this donor was a window case during that time.

Seroreactive donor specimens tested in IDT and MP4

Testing results for the 31 seroreactive donor specimens identified among the 4210 tested in IDT and for the 36 seroreactive specimens within the 6080 samples screened in MP4 are shown in Fig. 1B. Among the 31 specimens tested in IDT, 24 were HBsAg reactive, three were anti-HCV reactive, and three anti-HIV reactive. Twenty of the 24 HBV-seroreactive specimens were also dHBV reactive.

TABLE 4. Confirmation and possible status of HBV yield cases in Taiwan

Donor ID	Time (days)	HBV DNA dHBV	HBV DNA Alt PCR*	HBV DNA Viral load (IU/mL)†	HBV DNA Genotype‡	HBV serological markers HBsAg (PRISM)	HBV serological markers Anti-HBc§	HBV serological markers Anti-HBs (mIU/L)¶	Possible HBV status of donors
IDT-A1	Index	R[5]	P	7	B2	N	P	N	OBI
	81		P			N	P	N	
	199		P			N	P	N	
	261		N			N	P	N	
IDT-A2	Index	R	P	15	B2	N	P	488	OBI
	85		P			N	P	367	
	276		P			N	P	434	
IDT-A3	Index	R	P	N	B2	N	P	N	OBI
	82		P			N	P	13	
	144		N			N	P	8	
	215		N			N	P	6	
IDT-A4	Index	R	P	48	B2	N	P	N	OBI
	77		P			N	P	N	
IDT-A5	Index	R	P	<5	B2	P**	P	N	CHBV††
	215		P			P	P	N	
IDT-A6	Index	R	P	<5	B2	N	P	N	OBI
	160		P			N	P	11	
IDT-A7	Index	NR	P	N	B2	N	P	N	OBI
	189		P			N	P	N	
IDT-A8	Index	NR	N	N	B2	N	P	86	OBI
	185		N			N	P	65	
	256		N			N	P	66	
IDT-A9	Index‡‡	NR	N	N	NA	N	P	P	Ind§§
IDT-A10	Index‡‡	NR	N	6.4	NA	N	P	P	OBI
MP4-A1	Index	R	P	9	B2	N	P	N	OBI
	175		P			N	P	N	
MP4-A2	Index‡‡	R	P	N	B2	N	P	N	OBI
MP4-A3	Index	R	P	N	B2	N	N	N	WP
	253		P			N	P	N	New infection

* Alternative PCR by NGI HBV UltraQual.
† Results of Cambridge qPCR with numbers indicating viral load in IU/mL. <5 indicates a signal too low to allow reliable quantification.
‡ HBV genotyped by sequencing.
§ The results correspond to IgG anti-HBc. All the anti-HBc IgM determinations were N.
¶ Anti-HBs is given either qualitative (P or N) or quantitative in mIU/L.
** HBsAg N by Abbott Murex (S/CO = 0.9) and Ortho Assays; P by PRISM in subsequent analysis.
†† Chronic HBV infection with low and fluctuating HBsAg level.
‡‡ Donor was lost to follow-up.
§§ Indeterminate result, possibly contamination or OBI.
N = negative; NA = not available; NR = not reactive; P = positive; R = reactive.

while four were nondiscriminated and were further investigated (Table 5).

Thirty-six seroreactive specimens (25 HBsAg, four anti-HCV, and seven anti-HIV) were involved in NAT MP4 testing. Sixteen of the 25 HBsAg-reactive specimens were dHBV reactive and were considered true positive while nine were not and were further investigated as shown in Table 5.

Of the seven anti-HCV–reactive specimens (three IDT and four MP4), six were HCV RNA reactive. One of the three IDT-reactive specimens was found to be dHCV nonreactive. Of the 11 anti-HIV–reactive specimens (four IDT and seven MP4), none were HIV RNA reactive and none were confirmed antibody positive by Western blot (see Fig. 1B).

DISCUSSION

In a region where up to 90% of the population has evidence of past exposure or ongoing infection for HBV,[5] undetected OBIs pose a great threat to blood safety. While NAT only yield cases may occur under a number of circumstances—1) acute infection in the WP, 2) tail end of a chronic HBV infection, 3) persistence of low-level HBV replication in the presence of anti-HBs, and 4) escape mutant not detected by current HBsAg assays[22,23]—for this discussion we restrict the term of OBI to refer to HBV infection with the presence of anti-HBc and/or anti-HBs with no other detectable HBV markers except for HBV DNA.[24] While the transfusion transmission risk is lower for OBIs than for WP infections,[25] OBIs numerically pose a more significant threat to the blood supply, especially in HBV-endemic countries.[1,26]

In Asia, Taiwan in particular, many reports indicated that HBV DNA could be present, generally at a low level, in HBsAg-negative but anti-HBc–positive blood donations.[1,7,27] The proportion of this type of blood donation (1%-7%) was considerably higher than in low-prevalence Western countries (0%-3.5%).[26,28-31] Identifying and

TABLE 5. Profile of the 13 Ultrio-nonreactive initially HBsAg-positive (Abbott Murex) specimens

	HBV serologic markers					HBV DNA		
	HBsAg			HBV antibodies				
Donor ID	Murex (S/CO*)	PRISM	Neutralization	Anti-HBc	Anti-HBs†	Ultrio IDT (Reactive/Total)	Ultrio dHBV	Alt PCR‡
IDT-B1	28.56	P	P	P	N	NR (0/3)	NA	R
IDT-B2	10.89	P	P	P	N	NR (0/3)	NA	NR
IDT-B3	6.68	P	P	P	N	NR (0/3)	NA	NR
IDT-B4	3.56	P	P	P	N	R (1/3)	NR (0/3)	R
MP4-B1	50.66	P	P	P	N	R (3/3)	HBV	R
MP4-B2	3.47	P	P	P	N	R (1/3)	HBV	R
MP4-B3	1.59	P	P	P	N	R (2/3)	NR (0/3)	NR
MP4-B4	1.45	P	P	P	N	NR (0/3)	NA	R
MP4-B5	10.72	P	P	P	N	NR (0/3)	NA	NR
MP4-B6	1.32	N	Not confirmed	P	N	NR (0/3)	NA	NR
MP4-B7	1.12	N	Not confirmed	N	>1000	NR (0/3)	NA	NR
MP4-B8	2.22	N	Not confirmed	N	>1000	NR (0/3)	NA	NR
MP4-B9	1.00	N	Not confirmed	N	N	NR (0/3)	NA	NR

* Anti-HBs is given either qualitative (P or N) or quantitative in mIU/L.
† Alternative NAT: NGI HBV UltraQual assay used LOD = 0.9 IU/mL.
NA = not available; NR = nonreactive; R = reactive.

excluding such donations from the blood supply in Taiwan is important since it was demonstrated that this type of blood can be infectious by transfusion.[6,7,25] The risk of HBV transmission with the anti-HBc–"alone" blood has been reported to cover a wide range (0.4%-90%). In contrast, in a Japanese study, no donations containing both HBV DNA and anti-HBs were found infectious through transfusion.[25] However, a recent report from Slovenia presented two cases of HBV transmission by transfusion of an OBI unit containing low levels of anti-HBs.[32] Furthermore, vaccinated children with low levels of anti-HBs but relatively immunocompromised appeared to be susceptible to HBV infection after transfusion with HBsAg-negative blood products.[6] Therefore, on the basis of these studies, it appears important for blood safety in Taiwan that routine HBV NAT be implemented in addition to the current HBsAg screening.

Assay performance characteristics are critical to the interdiction of potentially infectious donations. A UK model, adjusted for test and processing errors, revealed that 22% of the risk of transfusion-transmitted infections (including HBV, HCV, and HIV) was the result of test failures and operational errors,[33] underscoring the need for a robust, reliable screening assay. The Ultrio assay in our hands had both a low invalid test rate of 0.27% and a low overall non–repeatable-reactive rate of 0.07% for IDT and 0.13% for MP4. These characteristics, along with its high assay sensitivity and specificity, provide a suitable system for routine screening of the blood supply in Taiwan.

The most critical assay attribute for detection of low-level viremia is analytical sensitivity. Our evaluation showed the Ultrio assay to be highly sensitive with 95% LODs of 18.41, 4.38, and 6.28 IU/mL for HIV-1, HCV, and HBV, respectively, and 13.97, 8.54, and 12.04 IU/mL for the respective discriminatory assays (Table 1). These results are consistent with the claims stated in the package insert (PROCLEIX ULTRIO assay, Package Insert INO167EN rev. 2, 2004, Gen-Probe Inc., San Diego, CA) and with the findings of other investigators.[6,11,31,35]

While it was demonstrated that testing in plasma pools of small sizes was essentially as efficient as IDT for HIV-1 and HCV, pooling had a substantial impact on the efficacy of detecting low-level HBV DNA. Results presented in Tables 3 and 4 show that proportionally more HBV DNA–positive samples were identified among HBV-containing donations in IDT (87.9%) than in MP4 (67.9%). Our study provides an opportunity to determine the distribution of concordant and discordant blood donor samples between the two main HBV tests: HBsAg and HBV DNA. Among the HBV-containing donations, IDT identified 60.6% positive for both HBsAg and HBV DNA, 12.1% HBsAg only, and 27.3% HBV DNA only, whereas MP4 identified 57.2% positive for both HBsAg and HBV DNA, 32.1% HBsAg only, and 10.7% HBV DNA only. This distribution is similar to the data in our previous study[13] (58.6, 26.8, and 14.6%, respectively). Although the two testing populations in this study show different HBsAg-reactive rates (0.57% for IDT and 0.41% for MP4), they are not much different compared to the 0.48% reactive rate of Taiwanese donor population in 2007 (from Taiwan Blood Services Foundation annual report 2007). The distribution observed in an area like Taiwan, where HBV Genotypes B and C are prevalent, considerably differs from data generated in Ghana, West Africa, where Genotype E is prevalent and, tested with the Cambridge qPCR used in this study, 84% of samples were HBsAg and HBV DNA positive, 6% HBsAg only, and 10% DNA only.[20]

Additionally, the data presented in Table 5 suggest that some HBsAg-positive samples may carry an extremely low level of HBV DNA, below the LOD of most assays currently available for blood testing. This lack of sensitivity would be further compounded by any level of

pooling. Several options can be offered to address this issue in addition to IDT-NAT, such as extraction from larger plasma volume or concentration of viral particles by high-speed centrifugation.[36] Nevertheless, data of our study demonstrate that, at least for the time being, HBsAg and HBV DNA screening are complementary and that both are beneficial for the blood safety.

One important issue for NAT is the confirmation and characterization of yield cases to appropriately inform the implicated donors. As shown in Table 4, there are three successive levels of supplementary testing that can help to achieve this goal: 1) alternative NAT assays for HBV DNA, 2) detection of other HBV serologic markers to refine the HBV infection profile, and 3) testing follow-up samples to reach a suitable diagnosis. To verify potential (HBsAg-negative, NAT repeat-reactive) and probable (HBsAg-negative, NAT-reactive, and alternative NAT-reactive on an alternate specimen) yield cases, we subjected index samples to molecular analysis and genotyping and we tested follow-up specimens from these donors with six different serologic tests and three alternative NAT assays. Parts of the HBV genome (pre-core, pre-S, and S) along with the full genome were amplified in most index cases. All yield cases were Genotype B2, which is the predominant genotype in Taiwan.[37] The qualitative NAT (NGI HBV UltraQual) with a 95% LOD of 0.9 IU/mL detected HBV DNA in follow-up specimens from 9 of 11 potential yield donors, whereas a quantitative NAT with a LOD of 100 IU/mL (Quest Diagnostics) was not able to quantify DNA in any of the follow-up specimens, although it detected an HBV signal in six donors (data not shown). A third highly sensitive quantitative NAT with a LOD of 20 IU/mL (in-house PCR, Cambridge University Laboratories), only being used for testing the index donations, found HBV DNA levels ranging from less than 5 to 48 IU/mL, underscoring the assay sensitivity as a defining factor for the detection of DNA in these low-level specimens. In addition, nested amplification of multiple regions of the HBV genome after concentration by ultracentrifugation proved to be the most reliable and sensitive method of confirmation (Table 4). These data illustrate the need for alternative NATs with high assay sensitivity in confirming the presence of HBV DNA in donation samples.

The seroconversion of HBsAg and/or other HBV markers in a donor with a totally seronegative index donation distinguishes between WP infection and other diagnoses. In Case MP4-A3, anti-HBc is detected after 8 months (Table 4). Both HBV DNA and anti-HBs levels are known to fluctuate in some cases. Here, examples of such fluctuations are seen in Cases IDT-A1 and IDT-A3.

The HBV yield rate for the IDT Ultrio assay (0.21%) in Taiwan was about five times higher than was observed in Hong Kong[8] and was 10- to 100-fold higher than reported in countries with low HBV prevalence. The 12 yield cases, 10 of which were verified by NAT reactivity in follow-up specimens, are consistent with the finding of our previous study[13] on a different cohort of our donor population and with a different NAT system.

The results of this study could be used to estimate the impact of adding NAT for the whole blood donor population in Taiwan. HBV DNA screening by IDT together with HBsAg testing would initially identify 3919 confirmed donations per 500,000 donors tested. Comparing to current HBsAg screening alone, it will interdict 1069 additional infectious donations potentially transfused to more than 1000 recipients.

In summary, our study demonstrated that the great majority of our yield cases were of OBI and that these yield samples had very low viral load, necessitating the use of a highly sensitive NAT for detection. The yield rate observed with the IDT approach was higher than that observed with MP4 approaches in this study which confirmed the higher clinical utility of the more sensitive IDT approach. Implementation of HBV NAT screening, especially with the IDT format, shows promise in enhancing the safety of the blood supply in Taiwan.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 7. 8	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	惠谷ゆり, 清原由起, 高野智子, 三善陽子, 位田忍, 田尻仁. 第46回日本肝臓学会総会; 2010 May 27-28; 山形	公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)			日本

研究報告の概要

○小児B型肝炎キャリア187例の感染実態と現在のHBV感染予防対策の問題点

目的:小児B型肝炎ウイルス(HBV)キャリア患者の感染経路・感染要因を解析し、現在のHBV感染予防対策の問題点を明らかにする。

方法:大阪府立母子保健総合医療センター消化器・内分泌科(施設1)、大阪大学医学部小児科(施設2)、及び大阪府立急性期・総合医療センター小児科(施設3)に通院歴のあるHBVキャリア小児について後方視的に検討した。

結果:施設1では32例、施設2では133例、施設3では22例の合計187例のHBVキャリアが診療を受けていた。男女比は1.43:1、診断時年齢は中央値2歳(0ヶ月～15歳)であった。母児感染予防処置が行われるようになった1986年以前の出生児と、以後の出生児に分けて検討した。1985年までに出生していた症例は102例で、母児感染59例(57.8%)、父子感染6例(5.9%)、輸血5例(4.9%)、水平感染31例(30.4%)、不明1例で母児感染が過半数を占めていた。一方、1986年以降に出生した症例は85例で、母児感染51例(60%)、父子感染13例(15.3%)、輸血2例(2.4%)、水平感染19例(22.4%)であった。母児感染の割合は1985年までに出生していた症例と変化なく、父子感染は増加した。母児感染のうち胎内感染が16例、予防処置実施中あるいは実施後にHBV感染が判明した症例が22例で、現在の予防法で防ぐことができなかった症例が合計38例(74.5%)であったが、予防処置の不完全施行や未施行によるものが8例(15.7%)存在した。父子感染や水平感染の症例でHBワクチンの投与を受けていたものはいなかった。

結論:HBV母児感染予防処置導入後も小児のHBVキャリアは発生している。母児感染のうち約15%は予防処置の不完全施行や未施行が原因であり、医療者の啓発を行うとともに、予防処置プロトコールを簡略な国際方式にすることにより完遂率が高まると思われる。また、父子感染・輸血を含めた水平感染例も4割を占めており、諸外国のように日本でも出生後早期にHBユニバーサルワクチンが導入されることが望まれる。胎内感染例については出生後の予防処置では防ぐことができず、HBVキャリア妊婦へのHBIGや抗ウイルス剤投与などを行うべきか、今後検討していく必要がある。

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	今後の対応
B型肝炎ウイルス(HBV)母児感染予防措置導入以前と以後の小児HBVキャリア患者の感染経路・感染要因を比較・解析し、ユニバーサルワクチン導入の必要性を述べた報告である。 これまで、本剤によるHBV感染の報告はない。また本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。さらに最終製品についてHBV-NAT陰性であることを確認しており、安全性は確保されていると考える。	これまでの使用実績やバリデーション成績に鑑み本製剤の安全性は確保されており、特別の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。なお、日本赤十字社では献血時のスクリーニング法としてより感度の高い化学発光酵素免疫測定法(CLEIA)および新NATシステムを導入した。

④

WS4-5 B型肝炎母子感染防止事業開始後に誕生した若年者におけるB型肝炎ウイルス感染についての検討

林 和彦, 片野義明, 後藤秀実
名古屋大学医学部消化器内科

【目的】1985年に厚生省B型肝炎母子感染防止事業による感染予防策が開始され, HBV感染者の新規発生が大幅に抑制された. しかしながら, 1985年以降に生まれた若年者にB型慢性肝炎(CHB)は存在しているが, その詳細は不明である. そこで1985年以降に誕生した若年者のCHBを対象に, その臨床的, ウイルス学的な解析を行った.

【方法】当院に通院中のCHB372例. 男220例, 女152例, 平均年齢43.9±1.4歳 (3-86歳) である. 1985年以降 (Young : Y群) と1960-1985 (Middle : M群), 1960年以前 (Old : O群) 誕生の3群に分類して比較した. HBVsubgenotypeは, preS領域のダイレクトシークエンス法で判定した. S領域のダイレクトシークエンスでワクチンエスケープ変異 (VEM) を検索した.

【成績】Y群12例, M群259例, O群101例とY群は全体の3.2%であった. Y群の感染経路は, 母子感染例が9例, 水平感染が, 3例. 母子感染では, ワクチン未接種例が2名で海外からの移民であった. 他の7例はすべて出産後に標準的な母子感染予防を施行したが, 感染が予防できなかった無効例であった. 水平感染例は, それぞれ手術, 鍼灸, 性行為が感染経路と推定された. Y群のHBVsubgenotypeは10例Ceで, BaとAeがそれぞれ1例であった. Baはフィリピンからの移民で, Aeは性行為感染後の慢性化例であった. M群, O群のgenotype Ceの分布は78.4%, 80.2%と同様であったが, genotype Aeの分布は6.9%, 1.9%とM群に広く感染していた. Y群のHBe抗原は11例陽性であり, すべてBCP/PC変異は野生型であった. Y群のG145Aなど既報のVEMはなかった. y群4例の全塩基配列を解析したが, 有意な変異は確認できなかった.

【考案】母子感染予防無効例にVEMを有するCHBはなくウイルス因子以外に, ホスト側の要因も重要であることが示唆された. また移民のHBV感染を認めており, 今後さらに海外交流が盛んになると推測するのでわが国も地球規模でのHBV予防対策が望まれる. 母子感染が75%を占めていたが, 水平感染例もあり, これら症例に対してはユニバーサルワクチンが有効と考える. また19歳での感染後の慢性化したgenotype Aeも存在し, M群のCHBにおいてgenotype Aeは増加しており, このhigh risk groupに対してもワクチンなどの対策が必要と思われる.

【結語】母子感染防止事業開始後に発症したCHBの多くは母子感染予防無効例で, 一部に移民や慢性化したgenotypeAeも存在した.

WS4-6 小児B型肝炎キャリア187例の感染実態と現在のHBV感染予防対策の問題点

惠谷ゆり[1], 清原由起[2], 高野智子[3], 三善陽子[2], 位田 忍[1], 田尻 仁[3]
大阪府立母子保健総合医療センター消化器・内分泌科[1], 大阪大学大学院医学系研究科医学部小児科学[2], 大阪府立急性期・総合医療センター小児科[3]

【目的】小児B型肝炎ウイルス (HBV) キャリア患者の感染経路・感染要因を解析し, 現在のHBV感染予防対策の問題点を明らかにする.

【方法】大阪府立母子保健総合医療センター消化器・内分泌科 (施設1), 大阪大学医学部小児科 (施設2), および大阪府立急性期・総合医療センター小児科 (施設3) に通院歴のあるHBVキャリア小児について後方視的に検討した.

【成績】施設1では32例, 施設2では133例, 施設3では22例の合計187例のHBVキャリアが診療を受けていた. 男児110例, 女児77例で男女比1.43 : 1と男児が多かった. 診断時年齢は中央値2歳 (0ヶ月~15歳) であった. これらの症例の感染経路について, 母児感染予防処置が行われるようになった1986年以前の出生児と, 以後の出生児に分けて検討した. 1985年までに出生していた症例は102例で, 母児感染59例 (57.8%) 父子感染6例 (5.9%) 輸血5例 (4.9%) 水平感染31例(30.4%)不明1例で母児感染が過半数を占めていた. 母親のHBV感染の詳細が判明したものは8例だけで, うち5例がHBeAg陽性, 3例がHBeAb陽性であった. 父親については3例の情報があり, 全例HBeAg陽性であった. 一方1986年以降に出生した症例は85例で, 母児感染51例 (60%), 父子感染13例 (15.3%), 輸血2例(2.4%), 水平感染19例(22.4%)であった. 母児感染の割合は1985年までに出生していた症例と変化なく, 父子感染は増加していた. 母親のHBV感染の詳細が判明したものは29例あり, 全例HBeAg陽性であった. 父親については3例がHBeAg陽性, 1例がHBeAb陽性であった. 母児感染のうち胎内感染が16例, 予防処置実施中あるいは実施後にHBV感染が判明した症例が22例で, 現在の予防法では感染を防ぐことができなかった症例が合計38例(74.5%)であったが, 予防処置の不完全施行や未施行によるものが8例(15.7%)存在した. 父子感染や水平感染の症例で, HBワクチンの投与を受けていたものはいなかった.

【結論】HBV母児感染予防処置導入後も小児のHBVキャリアは発生している. 母児感染のうち約15%は予防処置の不完全施行や未施行が原因であり, 医療者の啓発を行うとともに, 予防処置プロトコールを簡略な国際方式にすることによって完遂率が高まると思われる. また父子感染・輸血を含めた水平感染症例も4割を占めており, 諸外国のように日本でも出生後早期にHBユニバーサルワクチンが導入されることが望まれる. 胎内感染例については, 出生後の予防処置では防ぐことができず, HBVキャリア妊婦へのHBIGや抗ウイルス剤投与などを行うべきか, 今後検討していく必要がある.

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 6. 22	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		公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)		大塚裕司, 平力造, 百瀬俊也, 日野学. 第58回日本輸血・細胞治療学会総会; 2010 May 28-30; 愛知	日本

研究報告の概要

○2009年輸血関連感染症報告症例の解析と傾向

はじめに:2009年に全国の医療機関から報告された輸血関連感染症例(疑い例を含む)の解析結果と医療機関における「血液製剤等に係る遡及調査ガイドライン」(以下GL)に基づいた輸血前後の患者検体の検査実施状況等について報告する。

対象と方法:2009年に医療機関より報告された症例を対象とし、献血者検体(献血者の保管検体等の個別NAT、当該製剤(使用済みバッグ)等の無菌試験等)と患者検体の調査により輸血との因果関係を評価した。また、医療機関における患者の輸血前後の検査の実施項目等を2007、2008年時と比較した。

結果と考察:10月末現在の報告数は82例(HBV 37例、HCV 21例、細菌 20例、パルボB19 2例、HEV 1例、CMV 1例)であり、輸血との因果関係が高いと評価した症例は、HBV 5例、HEV 1例、及び細菌 1例であった。医療機関でのGLに基づく輸血前後の患者検体の検査実施数(輸血前:HBs抗原/HBs抗体/HBc抗体, 輸血後:HBV-DNA)はHBV症例で2007年6例(8%)、2008年12例(20%)、2009年9例(24%)であった。またHCV症例では(輸血前:HCV-RNA or HCVコア抗原/HCV抗体, 輸血後:HCV-RNA or HCVコア抗原)2007年12例(29%)、2008年5例(12%)、2009年5例(24%)であった。細菌症例での医療機関における患者血培の実施数は、2007年27例(90%)、2008年43例(94%)、2009年20例(100%)であった。また、医療機関からの使用済みバッグの提供が2007年17例(57%)、2008年35例(76%)、2009年17例(85%)であった。これらのことによりGLが医療機関に浸透していることが推察された。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
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
2009年に全国の医療機関から報告された輸血関連感染症例(疑い例を含む)の解析結果と医療機関における「血液製剤等に係る遡及調査ガイドライン」(以下GL)に基づいた輸血前後の患者検体の検査実施状況等についての報告である。なお、2009年12月末現在までの報告数は98件(HBV 45例、HCV 26例、細菌 23例、パルボB19 2例、HEV 1例、CMV 1例)、報告中、輸血との因果関係が高いと評価した症例はHBV 7例、HEV 1例、細菌 2例となっている。医療機関でのGLに基づく輸血前後の患者検体の2009年の検査実施数は、HBV症例 9例(20%)、HCV症例 9例(35%)、細菌症例の血培実施数23例(100%)、また医療機関からの使用済みバッグの提供は20例(87%)となっている。	これまで本製剤を介してこの報告で輸血後感染が示唆された病原微生物の感染はない。除菌工程やモデルウイルスによるバリデーション成績に鑑み、本製剤の安全性は確保されており、特別の対応を必要としないが、今後も輸血感染症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。なお、日本赤十字社では献血時のスクリーニング法としてより感度の高い化学発光酵素免疫測定法(CLEIA)および新NATシステムを導入した。

WS-1-2　2009年輸血関連感染症報告症例の解析と傾向

日本赤十字社血液事業本部
大塚裕司，平　力造，百瀬俊也，日野　学

【はじめに】2009年に全国の医療機関から報告された輸血関連感染症例（疑い例を含む）の解析結果と医療機関における「血液製剤等に係る遡及調査ガイドライン（以下GL）」に基づいた輸血前後の患者検体の検査実施状況等について報告する．
【対象と方法】2009年に医療機関より報告された症例を対象とし，献血者検体（献血者の保管検体等の個別-NAT，当該製剤（使用済みバッグ）等の無菌試験等）と患者検体の調査により輸血との因果関係を評価した．また，医療機関における患者の輸血前後の検査の実施項目等を2007，2008年時と比較した．
【結果と考察】10月末現在の報告数は82例（HBV 37例，HCV 21例，細菌20例，パルボB19 2例，HEV 1例，CMV 1例）であり，輸血との因果関係が高いと評価した症例は，HBV 5例，HEV 1例及び細菌の1例であった．
医療機関でのGLに基づく輸血前後の患者検体の検査実施数（輸血前：HBsAg/HBsAb/HBcAb，輸血後：HBV-DNA）はHBV症例で2007年6例（8%），2008年12例（20%），2009年9例（24%）であった．またHCV症例では（輸血前：HCV-RNA or HCVコア抗原/HCV-Ab，輸血後：HCV-RNA or HCVコア抗原）2007年12例（29%），2008年5例（12%），2009年5例（24%）であった．細菌症例では医療機関における患者血培の実施数は，2007年27例（90%），2008年43例（94%），2009年20例（100%）であった．また医療機関からの使用済みバッグの提供が2007年17例（57%），2008年35例（76%），2009年17例（85%）であった．これらのことによりGLが医療機関に浸透していることが推察された．今後，患者検体の日赤への提供状況等を併せて調査し，報告する予定である．

WS-1-3　献血由来の血漿分画製剤製造メーカーで実施したHEV-NAT検査と，遡及調査により判明した輸血後E型急性肝炎の1症例

武蔵野赤十字病院輸血部[1]，東京都赤十字血液センター学術二課[2]，中央血液研究所感染症解析部[3]
森　成典[1]，清水隆弘[1]，中村圭太[2]，鈴木　光[2]，内田茂治[3]，長田　薫[1]

【はじめに】日本国内で輸血によるE型肝炎ウイルス（HEV）感染が2002年に初めて報告され，現在まで数例の報告がある．今回我々は，献血由来の血漿分画製剤製造メーカーより，原料血漿の受け入れ試験として実施したHEV核酸増幅検査（NAT）によってHEV-RNAが検出されたとの報告があり，当該血液から製造された赤血球製剤の遡及調査により，輸血後E型急性肝炎が判明した事例を経験したので報告する．
【症例】患者は74歳男性，2008年5月に敗血症，脊髄硬膜外膿瘍，ARDS，急性腎不全などの重篤な病態にて当院救命救急科に入院．6月～10月までにRCC-LR計40単位の輸血を必要とした．8月下旬に一過性の急激なAST/ALTの上昇を認めたが，重篤な病態にて種々の薬剤が投与されていることもあり，原因の特定には至らなかった．肝機能は11月には正常化し，2009年1月に原疾患の回復により退院した．2009年5月，赤十字血液センターに血漿分画製剤製造メーカーより，献血由来の血液からHEV-NATにてHEV－RNAが検出されたとの報告があった．そして，当該血液由来のRCC-LRが当院に供給されたと遡及調査の依頼があり，2008年8月22日に前記患者に輸血されていたことが判明した．輸血前後の患者保管血漿によるHEV抗体，HEV-RNAが輸血前は陰性，輸血後は陽性，さらに献血者および患者のウイルス塩基配列も完全に一致したため，輸血によるHEV感染であることが証明された．よって，患者は輸血によるHEV感染から急性肝炎を発症したものと考えられた．
【考察】本症例は血漿分画製剤製造メーカーによるHEV-NATと，輸血前検体の保管により判明した輸血後E型急性肝炎であり，検体保管の重要性を再認識した．また，輸血後AST/ALTの急激な上昇が見られ，HBV，HCVの感染を認めないケースでは，HEV感染も要因の一つとして疑う必要があると思われた．

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
				2010. 6. 22	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		公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)		平力造, 大塚裕司, 鈴木光, 百瀬俊也, 内田茂治, 日野学. 第58回日本輸血・細胞治療学会総会; 2010 May 28-30; 愛知	日本

研究報告の概要

○スクリーニングNATのプール数の縮小効果について

はじめに:日本赤十字社では血液製剤等のHBV、HCV、HIVへの安全対策として1999年7月にプール検体(500本)によるスクリーニングNAT(試薬:AMPLINAT MPX(AMP-NAT))を開始した。その後、プール検体数を50本、20本へと縮小し、2008年8月から検出感度向上を目的に新NATシステム(試薬:TaqScreen MPX(Taq-NAT))を導入した。これらのプール数の縮小効果を医療機関から報告された感染症報告症例より検証した。

対象と方法:2000年1月から2009年10月までに医療機関より報告された感染症報告症例の内、輸血による感染を直接証明できた症例はHBV 91件、HCV 3件、HIV 1件であった。この原因となった輸血用血液の献血血液それぞれ87献血、3献血、1献血を対象にし、当該献血時のスクリーニングNATをプール検体数別・試薬別に分類した。

結果:献血血液の分類結果はHBV・HCV・HIV別に、50本プール前:8・0・0、 50本プール/AMP-NAT(2000年2月-2004年7月:4.5年間):46・2・1、 20本プール/AMP-NAT(2004年8月-2008年7月:4年間):30・1・0、 20本プール/Taq-NAT(2008年8月-2009年10月:1.25年間):3・0・0 であった。

考察:ウイルス増殖スピードの遅いHBVについて、プール検体数の縮小・試薬の検出感度向上により、輸血感染HBVの減少傾向が認められた。一方、ウイルス増殖スピードの速いHCV、HIVはスクリーニングNAT導入後約10年が経過した中で輸血感染HCVが3件、輸血感染HIVが1件と、NATの導入自体に効果があったことが推測された。2008年8月から導入された新NATシステムにより、更なる安全性向上に努めているところである。

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	今後の対応
日本赤十字社で実施した、スクリーニングNATにおける段階的なプール検体数の縮小と、2008年8月からの試薬の検出感度向上による効果の検証である。日本赤十字社では、血清学的検査に加え、HBV、HCV、HIVについて20プールでスクリーニングNATを行い、陽性血液を排除している。また、「血液製剤等に係る遡及調査ガイドライン」(平成20年12月26日付薬食発第1226011号)に基づき、輸血感染症の調査を行っている。	日本赤十字社では、従来の凝集法と比べてより感度の高い、化学発光酵素免疫測定法(CLEIA)及び精度を向上させたNATシステムを導入している。これらの措置によって原料血漿への病原微生物の負荷が減少し、本製剤の安全性はより高まっている。今後も輸血感染症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。

WS-1-6　スクリーニングNATのプール数の縮小効果について

日本赤十字社血液事業本部
平　力造，大塚裕司，鈴木　光，百瀬俊也，内田茂治，日野　学

[はじめに]日本赤十字社では血液製剤等のHBV，HCV，HIVへの安全対策として1999年7月にプール検体（500本）によるスクリーニングNAT（試薬：AMPLINAT MPX（AMP-NAT））を開始した．その後，プール検体数を50本，20本へと縮小し，2008年8月から検出感度向上を目的に新NATシステム（試薬：TaqScreen MPX（Taq-NAT））を導入した．これらのプール数の縮小効果を医療機関から報告された感染症報告症例より検証した．
[対象と方法]2000年1月から2009年10月までに医療機関より報告された感染症報告症例の内，輸血による感染を直接証明できた症例はHBV（TT-HBV）91件，HCV（TT-HCV）3件，HIV（TT-HIV）1件であった．この原因となった輸血用血液の献血血液87献血，3献血，1献血を対象とし当該献血時のスクリーニングNATをプール検体数別・試薬別に分類した．
[結果]献血血液の分類結果はHBV・HCV・HIV別に，50本プール前：8・0・0,50本プール/AMP-NAT（2000年2月－2004年7月：4.5年間）：46・2・1,20本プール/AMP-NAT（2004年8月－2008年7月：4年間）：30・1・0,20本プール/Taq-NAT（2008年8月－2009年10月：1.25年）：3・0・0であった．
[考察]ウイルス増殖スピードの遅いHBVについて，プール検体数の縮小・試薬の検出感度向上によりTT-HBVの減少傾向が認められた．一方，ウイルス増殖スピードの速いHCV・HIVは，スクリーニングNAT導入後約10年が経過した中でTT-HCVが3件，TT-HIVが1件とNATの導入自体に効果があったことが推測された．2008年8月から導入された新NATシステムにより，更なる安全性向上に努めているところである．今後も，安全対策の導入に際して，そのリスク評価を検討し，輸血医療の安全性向上に資することとしたい．

WS-2-1　当院における貯血式自己血輸血の現状と問題点

安城更生病院血液輸血センター[1]，安城更生病院血液・腫瘍内科[2]
原田康夫[1]，山本喜之[1]，山本敦子[1]，伊藤達也[2]

【はじめに】自己血輸血は同種血輸血の副作用を回避し得る最も安全な輸血療法とされ，近年，積極的に導入されつつあるが，返血実施のガイドラインは未だ確立されていない．そこで，今回，適正化に向けて当院における貯血式自己血の現状と問題点を検討したので報告する．
【対象と方法】2003年1月～2008年12月の貯血式自己血輸血の推移を診療科別に貯血数，実施数，同種血回避率，廃棄率等の実施状況について科別解析を行った．
【結果】6年間の貯血式自己血採血総数は1204症例，特に産科，婦人科，整形外科，泌尿器科において年次増加が顕著であった．自己血実施総数は1104症例で実施率は91.7%であった．同種血併用総数は52件（うち30件は心臓血管外科），同種血輸血回避率は95.3%で年間の変化は認められなかった．科別廃棄率は0～35%に分布していた．術後に実施された自己血輸血時の総平均Hb値は10.0g/dl（6.3g/dl～14.7g/dl）であったが，中にはHb値未測定症例や，比較的術後貧血が軽度な症例も含まれていた．科別では産科9.5g/dl，婦人科9.9g/dl，整形外科9.9g/dl，外科10.1g/dl，血液内科10.4 g/dl，泌尿器科10.7g/dl，心臓血管外科11.3g/dlであった．使用時期別解析では，術中使用率は74.5%，術後使用では，術後当日，翌日で大半を占めたが最長は7日までであった．科別術後実施率は，心臓血管外科の0.5%～整形外科の75.5%の分布を示した．
【結語】当院の貯血式自己血輸血総数は年々増加傾向にある．しかしながら，その実施基準は未だ不統一であり，廃棄状況にもばらつきが大きい．術式や患者の状況によっても大きく左右されるが，少なくとも，各科ではHb値と実施時期に関して一定の基準策定が望まれる．近年，自己血輸血による副作用も注目されており，リスク，ベネフィットをより厳密に考慮した更に適正な自己血輸血の体制整備を進める必要がある．

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 5. 11	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	47News. Available from: http://www.47news.jp/CN/201004/CN2010042901000540.html	公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)			日本

研究報告の概要

○A型肝炎が増加、死亡例も 魚介類や水、注意呼び掛け

A型肝炎の患者が3月以降増加し、既に昨年1年間の患者数を超えたことが、国立感染症研究所の集計で分かった。劇症化し死亡したケースもあった。A型肝炎ウイルスに汚染された水や食材の摂取によって感染する。同研究所は「広い範囲で散発的な集団発生が起きている可能性がある。55歳未満はほとんどが抗体を持たず、高齢者は重症化しやすい」として、魚介類の十分な加熱など、注意を呼び掛けている。同研究所によると、今年の患者の報告数は3月上旬から増加、4月4日までの1週間では18人と、2007年以降では1週間当たりの人数が最多で、その後も多い状態が続いている。4月18日までの合計(速報値)は121人で昨年の報告数(115人)を超えた。4月11日までの5週間の患者81人をみると、年齢は20～88歳、2例が劇症化し、うち1人が死亡した。福岡県、広島県などが多く、報告した医師が推定した原因食材は「カキ」が45%と最も多かった。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
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
A型肝炎の患者が3月以降増加し、既に昨年1年間の患者数を超えたことが、国立感染症研究所の集計で分かったとの報告である。これまで、本剤によるHAV感染の報告はない。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HAV-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。	本製剤の安全性は確保されていると考えるが、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、輸血後A型肝炎に対する対応として、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。

別紙2

JRC2010T-020

ニュース詳細 | 特集:菅政権へ | 日本の実力 | ランキング

A型肝炎が増加、死亡例も 魚介類や水、注意呼び掛け

A型肝炎の患者が3月以降増加し、既に昨年1年間の患者数を超えたことが、国立感染症研究所の集計で29日分かった。劇症化し死亡したケースもあった。

A型肝炎ウイルスに汚染された水や食材の摂取によって感染する。同研究所は「広い範囲で散発的な集団発生が起きている可能性がある。55歳未満はほとんどが抗体を持たず、高齢者は重症化しやすい」として、魚介類の十分な加熱など、注意を呼び掛けている。

同研究所によると、今年の患者の報告数は3月上旬から増加、4月4日までの1週間は18人と2007年以降では1週間当たり最多で、その後も多い状態が続く。4月18日までの合計(速報値)は121人で昨年の報告数(115人)を超えた。

11日までの5週間の81人をみると、患者の年齢は20~88歳、2例が劇症化し、うち1人が死亡した。福岡県、広島県などが多く、報告した医師が推定した原因食材は「カキ」が45%と最も多かった。

2010/04/29 17:26 【共同通信】

つぶやく

トップページへ

医薬品
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識別番号・報告回数			報告日	第一報入手日 2010 年 2 月 4 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 ⑤⑥乾燥濃縮人アンチトロンビンⅢ ⑦人ハプトグロビン ⑧乾燥濃縮人血液凝固第Ⅷ因子	研究報告の公表状況	Journal of Medical Virology 2010; 82(1): 69-76	公表国 日本
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ノイアート静注用 500 単位　（ベネシス） ⑥ノイアート静注用 1500 単位　（ベネシス） ⑦ノイアート　（ベネシス） ⑧ハプトグロビン静注 2000 単位「ベネシス」　（ベネシス） ⑨コンコエイトーHT　（ベネシス）			

研究報告の概要

ブタはヒトへ E 型肝炎ウイルス(HEV)を伝播するリザーバーと考えられる。
感染動態を調査するために、HEV に自然感染した国産ブタ 2 つの同産仔（A と B、10 匹の子豚を含む）を生後 6 箇月になるまで研究した。
母子移行 IgG および IgA 抗体は同産 A 群の子豚からは検出されたが、B 群からは検出されなかった。
生後 30-110 日のとき、全てのブタは糞便の中に HEV を排出し、17 匹は生後 40-100 日のときにウイルス血症を現した。系統発生分析では、全てのブタで HEV 遺伝子型 3 に非常に近い配列を示した。
特異的な IgG と IgA の血清レベルは IgA は糞便では検出されなかったが、全てのブタで同様だった。興味あることに、ウイルス血症と抗体陽転の開始は、同産児 A 群のブタで有意に遅れた。糞便に排出されたウイルスの動態は、両方の同産児群で同様であった。感染動態の違いは、母性抗体がウイルス血症と抗体陽転開始を遅延させることを示唆した。
定量的リアルタイム逆転写酵素-ポリメラーゼ連鎖反応法分析において、糞便中の HEV RNA は約 10^6copies/g で最初の排泄から 10 日後にピークに達することが明らかになった。生後 200 日で、HEV RNA は、13 匹のブタの 3 つの内臓で見つかった。この研究の発見は、ブタにおける HEV 自然感染の動態、ブタから人へのウイルス伝播の管理に役立つことができる。

使用上の注意記載状況・その他参考事項等

代表としてノイアート静注用 500 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献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体、抗 HTLV-I 抗体陰性で、かつ ALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人アンチトロンビン III を濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及びウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
ブタにおけるHEV自然感染の動態についての報告である。 万一、ヘパリンの原料であるブタ小腸粘膜にHEVが混入したとしても、HPV1及びPPVをモデルウイルスとしたウイルスバリデーション試験成績から、ヘパリンの製造工程において十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

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Long-Term Shedding of Hepatitis E Virus in the Feces of Pigs Infected Naturally, Born to Sows With and Without Maternal Antibodies

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Pigs are presumed reservoirs for hepatitis E virus (HEV) transmission to humans. To examine infection kinetics, two litters of domestic pigs (A and B, each containing 10 piglets) infected naturally with HEV were studied until pigs were 6 months old. Maternal IgG and IgA antibodies were detected in litter A piglets, but not in litter B ones. All pigs shed HEV in feces when they were 30–110 days old, and 17 developed viremia at 40–100 days of age. Phylogenetic analysis revealed a highly close sequence of HEV genotype 3 in all pigs. The serum levels of specific IgG and IgA were similar in all pigs, although IgA was not detected in the feces. Interestingly, the onset of both viremia and seroconversion was delayed significantly in litter A pigs. The kinetics of fecal virus shedding was similar in both litters; shedding was not detected after the pigs were 120 days old. The differences in the infection kinetics between litters A and B suggested that maternal antibodies delayed the onset of viremia and seroconversion. Quantitative real-time reverse transcriptase-polymerase chain reaction revealed that HEV RNA in feces peaked 10 days after initial shedding of approximately $10^{6.0}$ copies/g. The viral load was much lower in the serum than in the feces. At 200 days of age, HEV RNA was found in the internal organs of 3 out of 13 pigs. These study findings improve the understanding of the dynamics of natural HEV transmission in pigs, which could help in controlling virus transmission from pigs to humans. ***J. Med. Virol. 82:69–76, 2010.***

KEY WORDS: swine; transmission; time course; epidemiology

INTRODUCTION

Hepatitis E virus (HEV) is a causative agent of acute hepatitis in humans. HEV is a small non-enveloped single-stranded positive-sense RNA virus. Recently, HEV was classified as the sole member of the genus *Hepevirus* in the family *Hepeviridae* [Emerson and Purcell, 2003]. HEV isolates from mammals can be divided into at least four genotypes on the basis of complete sequence analysis [Lu et al., 2006]. Genotype 1 is distributed in Asia and Africa [Escribà et al., 2008; Sugitani et al., 2008], whereas genotype 2 is found in Mexico and Africa [Lu et al., 2006]. These two genotypes are transmitted to the human population via the fecal–oral route, and large human outbreaks have occurred in non-industrialized countries as a result of drinking water contaminated with feces [Jameel, 1999]. Genotype 3 has been detected in humans, domestic pigs, and several wild animals, and is distributed worldwide [Lu et al., 2006; Lewis et al., 2008; Lam et al., 2009]. Genotype 4 has been detected in humans and domestic pigs in Asian countries and Germany [Lu et al., 2006;

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Wichmann et al., 2008]. The genotypes 3 and 4 strains are considered to be zoonoses [Meng, 2005]. An HEV-related agent, the so-called avian HEV, has been detected in poultry but it does not seem to cause human infection [Huang et al., 2004].

Since the initial discovery of swine HEV in the USA [Meng et al., 1997], cases of HEV infection in pigs have been documented worldwide [Meng, 2005; Dalton et al., 2008]. Previous studies have shown the genetic similarity of swine and human HEV [Wang et al., 2000; Kabrane-Lazizi et al., 2001; Huang et al., 2002; Nishizawa et al., 2003; Takahashi et al., 2003; Yazaki et al., 2003; Ijaz et al., 2005], and have reported experimental cross-species infections from humans to pigs or from pigs to non-human primates [Meng et al., 1998; Halbur et al., 2001; Feagins et al., 2008; Ji et al., 2008]. All of these findings suggest that pigs are reservoirs of human HEV.

Epidemiological studies have revealed that HEV infections in pigs are ubiquitous, and that pigs over the age of 3 months have a high seroprevalence [Meng et al., 1999; Huang et al., 2002; Banks et al., 2004]. HEV shedding in feces has been observed in pigs of all ages, but is more frequently observed in 2–4 months old pigs as compared to slaughter-age (6-month old) or adult pigs [Meng et al., 1997; Yazaki et al., 2003; Cooper et al., 2005; Fernandez-Barredo et al., 2006; Seminati et al., 2008]. These results indicate that domestic pigs are infected easily with HEV at an early age, but that the majority of pigs stop shedding HEV RNA before they are 6 months old. Although many epidemiological studies have been conducted on this subject, longitudinal studies following individual pigs are limited [Meng et al., 1997; de Deus et al., 2008]. Of particular importance is the fact there have been no long-term quantitative analyses of virus shedding and serum antibody levels in individual piglets infected naturally with HEV.

In the present study, long-term follow-up characterization was performed until slaughter age of two litters of pigs infected naturally with HEV—one with HEV-specific maternal antibodies and the other without these antibodies—to investigate the dynamics of HEV RNA shedding in feces, as well as assess viremia, antibody levels, and the effect of maternal antibodies on HEV infection.

MATERIALS AND METHODS

Animals and Sample Collection

Twenty mixed-breed pigs, 10 born to sow A (litter A) and 10 to sow B (litter B), from a swine herd in Japan were followed up until they were 200 days old (day 200). The two litters were born on the same day in separate pens and raised together after day 30. They were separated again from day 83 till the end of the study.

The sera of sows A and B were collected before delivery and examined for HEV-specific IgG antibodies. During the study period, fecal and serum samples were collected every 10 days from each pig, and stored at −80°C until use. Thirteen pigs (five from litter A and eight from litter B) were euthanized on day 200, and tissue samples (liver, ileum, and colon), serum, bile, and intestinal contents (ileum, colon, and rectum) were collected and stored at −80°C before testing. The tissues were treated with RNAlater (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Euthanasia and tissue sampling were performed according to the Laboratory Animal Control Guidelines of Rakuno Gakuen University.

Enzyme-Linked Immunosorbent Assay for Detecting Anti-HEV Antibodies

The anti-HEV IgG antibodies in the sera collected before the delivery of the sows, the anti-HEV IgG and IgA antibodies in the serum samples, and the anti-HEV IgA antibodies in individual feces samples were detected using a commercial ELISA kit for the detection of hepatitis E antibodies (Viragent HEV-Ab kit; Cosmic Corporation, Tokyo, Japan) according to the manufacturer's instructions. Serum samples from five pigs in litter A and eight in litter B were used for detecting HEV-specific serum IgA. For detection of antibodies in feces, suspensions of 10% fecal matter in phosphate-buffered saline were prepared. The kit used a truncated recombinant HEV ORF2 protein expressed in silkworm pupae [Mizuo et al., 2002]. Rabbit anti-pig IgG or IgA antibodies coupled with horseradish peroxidase (Kirkegaard and Perry Laboratories, Gaithersburg, MD) were used as secondary antibodies. Antibody titres were recorded as index values and calculated according to the following formula:

$$\text{Index value} = \frac{\text{Optical density of sample}}{\text{Optical density of positive control}} \times 100.$$

RNA Extraction

Viral RNA was extracted from 140 μl of serum, bile, 10% fecal suspension, and a 10% suspension of the intestinal contents by using a QIAamp Viral RNA Mini Kit (Qiagen). The final elution was carried out using 50 μl of elution buffer. Viral RNA was extracted from the tissue samples with TRIzol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions.

Semi-Nested Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)

To detect HEV RNA, semi-nested RT-PCR was performed. The 5′-terminal region of ORF1 was amplified using broadly reactive primers [Hagiwara et al., 2007]. For the first round of PCR, the sense primer HE61 (5′-CACRTATGTGGTCGAYGCCATGGAG-3′; R = A or G, Y = C or T) and the anti-sense primer HE51 (5′-GCCKRACYACCACAGCATTCG-3′; K = G or T) were used. This produced an expected fragment of 125 base pairs (bp). For the second round of PCR, the internal sense primer HE50 (5′-AAGGCTCCTGGCRTYAC-

WAC-3′; W = A or T) and the anti-sense primer HE51 were used, producing an expected fragment of 85 bp. Reverse transcription and first-round amplification were carried out using the OneStep RT-PCR Kit (Qiagen). In each reaction, 5-μl aliquots of viral RNA solution were used. The reactions were performed in an Eppendorf Mastercycler (Eppendorf, Hamburg, Germany) under the following conditions: reverse transcription at 50°C for 30 min, denaturation at 95°C for 15 min, 45 cycles of denaturation at 95°C for 15 sec each, annealing at 55°C for 30 sec, elongation at 72°C for 30 sec, and final elongation at 72°C for 7 min. After first-round PCR, 1 μl of the PCR product was amplified under the following conditions: 20 cycles of denaturation at 95°C for 15 sec each, annealing at 60°C for 30 sec, and elongation at 72°C for 15 sec, followed by final incubation at 72°C for 7 min. The amplified second-round PCR products were characterized using 2% gel electrophoresis. A PCR amplicon of 85 bp was determined to be HEV-specific.

Quantitative Real-Time RT-PCR

The copy number of HEV RNA was measured by quantitative real-time RT-PCR according to the technique developed by Jothikumar et al. [2006] with a slight modification. TaqMan® probe (5′-FAM-TGATTCCCAGCCCTTCGC-TAMRA-3′) was designed based on the sequence of the HEV ORF3 region (accession number AB481228) from litter A pig. Five microliters of extracted RNA (equivalent to 1.4 mg of feces or 14 μl of sera) was used per reaction. A 5 μl aliquot of RNA was amplified using the forward primer 5′-GGTGGTTTCTGGGGTGAC-3′ and the reverse primer 5′-AGGGGTTGGTTGGATGAA-3′ in a LightCycler (Roche, Basel, Switzerland) under the following conditions: reverse transcription at 50°C for 30 min, denaturation at 95°C for 15 min, and 45 cycles of amplification, each consisting of 1 sec at 95°C followed by 1 min at 60°C. Viral RNA copy numbers were calculated on the basis of the calibration curve constructed using standard RNA as described below, using LightCycler Software 4.0.

To construct a calibration curve for quantification, in vitro transcribed RNA from the HEV ORF3 region was collected from a cloned plasmid. The copy number of standard RNA was calculated using a spectrophotometer. Preliminary examination using in vitro transcribed RNA showed that the detection limit of quantitative real-time RT-PCR was $10^{3.8}$ copies/g of feces, $10^{2.8}$ copies/ml of serum, and $10^{3.6}$ copies/ml of tissue.

Sequence and Phylogenetic Analysis

Four fecal samples from four pigs in litter A and one fecal sample from sow A, all of which were found to be positive for HEV by nested RT-PCR, were subjected to sequence analysis. The ORF2 region of the viral RNA was amplified using the primers HE044 (5′-CAAGG-HTGGCGYTCKGTTGAGAC-3′; H = A, C, or T) and HE041 (5′-TTMACWGTCRGCTCGCCATTGGC-3′; M = A or C), as described previously [Mizuo et al., 2002]. The PCR products were sequenced directly using the BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA). Sequence analysis was performed using Genetyx-Windows version 7 (Genetyx Corp., Tokyo, Japan). The sequence alignment was generated by CLUSTAL W [Thompson et al., 1994]. The four nucleotide sequences of swine HEV isolates, named swJB-M3, -M5, -M8, and -M10, have been deposited in the GenBank sequence database under the accession numbers AB471965–AB471968. A phylogenetic tree was constructed using prototype sequences of genotype 1, 2, 3, and 4 obtained from GenBank and the neighbor-joining method [Saitou and Nei, 1987], on the basis of a 412-nucleotide partial sequence of the ORF2 region; the tree was drawn using the TreeView program [Page, 1996].

Statistical Analysis

The number of pigs shedding virus in feces, the number with viremia, and the time to seroconversion were compared between litters A and B by using the Wilcoxon rank-sum test. Statistical analysis was performed using the JMP 5.1.2 software (SAS Institute, Inc., Cary, NC). $P \leq 0.05$ was considered statistically significant.

RESULTS

Detection of Anti-HEV IgG and IgA in Serum and Feces

A total of 20 piglets were studied, 10 from litter A and 10 from litter B. Before delivery, sow A tested positive for IgG antibodies specific to the HEV ORF2 protein, but sow B did not. Figure 1 shows the levels of HEV-specific IgG and IgA in the sera of the piglets when they were 1–180 days old. The serum samples from litter A pigs tested positive for both IgA and IgG antibodies on day 1, with ELISA index values of 122.6 and 144.5, respectively; the levels of these antibodies in their sera decreased rapidly until day 50. In contrast, the serum levels of IgG and IgA in litter B pigs were significantly low on day 1, with ELISA index values of 17.4 and 27.5, respectively. The serum IgG levels in the litter B pigs remained low during days 1–50. Seroconversion began on day 60 in litter A pigs and on day 50 in litter B pigs, after the onset of viremia (Fig. 1). The Wilcoxon rank-sum test revealed that there was a significant difference between litters A and B pigs with respect to the time of IgG seroconversion ($P < 0.001$) (data not shown), that is, seroconversion occurred significantly earlier in litter B pigs. The antibody titres peaked on days 90 and 70 in litters A and B, respectively, and then decreased gradually till the end of the study.

HEV-specific fecal IgA to HEV were not detected during the study period (data not shown).

Detection of HEV RNA in Feces and Serum

Pig feces were examined for HEV RNA during days 30–110 by using semi-nested RT-PCR (Fig. 1). On day

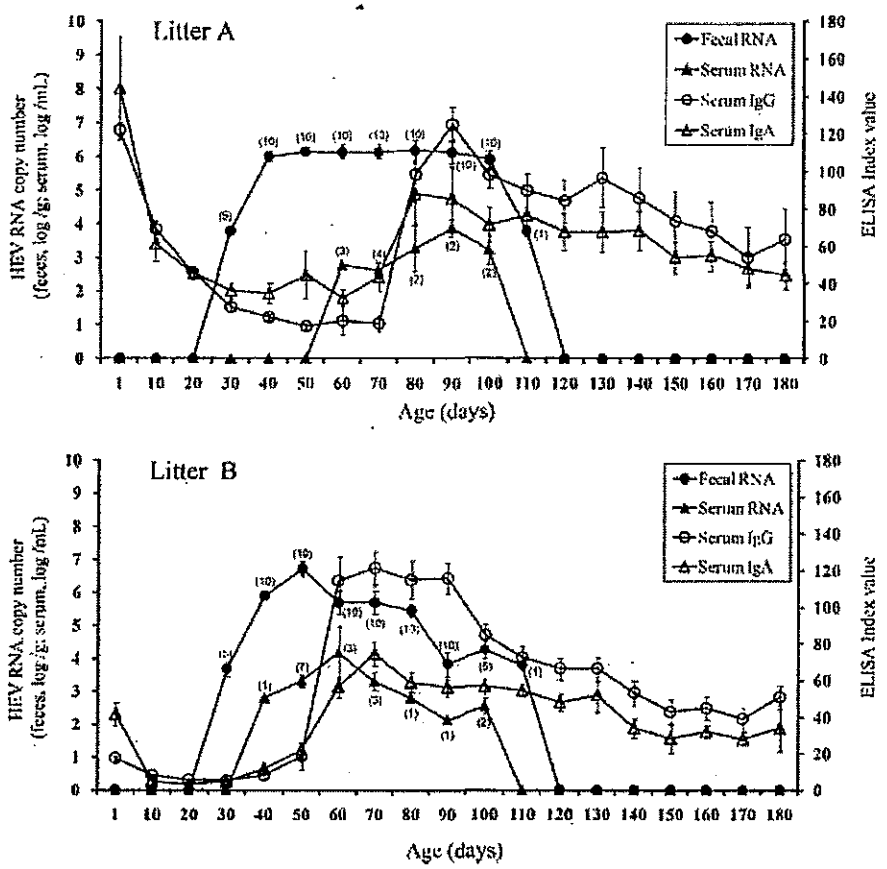

Fig. 1. Hepatitis E virus (HEV) shedding and seroconversion in two litters of pigs. The copy numbers of HEV RNA in feces and serum are shown, along with the enzyme-linked immunosorbent assay (ELISA) index values of anti-HEV IgG and IgA in the serum samples. HEV RNA copy numbers in feces and serum represent the average values among positive animals. The numbers of animals positive for fecal RNA and serum RNA are indicated in parentheses. The levels that were undetectable by quantitative real-time RT-PCR were approximated using the estimated detection limit ($10^{3.8}$ copies/g for fecal RNA, $10^{2.8}$ copies/ml for serum RNA). ELISA index value = (OD of sample/OD of positive control) × 100. Error bars represent standard error.

30, HEV RNA was detected in the feces of five pigs from each litter. During days 40–90, HEV RNA was detected in the feces of all 20 pigs. On day 100, all 10 of the pigs in litter A shed HEV RNA in their feces, but only 5 pigs from litter B did. On day 110, only one pig from each litter was found to be shedding HEV RNA in the feces. No HEV RNA was detected in feces after day 120.

The modified TaqMan® probe, designed to be specific to the present HEV strain, reacted strongly to every sample tested, indicating that the HEV detected in all of the litter A and B pigs belongs to the same strain. The dynamics of fecal shedding of HEV were quantitatively characterized by real-time PCR (Fig. 1). On day 30, HEV RNA could be detected in feces by semi-nested RT-PCR but not by real-time RT-PCR, indicating that the RNA copy number was below the detection limit of quantitative real-time RT-PCR ($10^{3.8}$ copies/g). On day 40, however, HEV RNA increased suddenly to $10^{6.0}$ copies/g in the feces from both litters. The pigs in litter A continued to shed large amounts of HEV RNA (approximately $10^{6.0}$ copies/g) until day 100, whereas the amounts of HEV RNA in the feces of litter B pigs decreased gradually. On day 110, the HEV RNA in the feces from both litters decreased to amounts below the detection limit of real-time RT-RCR.

During the study period, viremia was detected in 7 pigs in litter A and 10 in litter B. The onset of viremia occurred on day 60 in litter A pigs and on day 40 in litter B pigs (Fig. 1). The Wilcoxon rank-sum test showed that this difference between the time of onset of viremia in litter A and B pigs was statistically significant ($P = 0.024$; Fig. 1). Throughout the study, the amounts of HEV RNA in the serum were lower than those in the feces (Fig. 1). The highest serum HEV RNA titre was found on day 90 in a pig from litter A ($10^{4.2}$ copies/ml) and on day 60 in a pig from litter B ($10^{5.6}$ copies/ml).

Time Courses of Changes in Virus Shedding, Viremia, and Serum Antibody Titres

Based on the data obtained on virus shedding and antibody reaction in individual pigs (data of individual pigs not shown), the general time course of HEV infection in domestic pigs can be described as follows (data are expressed as mean (SD; range)): pigs begin to shed HEV in feces on day 30 (27.4; 0–70) after birth and

viremia and seroconversion of serum IgG and IgA occur 33.5 (7.0; 10–60) and 32.3 (7.4; 20–50) days, respectively, after the onset of HEV shedding in feces. HEV shedding in feces continues for 63.5 (7.4; 50–80) days, whereas viremia can appear transiently for 11.8 (12.9; 10–40) days. In this study, virus shedding in feces was observed in all pigs with high antibody titres, whereas viremia was observed in a total of 17 pigs, all of which had relatively low antibody titres. Serum IgG and IgA antibody levels peaked 8.5 (12.0; 0–30) and 6.2 (7.1; 0–20) days, respectively, after seroconversion. After peaking, they decreased gradually but remained detectable during the entire study period, even after the end of viremia and after the pigs stopped shedding virus in feces.

Sequence Analysis

Genomic sequencing of the ORF2 region of virus isolates from four piglets in litter A and from sow A revealed that the virus strains were identical. Phylogenetic analysis of the HEV isolates indicated that they belonged to HEV genotype 3 and that they were clustered with genotype 3_{us}, both of which are related to the strains of swine and human HEV found in the USA (Fig. 2) [Takahashi et al., 2003].

HEV RNA Detection in Tissue Samples From 200 Days Old Pigs

Of the 13 pigs (5 from litter A, 8 from litter B) euthanized on day 200, HEV RNA was detected in the internal organs of 3 pigs by semi-nested RT-PCR: in the gall bladder of one litter A pig, in the mesenteric lymph nodes and liver of one litter B pig, and in the hepatic and mesenteric lymph nodes of another litter B pig. According to real-time RT-PCR, in contrast, none of these samples tested positive for HEV RNA, indicating that the amounts of HEV RNA present in these samples were below the detection limit of real-time RT-PCR, that is, $10^{3.6}$ copies/g.

DISCUSSION

Although there a number of epidemiological surveys of HEV in pigs have been conducted, longitudinal studies of the time course of HEV infection in pigs infected naturally have been quite limited [Meng et al., 1997; de Deus et al., 2008]. The dynamic HEV life cycle in piglets infected naturally can only be evaluated through long-term follow-up studies with quantitative measurements of both HEV RNA and viral-specific antibodies in individual pigs from birth to slaughter. This is the first report on the quantitative dynamics of virus shedding in feces, viremia, and specific serum antibodies that were evaluated in a long-term follow-up study of pigs infected naturally with HEV.

Maternal antibodies, including IgG, IgA, and IgM, that are transmitted via the colostrum have been reported to protect piglets from infection by various pathogens [Andries et al., 1978]. Although maternal antibodies against HEV have been found in piglets born to HEV-positive sows, the protective role of these

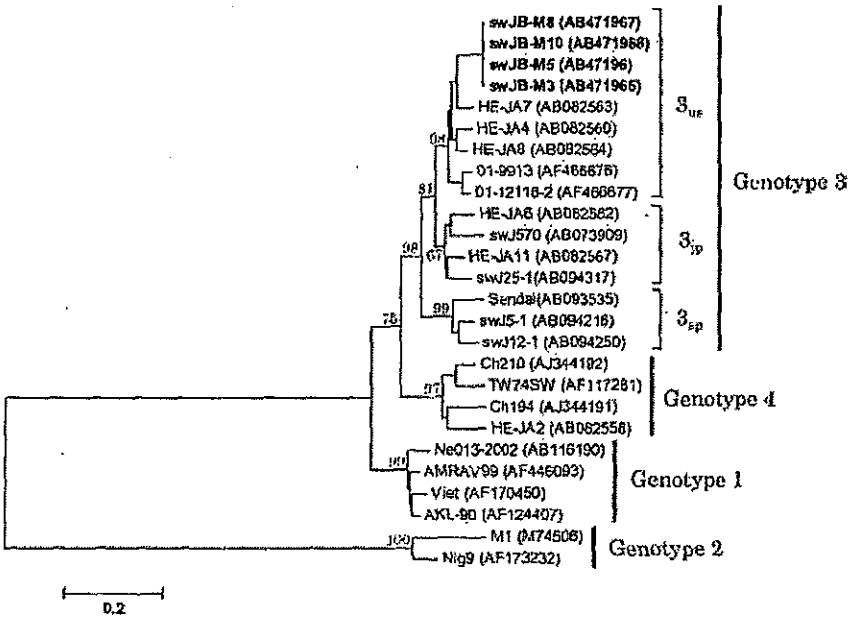

Fig. 2. Phylogenetic analysis of the nucleotide sequence of the ORF2 region of HEV (412 bp). Intragenotypic classification of genotype 3 (3_{us}, 3_{sp}, and 3_{jp}) was done according to a previous report [Takahashi et al., 2003]. HEV isolates obtained in this study (swJB-M3, -M5, -M8, and -M10) are indicated in bold letters. Prototype sequences of genotype 1, 2, 3, and 4 from GenBank are given with their accession numbers. Phylogenetic tree was constructed using the neighbor-joining method. The bootstrap values (n = 1,000) are given for the major nodes.

maternal antibodies has not yet been determined [Meng et al., 1997; Kasorndorkbua et al., 2003]. In the present study, two litters of piglets—one with maternal antibodies and the other without—were studied to determine whether the presence of maternal antibodies affected HEV shedding. The results showed that virus shedding in feces occurred from days 30 to 110 in both litters, though a significant delay in the onset of both seroconversion and viremia was observed in the litter A piglets, which had maternal antibodies. Although serum IgG and IgA of litter B pigs were slightly reactive to the HEV antigen on day 1, as determined using ELISA, this reactivity was considered to be non-specific because of the presence of large quantities of maternal antibodies to various pathogens.

The similarity between the litters in terms of the kinetics of fecal virus shedding indicates that maternal antibodies do not protect piglets from primary HEV infections in the early days of their lives. Interestingly, another study has reported that maternal antibodies can have an immunosuppressive effect [Siegrist, 2003]. Although the immunological mechanisms responsible for such an adverse affect remain unclear, it is possible that in this study, maternal antibodies delayed the piglets' immune responses against HEV infection, causing the delay in seroconversion that was seen in the litter A piglets.

Since this study followed up domestic pigs raised under normal conditions, it was not obvious whether HEV infection in the two litters occurred under similar conditions. Therefore, it was difficult to determine the exact effect of maternal antibodies on the kinetics of HEV infection. Further studies are required to clarify the role of maternal antibodies.

In previous epidemiological studies, fecal and serum HEV RNA and serum antibodies have been used as markers of HEV infection [Meng et al., 1998; Cooper et al., 2005]. In the present study, fecal RT-PCR was far more sensitive than serum RNA testing in detecting HEV RNA. Indeed, all of the pigs shed high copy numbers of HEV RNA in feces for 70–80 days, whereas viremia appeared transiently the copy number of the RNA shed was low. In addition, viremia remained undetectable in three pigs. It is possible that the sampling schedule, particularly the 10-day intervals between sampling days, may have led to the low rate of serum RNA detection. Fecal RT-PCR, in contrast, does not appear to have the same limitations, and can be recommended as an indicator of current HEV infection based on early occurrence, high viral load, and long duration of HEV RNA in feces. It may prove especially useful in quarantine situations when pigs are introduced to another herd.

The reactivity of the modified TaqMan® probe used in this study, which was designed according to the sequence of HEV obtained from litter A pigs, to the present HEV suggested that all the pigs were infected with the same viral strain. The strain in question was found to belong to genotype 3_{us}, which is related to the HEV strains found in humans and pigs in the USA. It is one of the three clusters into which genotype 3 has been divided: the other two are 3_{sp} and 3_{jp} [Takahashi et al., 2003]. HEV genotypes 3 and 4, both of which have been reported in Japan [Takahashi et al., 2003], are considered to be zoonoses, causing hepatitis in humans; genotype 4 has been reported to cause a particularly severe form of hepatitis [Ohnishi et al., 2006]. Some phenotypic variations between genotypes 3 and 4 have been reported. Though the results of the present study contribute significantly to the understanding of the infection of HEV genotype 3 in pigs, further studies on genotype 4 and the other two sub-clusters of genotype 3 will be required to develop a conclusive strategy to control HEV infection in domestic pigs.

In this study, HEV RNA was detected in the liver, gall bladder, or lymph nodes of 3 of 13 pigs examined on day 200, that is, 3 months after the pigs had stopped shedding the virus. The prevalence of HEV RNA in pig livers at grocery stores in Japan and the USA has been reported as 2% and 11%, respectively [Yazaki et al., 2003; Feagins et al., 2007]. Furthermore, HEV isolated from pig livers at grocery stores in the USA was found to be infectious. This could create public health problems stemming from HEV contamination in slaughtered pigs, even if no HEV shedding is observed before slaughter. In addition, the long-term shedding of large amounts of virus, which was observed in this study, supports the idea that farm workers exposed to infected pigs could be infected directly because of a contaminated working environment [Zheng et al., 2006]. Controlling HEV infection on pig farms would therefore help decrease the likelihood of the disease being transmitted to people.

CONCLUSIONS

To understand the time course of HEV infection in domestic pigs, pigs infected naturally with HEV genotype 3 were followed up from birth to slaughter age. These pigs shed HEV in feces when they were 30–110 days old, and developed viremia when they were 40–100 days old. Seroconversion of anti-HEV IgG and IgA antibodies occurred 20 days after the onset of viremia. HEV RNA in feces peaked at approximately $10^{6.0}$ copies/g 10 days after the onset of fecal shedding. The kinetics of HEV infection seemed to be influenced by the presence of maternal antibodies. At day 200, 3 of 13 pigs (23%) still had detectable levels of HEV RNA in their livers, gall bladders, and/or lymph nodes, though they had stopped shedding the virus in feces. Although the amounts of HEV RNA in these tissues were low, the presence of HEV in the internal organs after the virus shedding has stopped could have important implications for the prevention of virus transmission to people through food. The time course of HEV infection revealed in this study will be very helpful in understanding the kinetics of HEV transmission from pigs to humans, and in developing a control strategy to prevent zoonotic HEV infection from pigs.

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研究報告の概要

パルボウイルスPARV4は、ヒト宿主のパルボウイルス科の種類として最近記載された。
血中のPARV4の保有率を調査するため、定量的TaqMan PCRが開発され、様々な集団からのプラズマ、血清または全血について検討した。８つの検体がPARV4陽性であった（高いコピー数が１つ）。高力価陽性血漿は約 5 × 10^8genome equivalents/mLのウイルス量であった。間接免疫蛍光法でPARV4抗体陽性確認された２つのヒト血清が高力価ヒト血漿で自然のPARV4を視覚化する試みとして免疫電子顕微鏡に使用された。PARV4粒子はこれら２つの血清のうち１つで観察された。
我々の知る限りでは、自然のPARV4が可視化されたのはこれが初めてのことである。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(2) 溶血性・失血性貧血の患者〔ヒトパルボウイルスB19の感染を起こす可能性を否定できない。感染した場合には、発熱と急激な貧血を伴う重篤な全身症状を起こすことがある。〕
(3) 免疫不全患者・免疫抑制状態の患者〔ヒトパルボウイルスB19の感染を起こす可能性を否定できない。感染した場合には、持続性の貧血を起こすことがある。〕
2. 重要な基本的注意
(1)略
1) 血漿分画製剤の現在の製造工程では、ヒトパルボウイルスB19等のウイルスを完全に不活化・除去することが困難であるため、本剤の投与によりその感染の可能性を否定できないので、投与後の経過を十分に観察すること。
5. 妊婦、産婦、授乳婦等への投与
妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。〔妊娠中の投与に関する安全性は確立していない。本剤の投与によりヒトパルボウイルスB19の感染の可能性を否定できない。感染した場合には胎児への障害（流産、胎児水腫、胎児死亡）が起こる可能性がある。〕。

報告企業の意見	今後の対応
ヒト血清でPARV4が免疫電子顕微鏡法により可視化された最初の報告である。 パルボウイルス４（PARV4）は、パルボウイルス科パルボウイルス亜科のどの属にも分類されないウイルスである。また、PARV4が発見されたのは2005年であり、PARV4及びその関連変異型であるPARV5の病原性は現時点では明らかではない。血漿分画製剤からの伝播事例は報告されていないが、英国で1970年代及び1980年代に製造された第Ⅷ因子製剤からPARV4が検出されている。万一、原料血漿にPARV4が混入した場合、 CPV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は、PARV4の製造工程における不活化・除去が十分であるとはいえないので、今後注意深く追加情報をフォローする必要があると考える。	PARV4 に関する追加情報の入手に努める。

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Short Communication

Parvovirus PARV4 visualization and detection

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The parvovirus PARV4 is the most recently described member of the family *Parvoviridae* that has a human host. To investigate the prevalence of PARV4 in blood, a quantitative TaqMan PCR was developed and plasma, sera or whole blood from a variety of population groups were examined. Eight samples were positive for PARV4, one at high copy number. The high-titre-positive plasma had an approximate viral load of 5×10^8 genome equivalents ml^{-1}. Two human sera, identified as PARV4 antibody-positive by indirect immunofluorescence, were used in immune electron microscopy to try to visualize native PARV4 within the high-titre human plasma. PARV4 particles were observed using one of these two sera. To our knowledge, this is the first time that native PARV4 has been visualized.

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PARV4 is the most recently described member of the family *Parvoviridae* that has a human host (Jones *et al.*, 2005). It is currently a virus without any apparent disease association (Fryer *et al.*, 2007a). It was identified by a random amplification of nucleic acids extracted from a patient with acute virus infection who was co-infected with hepatitis B virus (HBV) (Jones *et al.*, 2005). Two further genotypes of PARV4 have now been described (Fryer *et al.*, 2006; Simmonds *et al.*, 2008). Very little is known about PARV4 and its biology. It was initially described as 'not closely related to any known parvoviruses' (Jones *et al.*, 2005). However, further work has shown that PARV4 is most similar to the recently discovered bovine and porcine HoKo viruses (Lau *et al.*, 2008) and that it groups together with these and also the more distantly related Myanmar erythrovirus (Hijikata *et al.*, 2001), another porcine virus.

The human parvovirus B19 can be present at very high titres in the blood of infected individuals. Plasma and whole-blood samples thought likely to harbour PARV4, namely samples being tested for hepatitis B or C or from human immunodeficiency virus (HIV)-positive patients, were therefore examined. For comparison, samples from UK blood donors were also tested. All samples analysed were anonymized. The frequency of detection of PARV4 in the UK blood-donor population is expected to be low, based on limited data from previously reported surveys (Fryer *et al.*, 2007b; Simmonds *et al.*, 2007; Schneider *et al.*, 2008), although large, formal studies have yet to be performed.

Nucleic acid was extracted from plasma, serum or whole blood, either manually using Qiagen blood kit spin columns or on a Qiagen BioRobot. A quantitative TaqMan PCR (Q-PCR) was designed with the aid of Beacon Designer 3 software (Premier Biosoft International) and optimized for open reading frame (ORF) 2 of PARV4. The Q-PCR was performed on an ABI 7500 platform (Applied Biosystems), using ABgene reagents, and was shown to have linearity of detection over the range 10^1–10^8 copies ml^{-1}, with a limit of sensitivity of 50 copies ml^{-1}. An oligonucleotide positive control of the target sequence was synthesized (Eurofins MWG Operon), but was subsequently replaced by a biological standard: a high-titre-positive plasma, once one had been identified. Murine cytomegalovirus was used as an internal extraction and amplification control. Samples tested and results are shown in Table 1. Q-PCR conditions were 95 °C for 15 min followed by 45 cycles of 95 °C for 15 s, 60 °C for 60 s. The TaqMan primers used were PWTPARV4.1F (5′-CCTCTCCGAGTCCATTAGCAGA-3′; 1937–1958) and PWTPARV4.1R (5′-GCTCCATACCTTTCAGCAGTTTC-3′; 2069–2047). The TaqMan probe was PWTPARV4-probe (5′-FAM-CGCCGCCGAGGACACCAGACAGT-TAM-3′; 1961–1983). Sequences are numbered according to GenBank accession no. AY622943.

In total, PARV4 DNA was detected in eight samples. Quantification of PARV4 in samples was initially carried out against a $\log_{10}$ dilution series of the oligonucleotide positive control and subsequently against a high-titre-positive control PARV4 plasma (designated plasma 129). This plasma had a viral load of 5×10^8 DNA copies ml^{-1} and was from a hepatitis C virus (HCV) RNA-positive, HCV antibody-negative patient. Viral loads of all eight positive samples are shown in Table 2. The four samples that had a viral load $\geqslant$760 copies ml^{-1} were amplified successfully for sequencing, but those with viral loads of $\leqslant$285 failed to amplify. Three samples (129, 135 and 342)

Table 1. Samples tested for PARV4 by Q-PCR

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; IVDU, intravenous drug user.

Population group tested	*n*	No. (%) PARV4-positive by Q-PCR
HCV antibody-negative, RNA-positive blood donors (HCV window phase)	94	3 (3.2)
Samples for routine HCV RNA testing	88	2 (2.3)
Samples for routine HBV DNA testing	140	2 (1.4)
HIV-1 proviral DNA-positive IVDUs	50	0*
Samples for routine HIV-1 RNA viral load testing	88	1 (1.1)*
UK blood donors – 20 pooled DNA extracts from 96 donors	–	0

*Overall detection frequency of 1 in 138 (0.7 %) in HIV-1-positive samples tested.

were amplified by using a semi-nested PCR to ORF2, initially with primers PARV4Seq1 (5′-CCGGAACC-TTCAAGTCAAGCCA-3′; 2465–2486) and PARV4Seq2 (5′-CCGCTCAAGGTCTGGTTCAACAA-3′; 3010–2988), followed by PARV4Seq1 and PARV4Seq3 (5′-CAAGG-TGGACTCCGACATCTGG-3′; 2954–2933). The resulting 490 bp fragments from these three samples were then sequenced with PARV4Seq1 and PARV4Seq3. All three were typed as PARV4 genotype 1. Sample 168 was also confirmed as PARV4 genotype 1 by sequencing with primers PVORF1F and PVORF1R (Fryer *et al.*, 2006). Sequence similarity was determined by using the FASTA program at http://www.ebi.ac.uk and searching the Viral Database.

For electron microscopy, 300 µl high-titre plasma 129 was centrifuged at 48 000 *g* for 45 min. The resultant pellet was resuspended in distilled water and stained with 1.5 % phosphotungstic acid (PTA), pH 6.6. Grids were examined in a Philips 420 transmission electron microscope fitted with an AMT XR60 digital imaging system. Parvovirus particles were not seen. Small, round, featureless virus particles, such as parvoviruses, however, can be extremely difficult to detect, particularly amongst the background debris of plasma or serum. Immune electron microscopy (IEM), a technique that has been employed successfully to detect other small viruses, including parvovirus B19 (Cossart *et al.*, 1975; Curry *et al.*, 2006), was used in a further attempt to visualize the native PARV4 particles. Two serum samples containing antibody to PARV4 had been identified in our laboratory on the basis of their reactivity in an indirect immunofluorescence test (R. P. Parry, unpublished data). These two antibody-positive sera were each mixed with an aliquot of high-titre plasma 129, incubated at room temperature for 1 h and centrifuged at 48 000 *g* for 45 min. Pellets were resuspended in distilled water and stained with 1.5 % PTA or 2 % methylamine tungstate, pH 6.6, and examined as described above. Parvovirus-like particles that had been aggregated into clumps by one of the sera were seen (Fig. 1a). The particles measured around 20–22 nm in diameter and were morphologically typical of parvoviruses. For comparison, recombinant PARV4 capsids expressed in *Sf*9 cells by baculovirus (PARV4 capsids provided by Dr Kevin E. Brown, Health Protection Agency) can be seen in Fig. 1(b). The recombinant capsids and the particles found in plasma 129 are similar in size and have the characteristic hexagonal appearance of parvoviruses. Stain has penetrated into several of the recombinant particles, as would be expected, whereas the particles from plasma 129 appear complete.

Table 2. Viral loads of PARV4-positive samples

Sample	Viral load (DNA copies ml^{-1})				
	PARV4	HCV	HCV genotype	HBV	HIV
129	5×10^8	2.70×10^3	2b		
135	760	1.22×10^6	3a		
168	4.6×10^3	1.05×10^5	3a		
A5	1	5.04×10^6			
C10	5	+		+	
342	3.4×10^3			+	+
490	170			+	
H10	285				+

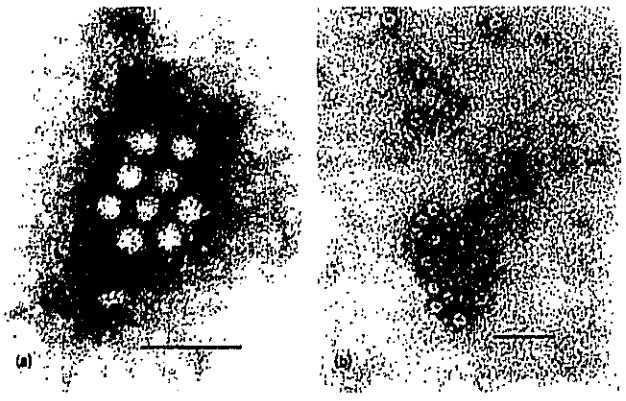

Fig. 1. Electron micrographs of parvovirus particles. (a) IEM of particles seen in plasma 129; antibody can be seen coating the particles. Stained with methylamine tungstate. (b) Recombinant viral capsids of PARV4, stained with PTA. Bars, 100 nm.

The antibody-aggregated clumps of particles observed in plasma 129 resembled the appearance of B19 virus when visualized by IEM. Plasma 129 and the two serum samples containing antibody to PARV4, however, were negative by PCR for B19 and human bocavirus, and it was concluded that the particles seen were PARV4.

Failure to detect virus particles with the second serum may have been related to the titre of the reagents. The sera were only tested at one dilution by immunofluorescence, but results from a prototype ELISA suggested that this second serum had a lower antibody titre to PARV4. For IEM purposes, the titre of PARV4 in plasma 129 was also low and probably near the limits of sensitivity for IEM detection. This may account for the fact that virus particles from this sample were not seen with PTA staining, rather than any difference between the stains.

PARV4 was detected at low frequency in samples from the blood of patients infected with HIV-1, HCV and HBV. In a study of the three human parvoviruses, B19, bocavirus and PARV4, in HIV-1-infected and non-infected individuals, Manning *et al.* (2007) established that a high proportion (70.8 %) of HIV-1-infected individuals harbour PARV4 in lymphoid and bone-marrow tissues, but none had viraemia. It is interesting to note that seven of the eight individuals in whom PARV4 was detected in the plasma were co-infected with hepatitis viruses (Table 1). The original discovery of PARV4 was in an intravenous drug user (IVDU) from the USA. The 94 HCV window-phase plasma samples analysed in our study for PARV4 were USA-sourced plasmas and the donors may have been remunerated financially. PARV4 was not detected in any of the UK blood donors tested.

These data contrast with those of a recent study in Thailand, which revealed PARV4 in sera both from IVDUs (8 %) and in blood donors (4 %) (Lurcharchaiwong *et al.*, 2008). Both of these figures are higher than those reported previously from the UK and elsewhere. It is again of interest that the majority of the PARV4-positive IVDUs in the Thai study, seven of eight (87.5 %), were HCV-co-infected; this may of course simply be coincidental, as the proportion of HCV positives within this group of IVDUs was very high (88.6 %). The determination of the prevalence of past infection with PARV4 in these different populations awaits the results of serological studies. Whether co-infection is a reflection of the natural history of the virus infection, a commonality of transmission routes or a consequence of underlying disease also awaits further elucidation.

The high viral load found in sample 129 (5×10^8 DNA copies ml^{-1}) suggests that this patient was experiencing active virus replication and may represent primary infection. The only other known high-level samples were from the original patient, which contained 6 $\log_{10}$ copies ml^{-1} (E. Delwart, personal communication), and from archived plasma pools with 6.58 $\log_{10}$ copies ml^{-1} (Fryer *et al.*, 2007b). It is not known whether the lower viral loads found in this (Table 2) and other studies represent virus replication, waning virus levels as antibody develops or a chronic virus carrier state. Fluctuating low levels of B19 DNA were observed in the plasma of 7.9 % of patients with congenital haemoglobinopathy. It has been postulated that this may be due to minor reactivation from sites of virus persistence (Lefrère *et al.*, 2005), which may also explain the 1 % of pregnant women (Lefrère *et al.*, 2005) and blood donors (Candotti *et al.*, 2004) who are B19 DNA-positive. A similar phenomenon may be occurring with PARV4. Further development of antibody assays and follow-up studies on PARV4-positive patients are required to investigate these hypotheses.

The high level of sequence conservation observed within the samples that tested positive for PARV4 is consistent with the findings of other groups. This argues for a recent evolutionary origin or a high conservation pressure. Manning *et al.* (2007) observed an apparent temporal shift in PARV4 genotypes, with genotype 1 representing the current 'modern' infection and genotype 2 the older strain. Study subjects positive for genotype 1 were all born after 1958 and those infected with genotype 2 were born between 1949 and 1956. A similar situation has recently been described for B19 variants, with genotype 1 superseding genotype 2 in the skin (Norja *et al.*, 2006). Demographic information on the patients and donors in our study was not available, as all samples were obtained in a random, anonymized manner.

The three genotypes of PARV4 now identified (Simmonds *et al.*, 2008) have not yet been related to any disease. However, 8 years elapsed between the discovery of B19 and its association with fifth disease (erythema infectiosum) (Anderson *et al.*, 1983). Our findings and those of others suggest that a parenteral transmission route is likely. It remains to be seen where PARV4 replicates and whether there are any disease associations.

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 7. 8	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	Houfar MK, Mayr-Wohlfart U, Sireis W, Seifried E, Schrezenmeier H, Schmidt M. XXXIst International Congress of the ISBT; 2010 Jun 26-Jul 1; Berlin, Germany	公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)			ドイツ

研究報告の概要

○ヒトパルボウイルスB19(B19)DNA陽性血液製剤の感染性

背景:2000年以降、ドイツのウルム研究所では、B19に対する供血者NATスクリーニングを供血6～8週間後(すなわち血液製剤供給後)に実施している。本研究において、輸血された血液製剤中のウイルス濃度との関連においてB19陽性血液製剤の感染性を評価した。

研究方法:後方視的研究において、受血者を次の2群に分けた:A) B19ウイルス量≦10^5IU/mLの血液製剤受血者;B) B19ウイルス量＞10^5IU/mLの血液製剤受血者.

VP-1uゲノム領域の系統発生解析を、B19 DNA陽性供血者と受血者の対で実施した。また、すべての検体のIgM、IgG抗体を調べた。

結果:B19 DNAはB群の赤血球濃厚液受血者18名 中9名に検出されたが、A群の受血者16名にはB19 DNAは検出されなかった(p=0.016)。系統発生解析では、供血者と受血者間で同一ゲノム配列を示した。

結論:血液製剤によるB19伝播は、ウイルス濃度と中和抗体価に相関することが分かった。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
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
輸血された血液製剤中のヒトパルボウイルスB19(B19)濃度と感染性について評価を行ったところ、B19伝播は、ウイルス濃度と中和抗体価に相関することが分かったとの報告である。 パルボウイルスB19は脂質膜のない小型DNAウイルスである。これまで本製剤によるB19感染の報告はない。B19は耐熱性とされていたが最近、液状加熱で容易に不活化できることが明らかにされた。本製剤の製造工程には、当該工程が含まれている。また最終製品についてB19-NAT陰性であることを確認していることから、本製剤の安全性は確保されている。	日本赤十字社では、以前よりRHA法によるB19抗原検査を導入しウイルス量の多い血液を排除してきた。2008年からさらに感度の高い化学発光酵素免疫測定法(CLEIA)を導入し、10^6IU/mL以上のB19を含む血液を陽性と判定し排除するものであることから、現在は原料血漿プール中のウイルス濃度が10^4IU/mL以下となっている。今後も輸血用血液及び血漿分画製剤の安全性向上のために努力する。

Materials: Test results of all blood samples from 929 RR blood donors recorded during the 2006–2009 period obtained at CITM by testing a total of 313,564 blood units were analyzed.
Results: In 929 RR donors, HCV predominated (51%) due to the use of combined anti HCV/HCV Ag-Ab test, followed by HIV (18.9%) and a comparable proportion of HBsAg and anti TP RR donors (14.4% and 15.8%, respectively). The HBsAg test yielded the highest rate of confirmed reactivity (42%), followed by syphilis-EIA (22.4%) and the lowest rate for HCV and HIV (4.4% and 1.1%, respectively). Table 1 summarizes the results of all RR donors analyzed during the study period, showing that 742 (79.9%) RR donors met the requirements for subsequent blood donation. In Table 2, next donations by these 742 donors are classified as follows: 475 (64%) presented for donation, 246 (51.8%) of them were seronegative and 229 (48.2%) showed repeat reactivity. Repeat reactivity was later recorded in 4 of 246 donors having continued with blood donation.

Table 1

2006-2009	HBV	HCV	HIV	SYPH.	Total	%
RR DONORS	134	473	175	147	929	100.0
Permanently deferred confirmed positive	56	21	2	33	112	12.0
Permanently deferred confirmed indetermined	3	28	2	9	42	4.5
Temporarily deferred/ To follow up	2	19	7	5	33	3.6
Free to donate/ Confirmed negative/flagged	73	405	164	100	742	79.9

Table 2

2006-2009	HBV	HCV	HIV	SYPH.	Total	%
Presented for donation	58	233	122	62	475	64.0
Next donations negative	33	119	65	29	246	51.8
Next donations reactive	25	1114	57	33	229	48.2

Conclusions: Testing for blood transmissible infections yielded nonspecific reactivity in the majority of 929 RR donors and repeat reactivity in nearly half of subjects (HBV 43%, HCV 48%, HIV 46% and syphilis 53%). None of RR donors developed infection (PCR negative) on follow up, whereas blood unit reactivity was recorded in 4 of 246 RR donors having continued with blood donation. Thus, the use of PCR on their reinclusion in the donor pool is justified. Further follow up in 229 blood donors scheduled for monitoring and additional testing resulted in permanent deferral in 108 and temporary deferral in 97 donors, whereas subsequent donation was approved in 24 donors.

P-0516

INFECTIVITY OF B19 DNA POSITIVE BLOOD PRODUCTS

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Background: Since 2000, blood donor screening for B19 by NAT at the Ulm Institute has been conducted 6–8 weeks post donation, i.e. after transfusion of cellular blood products whereas at the Frankfurt Institute all donations are screened before releasing any blood product. In the current study, we evaluated the infectivity of B19 positive blood products in relation to the virus concentration in the transfused blood component.
Study design: In a retrospective study, recipients were classified into two groups (A: transfused with blood products with B19 virus load less than 10^5 IU/ml; B: transfused with blood products with B19 virus load $>10^5$ IU/ml). Phylogenetic analyses were done for B19 DNA positive donor and recipient pairs in the variant VP-1u genome region. All samples were investigated for IgM and IgG B19 antibodies.
Results: B19 DNA was detected in 9 out of 18 recipients of red blood cell concentrates from group B whereas none out of 16 recipients from group A were B19 DNA positive ($P = 0.016$). Phylogenetic analysis demonstrated identical genome sequences between donors and recipients.
Conclusions: B19 transmission by cellular blood products correlates with the virus concentration as well as with the concentration of neutralizing antibodies. As a consequence, blood donor screening for B19 by mini-pool NAT should be implemented for all products in order to discard all donations with a high virus burden and to enable transfusion of B19 negative blood products for at-risk patients.

P-0517

WHO WORKSHOPS ON DEVELOPING NATIONAL SYSTEMS FOR 100% QUALITY-ASSURED SCREENING OF BLOOD DONATIONS FOR TRANSFUSION-TRANSMISSIBLE INFECTIONS

Abu Amin N, Dhingra N

World Health Organization, Geneva, Switzerland

Background: The provision of safe blood and blood products for transfusion or manufacturing use involves a number of processes, from the selection of blood donors and the collection, processing and testing of blood donations to its administration to patients. There is a risk of error in each process in this "transfusion chain"which can have serious implications for transfused patients. Thus, while blood transfusion can be life-saving, there are associated risks, particularly the transmission of bloodborne infections. It is the responsibility of governments to assure a safe and sufficient supply of blood and blood products for all patients requiring transfusion. However, in 2007, 41 countries are not able to screen all blood donations for one or more of the transfusion-transmissible infections (TTIs) – including HIV, hepatitis B, hepatitis C and syphilis.
Aim: The main aims of the WHO workshops are to: provide an opportunity for the sharing of experience among countries on the challenges and strategies in developing national systems for quality-assured blood screening; identify needs and areas of concern in strengthening national blood screening programmes; develop country action plans for priority activities for national blood screening programmes, and make recommendations to international organizations for supporting countries to meet their needs in achieving 100% quality-assured screening of donated blood.
Methods: WHO Blood Transfusion Safety Programme had organized two 3-day workshop on "Developing National Systems for 100% Quality-Assured Screening of Donated Blood for Transfusion-Transmissible Infections". The WHO document, "Recommendations on Screening Donated Blood for Transfusion-Transmissible Infections" were used as the basis of the training workshop.
Results: Sixty participants from 25 countries in the African, South-East Asian and Western Pacific regions attended the workshops. These represent the countries that were not able to screen all donated blood for major transfusion-transmissible infections or to perform screening within a quality system. Invited participants from each country will include the national blood programme manager and a senior laboratory manager in the blood transfusion service (medical/scientific/technical) who is involved in setting up national systems for the quality-assured screening of donated blood. The working methodology of the workshop will include country presentations, group work and the development of country plans.
Conclusions: The workshops were able to facilitate the sharing of experience among countries on the challenges and strategies in developing national systems for quality-assured blood screening; identify variations in screening strategies, practices and areas of concern of the countries; provide opportunity for participants to develop country action plans for priority activities to strengthen national blood screening programmes, and strengthen the strategies and capacity of international organizations and institutions to respond to countries' needs on policy and technical guidance in supporting countries to meet their needs in achieving 100% quality-assured screening of donated blood.

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
				2010. 5. 7	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		公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)		BID Jnl. Vol.16 No.5	米国

研究報告の概要

○ヒトスジシマカにおけるLa Crosseウイルス(LACV)(2009年米国テキサス州ダラス)
2009年8月にテキサス州ダラスで採取した、ヒトスジシマカにおけるLACVについて報告する。LACVは主にAedes triseriatusが媒介する、北アメリカでの小児脳炎の主要な原因である。しかし近年、LACV脳炎が南東部地域で増加し、南部でも報告されている。同時にアジアからの外来種であるヒトスジシマカが増加しているが、今までヒトスジシマカとLACV伝播の関連は不明であった。今回の調査で、テキサス州ダラスで採取したヒトスジシマカからLACVが検出された。これまで流行が確認されていた範囲外で、外来性の蚊に当該ウイルスが認められたことは、公衆衛生上の懸念である。

報告企業の意見	今後の対応
2009年8月にテキサス州ダラスで採取した、外来種であるヒトスジシマカからLa Crosseウイルスが検出されたとの報告である。 La Crosseウイルスはブニヤウイルス科の脂質膜を持つRNAウイルスである。これまで、本製剤によるLa Crosseウイルス感染の報告はない。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。	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。

使用上の注意記載状況・その他参考事項等

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血液を原料とすることに由来する感染症伝播等

La Crosse Virus in *Aedes albopictus* Mosquitoes, Texas, USA, 2009

Amy J. Lambert, Carol D. Blair, Mary D'Anton, Winnann Ewing, Michelle Harborth, Robyn Seiferth, Jeannie Xiang, and Robert S. Lanciotti

We report the arthropod-borne pediatric encephalitic agent La Crosse virus in *Aedes albopictus* mosquitoes collected in Dallas County, Texas, USA, in August 2009. The presence of this virus in an invasive vector species within a region that lies outside the virus's historically recognized geographic range is of public health concern.

La Crosse virus (LACV) is the most common cause of arthropod-borne, pediatric encephalitis in North America. A member of the California serogroup within the family *Bunyaviridae* and the genus *Orthobunyavirus*, LACV is enveloped and contains a negative-sense, tripartite genome with segments designated small (S), medium (M), and large (L). Cases of LACV-associated encephalitis, which can be fatal, occur within the geographic range of its principal vector, *Aedes triseriatus* mosquitoes. This native tree-hole breeding mosquito is distributed throughout wooded regions east of the Rocky Mountains within the United States. Historically, most LACV-associated encephalitis cases have occurred in upper midwestern states, including Wisconsin, Illinois, Minnesota, Indiana, and Ohio (Figure 1). In recent years, LACV encephalitis activity has increased above endemic levels in regions of the southeastern United States, including West Virginia, North Carolina, and Tennessee (Figure 1) (*1*). In addition, recent cases of LACV encephalitis have been reported as far south as Louisiana, Alabama, Georgia, and Florida (Figure 1).

Ae. albopictus is an invasive mosquito species that was first discovered in Houston, Texas, in 1985 (*2*); having apparently arrived in the United States in a shipment of used tires from Asia (*3*). An opportunistic container-breeder, its vector competence for many arthropod-borne viruses (arboviruses), including LACV, and its catholic feeding habit have made the invasion of *Ae. albopictus* mosquitoes disconcerting to researchers, who have warned of the potential for an increased incidence of vector-borne diseases as a result (*4*,*5*). Since 1985, the geographic distribution of these mosquitoes has grown to include most of the southeastern United States. The concurrent increase in LACV encephalitis activity has led to speculation on the possible transmission of LACV by *Ae. albopictus* mosquitoes as an accessory mechanism to the historically recognized transmission by *Ae. triseriatus* mosquitoes (*6*). LACV has been isolated from *Ae. albopictus* mosquitoes in Tennessee and North Carolina in 1999 and 2000, respectively, during a period of greatly increased LACV activity in those areas (*6*). However, the role of this species in LACV transmission remains unknown.

We report the isolation of LACV from a pool of 3 *Ae. albopictus* mosquitoes collected outside the known geographic range of the virus, in Dallas County, Texas, on August 13, 2009 (Figure 1). This is one of only several isolations of LACV within the state; the first isolate was derived from a pool of *Ae. infirmatus* mosquitoes collected in Houston in 1970 (*7*). After the identification of LACV in the Dallas pool, an additional isolation of LACV was made from a mixed pool of 29 *Ae. albopictus* and 2 *Ae. triseriatus* mosquitoes collected in Fort Bend County, Texas, in October 2009 (Figure 1). The Fort Bend County location is relatively near the site of collection of the 1970 Texas

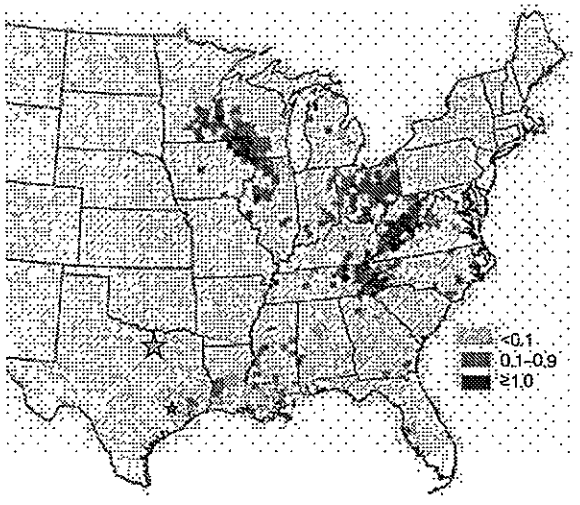

Figure 1. Geographic distribution of La Crosse virus (LACV) in accordance with the habitat range of *Aedes triseriatus* mosquitoes in the United States as inferred from the California serogroup virus neuroinvasive disease average annual incidence by county, 1996–2008. Incidence rates are shown in shades of blue. Dallas County and Fort Bend County locations of the 2009 LACV isolations from pools containing *Ae.albopictus* and *Ae. triseriatus* mosquitoes are indicated by green and red stars, respectively. Data and figure adapted from the Centers for Disease Control and Prevention website (www.cdc.gov/lac/tech/epi.html).

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LACV-positive pool and the known geographic distribution of LACV activity in southeastern Texas and Louisiana (Figure 1). Taken together, our results represent an unprecedented number of LACV findings within the state of Texas.

The Study

As part of ongoing arbovirus surveillance efforts, the City of Dallas Vector Control Division collected 65 mosquitoes in a gravid trap at the edge of a wooded area near a residential district in Dallas County on August 13, 2009. Upon their receipt at the Texas State Department of Health Services, none of the mosquitoes was viable. The mosquitoes were sorted and identified by sex. Female mosquitoes were grouped into 3 pools by species: pool no. AR6318, consisting of 50 *Culex quinquefasciatus* mosquitoes, pool no. AR6319, consisting of 3 *Ae. albopictus* mosquitoes; and pool no. AR6320, consisting of 1 *Ae. triseriatus* mosquito.

Generated pools were macerated in 1.5 mL of bovine albumin diluent arbovirus medium followed by 2 rounds of centrifugation at 10,000 rpm for 5 min each. Between each round of centrifugation, a rest period of 15 min was used to facilitate pellet formation. After centrifugation, 50 µL of the resultant supernatant was injected onto BHK and Vero cells. These cells were incubated at 37°C and examined for cytopathic effect (CPE) over the next 10 days. At day 5 postinoculation, Vero cells inoculated with the supernatant derived from pool no. AR6319 (*Ae. albopictus*) demonstrated marked CPE. This condition represented a preliminary virus isolation-positive result. No CPE was observed in the BHK cells. Infected cells were then subjected to immunofluorescent antibody assays with antibodies directed against various arboviruses, followed by the use of fluorescein isothiocyanate–conjugated antimouse antibodies for detection. From these analyses, the isolate derived from pool no. AR6319 (*Ae. albopictus*) was determined to be a California serogroup virus. Furthermore, pool no. 6318 (*Cx. quinquefasciatus*) tested positive for West Nile virus, and pool no. 6320 (*Ae. triseriatus*) was negative for virus by the above described methods.

To further identify the California serogroup virus identified in pool no. AR6319 (*Ae. albopictus*), the pool and the Vero cell–derived isolate were sent to the Centers for Disease Control and Prevention in Fort Collins, CO, USA, for additional testing. Upon receipt of the samples in Fort Collins, a reverse transcription–PCR was performed to amplify cDNAs from all 3 segments of the orthobunyavirus genome by using the consensus oligonucleotide primers shown in the Table and conditions and methods previously described (*8*). Generated cDNAs were then subjected to nucleotide sequencing and BLAST (www.ncbi.nlm.nih.gov/BLAST) analyses; the results indicated that the pool and the isolate were positive for LACV S, M, and L segment RNAs.

Subsequently, a pool (AR8973) of 29 *Ae. albopictus* and 2 *Ae. triseriatus* mosquitoes collected in Fort Bend County, Texas on October 5, 2009, was identified as positive for LACV S, M, and L segment RNAs by using the same processing and characterization methods described above. After these analyses, full-length S, M, and L segment genomic sequences (GenBank accession nos. GU591164–9) were generated for LACV RNAs extracted from LACV-positive pools and Vero cell isolates by using oligonucleotide primers specific for the previously published LACV prototype genome (human 1960, GenBank accession nos. EF485030–2) and methods previously described (*9*).

Phylogenetic analyses of partial LACV M segment sequences (Figure 2) indicate that the LACVs present in the Texas 2009 pools are closely related to LACVs isolated from Alabama, Georgia, and New York of the previously described lineage 2 (*11*) and genotype C (*7*) designations. These findings suggest a likely southeastern ancestry for the Texas 2009 LACV isolates.

Conclusions

The presence of LACV in *Ae. albopictus* mosquitoes in Dallas County, Texas, in late summer 2009 represents the possible expansion of the geographic range of an endemic pathogen within this invasive mosquito species in the United States. The subsequent occurrence of LACV in Fort Bend County in October 2009 should be of concern to public health practitioners who have been alerted to the

Table. Orthobunyavirus consensus oligonucleotide primers used for amplification and sequencing of La Crosse virus partial S, M, and L segment cDNAs, Texas, 2009*

Targeted genomic regions	Name	Primer sequence (5′ → 3′)	Approximate amplicon size, bp
S segment nucleocapsid ORF	Cal S forward	GCAAATGGATTTGATCCTGATGCAG	210
	Cal S reverse	TTGTTCCTGTTTGCTGGAAAATGAT	
M segment 5′ terminus/glycoprotein ORF	Ortho M 5′ terminus	AGTAGTGTACTACC	410
	Ortho M ORF reverse	TTRAARCADGCATGGAA	
L segment 5′ terminus/polymerase ORF	Ortho L 5′ terminus	AGTAGTGTACTCCTA	550
	Ortho L ORF reverse	AATTCYTCATCATCA	

*Oligonucleotide primers designed against conserved regions of the orthobunyavirus genome. S segment primers appear in a previous publication (*8*). All primers were applied in singleplex reactions using methods described previously (*8*) with altered primer annealing conditions of 50°C for 1 min. S, small; M, medium; L, large; ORF, open reading frame.

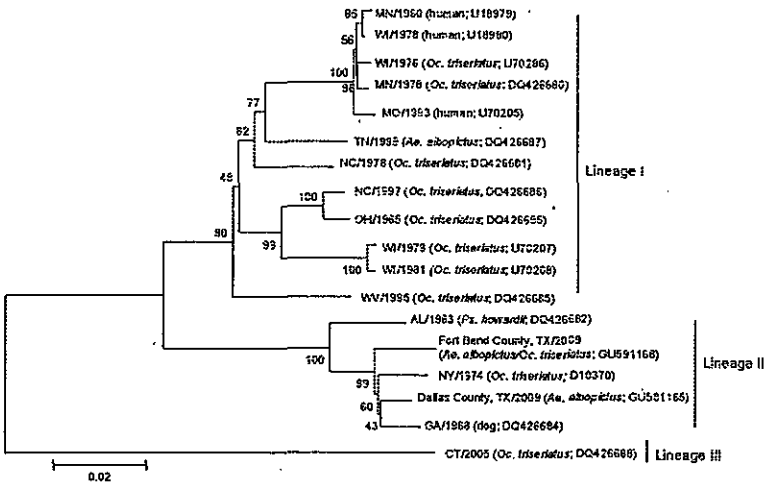

Figure 2. Phylogeny of La Crosse virus (LACV) medium (M) segment sequences of diverse origins. According to a limited availability of full-length sequences in GenBank, 1,663 nt of the M segment glycoprotein gene open-reading frame are compared. Isolate source and GenBank accession nos. appear after the isolate designation for each taxon. Sequences were aligned by ClustalW (*10*) and neighbor-joining and maximum-parsimony trees were generated by using 2,000 bootstrap replicates with MEGA version 4 software (*10*). Highly similar topologies and confidence values were derived by all methods and a neighbor-joining tree is shown. Scale bar represents the number of nucleotide substitutions per site. The 2009 Texas (TX) isolates group with strong support with lineage 2 viruses of the extreme south and New York (NY), which suggests a likely southern origin for LACV isolates. MN, Minnesota; WI, Wisconsin; *Oc., Ochlerotatus*; MO, Missouri; TN, Tennessee; *Ae., Aedes*; NC, North Carolina; OH, Ohio; WV, West Virginia; AL, Alabama; *Ps., psorophora*; GA, Georgia; CT, Connecticut.

presence of this pathogen near 2 major urban centers, Dallas and Houston. Of interest, San Angelo virus, which is serologically related to LACV, is known to occur in Texas and has been shown to replicate in and be transovarially transmitted by *Ae. albopictus* mosquitoes (*12*), although this virus has no known association with human disease. Cocirculation enables possible reassortment of genomic segments between LAGV and San Angelo virus, a phenomenon that has been described for viruses of the California serogroup within *Ae. albopictus* mosquitoes (*13*) with unknown public health outcomes.

Ms Lambert is a research microbiologist at the Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colorado. Her primary research interests lie in the molecular characterization, detection, and evolution of viruses of the family *Bunyaviridae*.

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医薬品 研究報告 調査報告書

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				2010. 7. 8	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		公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)		MMWR Vol. 59 No. 25	米国

研究報告の概要

○2009年の米国におけるウエストナイルウイルス(WNV)の流行状況
米国疾病管理予防センター(CDC)が発表した2009年の米国におけるWNVの流行状況である。米国の38州の262郡と、コロンビア特別区から720症例のWNV感染症が報告された。そのうち386例(54%)が神経侵襲性疾患で、334例(46%)が非神経侵襲性疾患であった。WNV感染症での死亡者は全部で33人が報告され、そのうち32人が神経侵襲性疾患であった。神経侵襲性疾患のうち229例(59%)が脳炎、117例(30%)が髄膜炎、40例(10%)が急性弛緩性麻痺であった。急性弛緩性麻痺40例のうち、27例(68%)が脳炎または髄膜炎を併発した。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
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
2009年、米国におけるウエストナイルウイルス感染症例は38州及びコロンビア特別区から720症例が報告され、そのうち386例が神経侵襲性疾患であり、全体の死者は33人であったとの報告である。 ウエストナイルウイルスは脂質膜を持つRNAウイルスである。これまで、本剤によるウエストナイルウイルス感染の報告はない。本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本剤の安全性は確保されていると考える。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、ウエストナイルウイルス感染の国内発生に備え、平成17年10月25日付血液対策課発事務連絡に基づき緊急対応の準備を進めているほか、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して対応について検討している。今後も引き続き情報の収集に努める。

(12)

Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
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West Nile Virus Activity — United States, 2009

West Nile virus (WNV) was first detected in the Western Hemisphere in 1999 in New York City and has since caused seasonal epidemics of febrile illness and neurologic disease across the United States, where it is now the leading cause of arboviral encephalitis (*1*). This report updates a previous report (*2*) and summarizes WNV activity in the United States reported to CDC in 2009. A total of 38 states and the District of Columbia (DC) reported 720 cases of WNV disease. Of these, 33 states and DC reported 386 cases of WNV neuroinvasive disease, for an incidence of 0.13 per 100,000 population. The five states with the highest incidence of WNV neuroinvasive disease were Mississippi (1.05 per 100,000), South Dakota (0.74), Wyoming (0.73), Colorado (0.72), and Nebraska (0.61). Neuroinvasive disease incidence increased with increasing age, with the highest incidence among persons aged ≥70 years. A total of 33 WNV deaths were reported, 32 from neuroinvasive disease. Calculating from the number of neuroinvasive disease cases and projections from 1999 serosurvey data, CDC estimated that 54,000 persons were infected with WNV in 2009, of whom 10,000 developed nonneuroinvasive WNV disease. The continuing disease burden caused by WNV affirms the need for ongoing surveillance, mosquito control, promotion of personal protection from mosquito bites, and research into additional prevention strategies.

WNV is a nationally notifiable disease. Data are reported to CDC through ArboNET, an Internet-based arbovirus surveillance system managed by state health departments and CDC (*2*). Using standard case definitions,* human WNV disease cases are classified as WNV neuroinvasive disease (e.g., meningitis, encephalitis, or acute flaccid paralysis) or WNV nonneuroinvasive disease (e.g., acute systemic febrile illness that often includes headache, myalgia, or arthralgia). Nonneuroinvasive disease reporting varies greatly by jurisdiction, depending on disease awareness, health-care–seeking behaviors, and testing practices. Therefore, this report focuses on WNV neuroinvasive disease cases, which are thought to be identified and reported more consistently because of the severity of the illness. In addition to human disease cases, ArboNET captures data on presumptively viremic blood donors (PVDs), veterinary cases, and WNV infections in sentinel animals (most commonly chickens), dead birds, and mosquitoes. Not all jurisdictions conduct nonhuman surveillance.

*Available at http://www.cdc.gov/ncphi/disss/nndss/casedef/arboviral_current.htm.

Human Surveillance

During 2009, a total of 720 cases of WNV disease were reported from 262 counties in 38 states and DC. Of these 720 cases, 386 (54%) were reported as WNV neuroinvasive disease and 334 (46%) as nonneuroinvasive disease. A total of 116 PVDs, identified through routine screening of the blood supply, also were reported. Of these PVDs, 92 (79%) were asymptomatic, 23 (20%) developed nonneuroinvasive disease, and one (1%) subsequently developed neuroinvasive disease. PVDs who developed symptomatic disease were included in disease case counts.

The 386 reported cases of neuroinvasive disease represented a rate of 0.13 per 100,000 population in the United States, based on July 1, 2009 U.S. Census population estimates (Figure 1). States reporting the most WNV neuroinvasive disease cases were Texas with 93 (24% of U.S. cases) and California with 67 (17%). Washington, which reported only two neuroinvasive disease cases in 2008, reported 26 (7%) cases in 2009. The five states with the highest incidence were Mississippi (31 cases,

INSIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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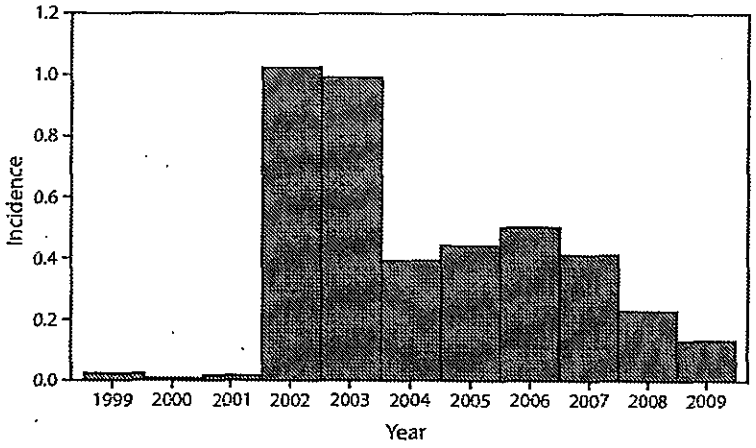
FIGURE 1. Annual incidence* of cases of West Nile virus neuroinvasive disease† — ArboNET, United States, 1999–2009§



* Per 100,000 population, based on July 1 U.S. Census estimates for each year.
† Meningitis, encephalitis, or acute flaccid paralysis.
§ N = 12,208 during 1999–2009; N = 386 in 2009

1.05 cases per 100,000 residents), South Dakota (six cases, 0.74), Wyoming (four cases, 0.73), Colorado (36 cases, 0.72), and Nebraska (11 cases, 0.61) (Figure 2). WNV neuroinvasive disease peaked in the United States during mid-August, and 352 (91%) of the 386 cases were reported during July–September. This seasonality was consistent with trends observed over the preceding 10 years (*2*).

Of the 386 neuroinvasive disease cases, 226 (59%) occurred in males. The median age of patients was 60 years (range: 2–91 years), with increasing incidence among persons in older age groups (Figure 3). Overall, 368 (95%) patients with neuroinvasive disease were hospitalized, and 32 (8.3%) died (median age: 72 years; range: 19–89 years). A total of 229 (59%) neuroinvasive disease cases were classified as encephalitis, 117 (30%) as meningitis, and 40 (10%) as acute flaccid paralysis; 27 (68%) of the 40 cases classified as acute flaccid paralysis had coincident encephalitis or meningitis.

Serologic surveys indicate that for every case of WNV neuroinvasive disease there are approximately 140 infections and approximately 20% of infected persons develop nonneuroinvasive disease (*3*). Using the 386 reported neuroinvasive disease cases, CDC estimated that 54,000 infections and 10,000 cases of WNV nonneuroinvasive disease occurred in the United States in 2009. Only 334 nonneuroinvasive disease cases were reported to ArboNET in 2009, representing approximately 3% of the estimated number.

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Animal Surveillance

Of 298 reported veterinary cases of WNV disease, 275 (92%) occurred in equines and 23 (8%) occurred in other species: squirrels, 13; canines, eight; camelids, one; and deer, one. The equine cases were reported from 168 counties in 36 states, with 72 (26%) reported from Washington. The number of reported WNV-infected equines peaked during the first week of September.

In 2009, a total of 759 dead WNV-infected birds were reported from 141 counties in 25 states and the District of Columbia; California reported 515 (68%) dead birds. Of the 141 counties reporting WNV-infected birds, 92 (65%) counties in 19 states reported infected dead birds but no human disease cases. The number of reported WNV-infected birds peaked during the first week of September. Corvids (e.g., crows, jays, and magpies), which are targeted for surveillance by most states, accounted for 534 (70%) of the birds. Since 1999, WNV infection has been reported in 328 avian species, including two species, MacGillivray's warbler and tricolored blackbird, in which WNV was identified for the first time during 2009.

Mosquito Surveillance

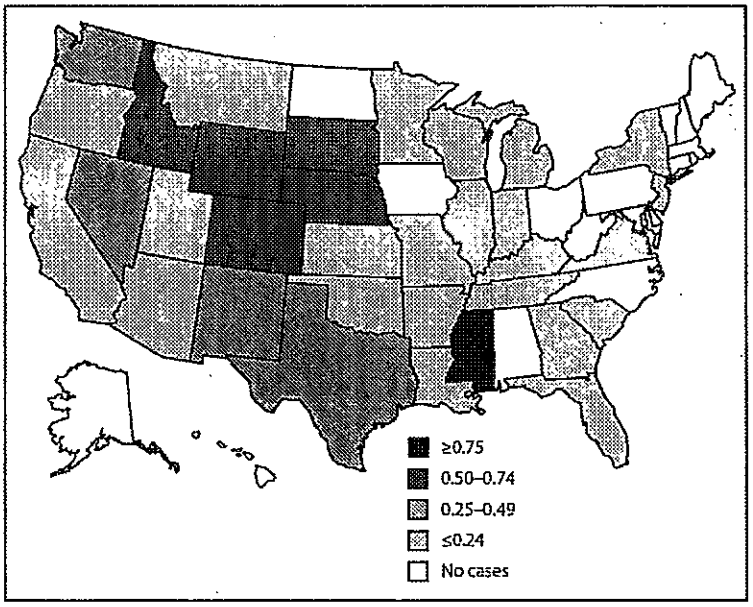
In 2009, a total of 6,646 mosquito pools† from 351 counties in 40 states and DC were reported as testing positive for WNV. Among the WNV-positive pools, 4,987 (75%) had species of *Culex* mosquitoes thought to be the principal vectors of WNV (e.g., *Culex pipiens*, *Culex quinquefasciatus*, *Culex restuans*, *Culex salinarius*, and *Culex tarsalis*). Unidentified or other species of *Culex* mosquitoes made up 1,488 (22%) pools, and non-*Culex* mosquito species (e.g., *Aedes* sp., *Anopheles* sp., *Coquillettidia perturbans*, *Culiseta* sp., *Mansonia titillans*, *Psorophora columbiae*, and *Uranotaenia sapphirina*) made up 171 (3%) pools. Data from 2009 also included the first report of WNV infection in *Aedes epactius*, which was collected in Texas. The number of reported WNV-infected mosquito pools peaked during mid-August.

Reported by

NP Lindsey, MS, JA Lehman, AL Greiner, JE Staples, MD, N Komar, ScD, E Zielinski-Gutierrez, DrPh, RS Nasci, PhD, M Fischer, MD, Arboviral Diseases Br, Div of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC.

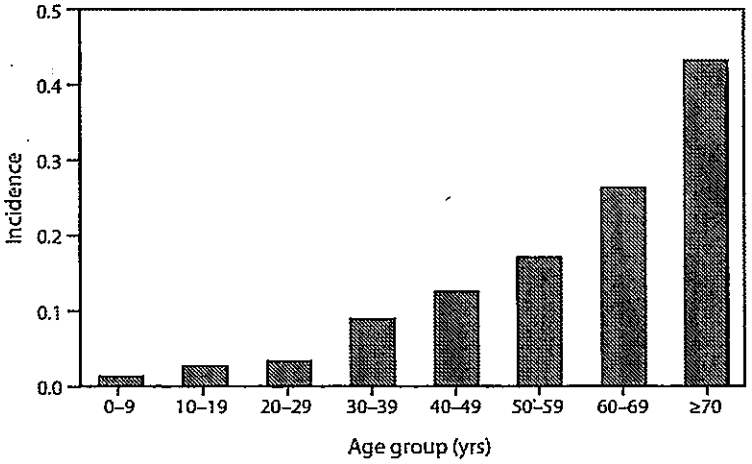
† A sample of mosquitoes (usually no more than 50) of the same species and sex, collected within a defined sampling area and period.

FIGURE 2. Incidence* of cases (N = 386) of West Nile virus neuroinvasive disease† — ArboNET, United States, 2009



* Per 100,000 population, based on July 1, 2009 U.S. Census estimates.
† Meningitis, encephalitis, or acute flaccid paralysis.

FIGURE 3. Incidence* of cases (N = 386) of West Nile virus neuroinvasive disease,† by age group — ArboNET, United States, 2009



* Per 100,000 population, based on July 1, 2009 U.S. Census estimates.
† Meningitis, encephalitis, or acute flaccid paralysis.

Editorial Note

Since introduced into the United States in 1999, WNV has become the leading cause of arboviral encephalitis in the country. However, in 2009, the reported incidence of WNV neuroinvasive disease in the United States was 0.13 per 100,000 population, the lowest recorded since 2001 (*2*). During

What is already known on this topic?

Since introduced into the United States in 1999, West Nile virus (WNV) has become the leading cause of arboviral encephalitis in the country.

What is added by this report?

In 2009, 386 cases of WNV neuroinvasive disease were reported in the United States, or 0.13 cases per 100,000 population, the lowest incidence recorded since 2001; however, CDC also estimated that 54,000 persons were infected with WNV in 2009, including 10,000 with nonneuroinvasive WNV disease.

What are the implications for public health practice?

The continuing disease burden caused by WNV affirms the need for ongoing surveillance, mosquito control, promotion of personal protection from mosquito bites, and research into additional prevention strategies.

2004–2007, WNV had appeared to reach a stable incidence of approximately 0.4 per 100,000, but incidence dropped to 0.2 per 100,000 in 2008 (*2*) and continued to decline in 2009. This trend might be attributed to variation in populations of vectors and vertebrate hosts, accumulation of immunity in avian amplifying hosts, human behavior (e.g., use of repellents and protective clothing), community-level interventions, reporting practices, or environmental factors (e.g., temperature and rainfall) (*4,5*).

In 2009, evidence of WNV human disease again was detected in all geographic regions of the continental United States. The highest incidence of WNV neuroinvasive disease continued to occur mainly in the west-central United States, likely because of the high efficiency of *Cx. tarsalis* as a WNV vector. Mississippi (31 cases, 1.05 cases per 100,000) continued to be among those states with the highest incidence of WNV neuroinvasive disease. Arizona, which had the second highest incidence of WNV neuroinvasive disease in 2008 (62 cases, 1.0 per 100,000), reported an 81% decrease in cases with 12 cases and an incidence of only 0.18 per 100,000 in 2009 (*1*). After reporting its first two neuroinvasive disease cases in 2008, Washington reported the seventh highest state incidence in 2009 (26 cases, 0.39 per 100,000). These findings illustrate the wide annual variability and focality of WNV transmission.

The findings in this report are subject to at least two limitations. First, ArboNET is a passive surveillance system that depends on clinicians to consider the diagnosis of an arboviral disease, obtain the appropriate diagnostic test, and report any positive results. Diagnosis and reporting likely are incomplete, leading to underestimation of the true incidence of disease. Second, arboviral surveillance programs, testing capacity, and reporting can vary by county, state, or region, affecting incidence estimates.

In the absence of an effective human vaccine, prevention of WNV disease depends on community-level mosquito control and promotion of personal protective measures. Such measures include use of mosquito repellents, barrier protection (e.g., long-sleeved shirts, long pants, and socks), avoiding outdoor exposure, or using personal protection from dusk to dawn. Household measures, such as window screens and covering or draining peridomestic water-holding containers can further decrease the risk for WNV exposure.

Additional information on prevention of WNV infection is available from CDC at http://www.cdc.gov/ncidod/dvbid/westnile/index.htm. An overview of current year WNV transmission activity is available at http://diseasemaps.usgs.gov/wnv_us_human.html.

Acknowledgments

This report is based, in part, on data provided by ArboNET surveillance coordinators in local and state health departments and ArboNET technical staff, Div of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC.

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医薬品　研究報告　調査報告書

			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 4. 27	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	ABC Newsletter #15. 2010 Apr 23; 15.	公表国	ニュージーランド・オーストラリア
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

○ニュージーランドの血液銀行は慢性疲労症候群(CFS)の既往を持つ供血者の供血延期を開始し、オーストラリア当局は、供血ガイドラインの見直しを行っている
ニュージーランドの決定は、前立腺癌と関連性があるXMRVが、健常集団と比較してCFS患者の血中に非常に多く認められたという米国の試験を受けてなされた。他の科学者は、この結果を確認することができなかったが、米国保健当局は、CFSとXMRV間の関連の可能性について調査を行っており、カナダ血液サービスはすでにCFSの診断を受けた供血者からの供血を無期限延期としている。一方、オーストラリア赤十字血液サービスは、独自にリスク分析を行い、完全に回復するまでのCFS患者からの供血を延期することを現行のガイドラインで求めている。

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
ニュージーランドの血液銀行は慢性疲労症候群の既往を持つ供血者の供血延期を開始し、オーストラリア当局は、供血ガイドラインの見直しを行っているとの報告である。 XMRVの病原性の有無は未だ定かではない。XMRVはマウス白血病ウイルスと類縁な脂質膜を持つ大型RNAウイルスである。この性状から本製剤の製造工程でウイルスが不活化・除去されると期待しうることから、本製剤の安全性は確保されていると考える。	注目すべきウイルスとして今後も引き続き、新たなウイルス等に関する情報の収集に努める。

GLOBAL NEWS

Members of the Dutch Parliament met last week to discuss the cost of blood in that country, and one of their topics was the transparency of operations at Sanquin, the foundation responsible for managing the blood supply in the Netherlands. Last August, a benchmark report compared the price of blood products in a number of European countries, and it concluded that prices in the Netherlands were higher than those in Ireland, Belgium, France, and Finland. In response, the Minister of Health wrote a letter in which he indicated a number of steps that would improve transparency at Sanquin, and he also announced a follow-up study that would focus on the current law on blood supply. The meeting this week was also attended by representatives from patient organizations, donor organizations, physicians, the Plasma Proteins Therapeutics Association, the Dutch Red Cross, and Sanquin. (Source: *PPTA Leadership Briefing*, 4/16/10) ♦

INFECTIOUS DISEASE UPDATES

CFS

Blood banks in New Zealand will begin deferring any potential blood donor who has a record of chronic fatigue syndrome (CFS), and officials in Australia are reviewing donation guidelines there. The decision in New Zealand was made in the wake of a US research study that found xenotropic murine leukemia virus-related virus (XMRV), a virus that has been linked to prostate cancer, in the blood of far more people with CFS than the healthy population. Other scientists have been unable to confirm those results, but health authorities in the US are investigating the possible link between CFS and XMRV, and Canadian Blood Services (CBS) has already instituted a lifetime deferral for potential blood donors who have been diagnosed with CFS (see *ABC Newsletter*, 4/9/10). The national medical director for New Zealand's blood banks, Peter Flanagan, said the New Zealand Blood Service (NZBS) reviewed the issue at a meeting held earlier this month and decided that the present exclusion of blood from people still suffering from CFS or patients who had been diagnosed in the past two years "should be extended to also exclude donors who report ever having been diagnosed with chronic fatigue syndrome." He admitted that the decision was made despite a lack of good scientific data on the issue. Meanwhile, the Australian Red Cross Blood Service is conducting its own risk analysis, and it says existing donor guidelines require people with CFS to defer giving blood until they make a full recovery. It said it collects more than 500,000 blood donations each year, but only 70 donors with CFS have been deferred in the past two years. The blood service said in a statement that it "currently defers donors who suffer from [CFS and] before we can accept their blood again, they need to bring us a letter from their treating physician advising us that they are completely recovered." (Sources: www.stuff.co.nz, 4/21/10; www.heraldsun.com.au, 4/20/10) ♦

We Welcome Your Articles

We at the *ABC Newsletter* welcome freelance articles on any subject relevant to the blood banking community. Writers are encouraged to submit short proposals or unsolicited manuscripts of no more than 1,100 words. While ABC cannot pay for freelance pieces, the writer's name and title will be included at the end of the story, brief news item, or commentary. If proposing a story, please write a few paragraphs describing the idea and sources of information you will use, your present job and background, and your qualifications for writing on the topic. ABC staff cannot guarantee all stories will be published, and all outside writing will be subject to editing for style, clarity, brevity, and good taste. Please submit ideas and manuscripts to Editor Robert Kapler at rkapler@americasblood.org. You will be sent a writer's guide that provides information on style conventions, story structure, deadlines, etc.

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
一般的名称	－		研究報告の公表状況	http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm223277.htm	公表国	
販売名（企業名）	－			http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm223232.htm	米国	

研究報告の概要

米国食品医薬品局生物製剤評価・研究センターおよび米国国立衛生研究所臨床センターの研究者が、慢性疲労症候群（CFS）と診断された患者37名と健常血液ドナー44名から採取した血液サンプルを検査したところ、CFS患者37名のうち32名のサンプル（87%）、および健常血液ドナー44名のうち3名のサンプル（7%）において複数の異なるマウス白血病ウイルス（MLV）遺伝子配列を特定した。本研究は、MLV様ウイルスの遺伝的変異体であるXMRV（異種指向性マウス白血病ウイルス関連ウイルス）がCFS患者の血液中に存在することを明らかにした過去の研究結果を裏付けており、CFSの診断と血液中のMLV様ウイルス遺伝子配列の存在との間に強い関連性があることを実証している。さらに、ごく一部の健常血液ドナーにおいてMLV様ウイルス遺伝子配列が検出された。CFSとの統計的関連性は強いとはいえ、これらのレトロウイルスがCFSの原因であることを証明するものではない。XMRVやその他のMLV関連ウイルスがCFSを引き起こす可能性を確定するためには、今後も研究を継続する必要がある。

「MLVやXMRVは血液製剤や組織由来製剤によって伝播するか？」については、これらウイルスが血液やヒトの組織によって伝播する可能性があるかどうか、そして、これらのウイルスが疾患を引き起こすかどうかを調査するためには追加研究を行う必要がある。FDA、NIH、CDCおよびその他の科学機関の研究者は、血液中のXMRVやMLV関連ウイルスの検出用として多くの研究所が使用している試験の能力を検証するため、複数の研究を実施中である。これらの研究は、XMRVが血液や組織のレシピエントに伝播する可能性だけでなく、XMRVと疾患との関連性についてもより詳しく調べるために、感受性が高く、特異的なXMRV試験の開発や標準化を目的としている。

報告企業の意見	今後の対応
慢性疲労症候群の原因である可能性があるXMRVやその他のMLVの血液からの検出に関する情報である。 現時点で疾患の原因として特定されておらず、検出法についても検討中との情報であった。	今後ともXMRVやその他のMLVに関する安全性情報等に留意していく。

使用上の注意記載状況・その他参考事項等

重要な基本的注意
［患者への説明］
本剤の投与にあたっては、疾病の治療における本剤の必要性とともに、本剤の製造に際し感染症の伝播を防止するための安全対策が講じられているが、ヒト血液を原料としていることに由来する感染症伝播のリスクを完全に排除することができないことを、患者に対して説明し、理解を得るよう努めること。

14

News & Events

FDA Note to Correspondents

For Immediate Release: August 23, 2010
Media Inquiries: Shelly Burgess, 301-796-4651, shelly.burgess@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

Study: Presence of murine leukemia virus related gene sequences found in CFS patients

Researchers have found murine leukemia viruses (MLV) related gene sequences in blood samples collected from patients diagnosed with chronic fatigue syndrome (CFS) and some healthy blood donors, according to a study published online today by the scientific journal Proceedings of the National Academy of Sciences (PNAS).

Investigators from the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research and the National Institutes of Health Clinical Center, in collaboration with a physician scientist at Harvard Medical School, examined blood samples from 37 patients diagnosed with CFS and from 44 healthy blood donors.

MLV is a type of retrovirus known to cause cancer in mice. Several different MLV gene sequences were identified in samples from 32 of the 37 patients with CFS (87 percent) and 3 of the 44 (7 percent) healthy blood donors. Investigators performed DNA sequencing on all positively amplified samples to confirm MLV like gene sequences.

This study supports a previous investigation [Lombardi et al. Science October 23, 2009 326: 585] that showed XMRV, a genetic variant of MLV-like viruses, to be present in the blood of people with CFS. The study demonstrates a strong association between a diagnosis of CFS and the presence of MLV-like virus gene sequences in the blood. The study also showed that MLV-like viral gene sequences were detected in a small fraction of healthy blood donors. Although the statistical association with CFS is strong, this study does NOT prove that these retroviruses are the cause of CFS. Further studies are necessary to determine if XMRV or other MLV-related viruses can cause CFS.

A previous study, published in 2009, reported finding XMRV infections in a high percentage of CFS patients and a small percentage of healthy blood donors. However, several other studies from the United States (including a recent report from the Centers for Disease Control and Prevention), the United Kingdom, and the Netherlands have found no evidence of XMRV or other MLV-like viruses in the blood of people with CFS.

For more information:

- Murine Leukemia Virus Gene Sequence Study - Questions and Answers[1]
- Xenotropic Murine Leukemia Virus-related Virus - Overview[2] (CDC)
- Xenotropic Murine Leukemia Virus-related Virus - Questions and Answers[3] (CDC)

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Links on this page:

1. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm223232.htm
2. http://www.cdc.gov/xmrv/index.html
3. http://www.cdc.gov/xmrv/questions-answers.html

U.S. Food and Drug Administration

Vaccines, Blood & Biologics

New study on the detection of murine leukemia virus-related virus gene sequences in the blood of patients with chronic fatigue syndrome (CFS) and healthy blood donors - Questions and Answers

Questions and Answers

1. What are murine leukemia viruses?

Murine leukemia viruses (MLV) are retroviruses known to cause cancer in certain mice. In 2006, investigators found that a type of MLV, called xenotropic murine leukemia virus-relate virus (XMRV), could potentially infect humans. XMRV is one of a number of MLVs that appear to be transmitted to humans.

2. What is CFS?

Chronic fatigue syndrome (CFS) is a debilitating disorder defined solely by clinical symptoms and the absence of other causes. It's unknown what causes CFS.

3. Has MLV or XMRV previously been associated with CFS or other disease?

A previous study, published in the journal [Lombardi et. al. *Science* October 23, 2009 326: 585], reported finding XMRV in a high percentage of CFS patients and a small percentage of healthy blood donors. However, other studies conducted in the U.S., Netherlands, and UK did not detect evidence of XMRV or other MLV-related viruses in CFS patients.

XMRV was first identified in tissue samples from some prostate cancer patients in 2006. However, one subsequent study failed to find XMRV in prostate cancer tissues, and another study found the virus only rarely in such tissues.

4. What did the new study evaluate?

Investigators from the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research, the National Institutes of Health (NIH) Clinical Center, and Harvard Medical School have published a study in the scientific journal *Proceedings of the National Academy of Sciences* that examines the presence of MLVs in blood collected from two groups -- patients diagnosed with CFS and healthy blood donors.

This study tested blood samples collected from the New England area in the mid-1990s from 37 patients diagnosed with CFS, as well as samples from 44 healthy blood donors collectec in the Clinical Center Blood Bank, NIH, between 2003 and 2006. Investigators performed DNA sequencing on each sample that produced positive product for verification of MLV-like gene sequences. Diverse MLV gene sequences, similar to that of the recently discovered XMRV, were identified in samples from 32 of the 37 patients with CFS (86.5%) and 3 of the 44 (6.8%) healthy blood donors that were tested.

Follow-up samples were collected from 8 of the CFS patients in 2010, and 7 of these again tested positive for MLV-like gene sequences.

5. What did the new study conclude?

This study supports a previous investigation[Lombardi et al. *Science* October 23, 2009 326: 585]that showed XMRV, a genetic variant of MLV-like viruses, to be present in the blood of people with CFS. The study demonstrates a strong association between a diagnosis of CFS and the presence of MLV-like virus gene sequences in the blood. The study also showed tha MLV-like viral gene sequences were detected in a small fraction of healthy blood donors. Although the statistical association with CFS is strong, this study does NOT prove that these retroviruses are the cause of CFS. Further studies are necessary to determine if XMRV or other MLV-related viruses can cause CFS.

6. Are there studies that support different conclusions?

Some previous studies from the United States (including a study by the Centers for Disease Control and Prevention), the United Kingdom and the Netherlands reported finding no evidence of XMRV or other MLV-related infections in people with CFS. These different findings could be caused by a variety of factors (for example, difference in study populations), and underscore the need for additional studies and standardized methods.

7. Can MLV or XMRV be transmitted by blood or tissue products?

Additional research is needed to investigate the possibility that these MLV-related viruses and XMRV may be transmitted by blood or human tissue and are capable of causing disease. Investigators at FDA, NIH, CDC and other scientific institutions are in the process of conducting studies to verify the capabilities of the tests used by the different laboratories for the detection of XMRV or MLV-related viruses in blood. These studies are intended to develop and standardize a highly sensitive and specific XMRV test to better study its association with disease, as well as the possibility that XMRV can be transmitted to blood or tissue recipients.

8. What are the implications for blood donors?

At present, FDA does not have a donor policy specific to XMRV or other MLVs. There is currently no evidence that XMRV or MLVs are transmitted by transfusion in humans or that XMR or other MLVs cause human disease. FDA regulations require that donors be in good health at the time of donation.

9. Does FDA agree with the AABB recommendation to discourage donation by people with history of CFS?

FDA does not object to the AABB recommendation. The AABB recommendation is consistent with a long-standing position of the Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) Association of America that individuals with CFS voluntarily should not donate blood.

10. How are the differences between the CDC and FDA study results being evaluated?

Differences in the results could reflect differences in the patient populations that provided the samples. Alternatively, undefined differences in the method of sample preparation could be contributing to the discordant test results. All of the scientists involved are working collaboratively to design experiments to quickly answer this scientifically puzzling question. An independent investigator at the National Heart, Lung, and Blood Institute (NHLBI) set up a test set of 36 samples, including known positives and presumed negatives. Both the FDA/NIH and CDC labs participated in this test, and the results showed that both labs were able to detect XMRV present at low levels in blinded samples. Additionally, the CDC laboratory provided 82 samples from their published negative study to FDA, who tested the samples blindly. Initial analysis shows that the FDA test results are generally consistent with CDC, with no XMRV-positive results in the CFS samples CDC provided (34 samples were tested, 31 were negative, 3 were indeterminate).

11. What do these findings mean to CFS patients and clinicians who treat them?

Although this study found MLV-like viral gene sequences in a high percentage of CFS patients, this does not prove that these retroviruses are the cause of CFS or of any other disease. Moreover, other studies have not found evidence of such retroviruses in patients with CFS. Further studies are necessary to determine if XMRV or other MLV-like viruses are reproducibly associated with CFS, and if so whether the virus is a causative agent or a harmless co-traveler. The different findings from various studies reinforce the need for more research--including careful analysis of other cohorts of CFS patients from different geographic regions, studies of larger populations of healthy people, and testing of transmissibility of the agents through blood transfusions in animal models. FDA, NIH, and CDC have and will continue to collaborate with other agencies and groups involved in this research.

Links on this page:

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
				2010. 5. 18	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		公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 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)		ProMED 20100513.1557, 2010 May 13, 情報源: WHO Global Alert and Response (GAR) Disease Outbreak News	WHO

研究報告の概要

○南アフリカのリフトバレー熱(RVF)
2010年5月10日の時点で南アフリカ保健省は、18人の死者を含む186人のRVF症例を報告している。主要な感染経路は、感染した家畜の血液や組織に触れることであるが、蚊に刺されることも感染原因となる。世界保健機関(WHO)は、南アフリカへの旅行に対して規制の勧告は行っていないが、特に農場や動物保護区に行く者は、動物組織や血液との接触を避け、未殺菌、非加熱ミルクや生肉の摂取をしないことを勧めている。そして、全旅行者に対し、長袖長ズボンの着用や防虫剤、蚊帳を使用するなどして、蚊や吸血昆虫に刺されないよう注意を呼びかけている。また、ドイツ保健当局は、4月に、南アフリカ旅行から帰国したドイツ人のRVF検査確定症例を報告したが、その後の追加検査により、この症例はRVFではなくリケッチア感染であったと報告した。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
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
南アフリカでは2010年5月10日現在、18名の死者を含む186名のリフトバレー熱症例が報告されているとのことである。 リフトバレー熱ウイルスはブニヤウイルス科の脂質膜を持つウイルスである。これまで、本製剤によるリフトバレー熱ウイルス感染の報告はない。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。	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。

World Health Organization

Rift Valley fever in South Africa- update 2

12 May 2010 -- On 11 May 2010 Bernhard-Nocht-Institute for Tropical Medicine in Germany reported that additional laboratory analyses conducted both in Germany and South Africa on the German tourist who was preliminarily diagnosed with Rift Valley Fever (RVF) following her return from South Africa, was in-fact infected with Rickettsia and not with RVF virus.

Rickettsia, commonly known as tick fever is a bacterium which can cause many diseases that are transmitted by blood-sucking parasitic arthropods such as fleas, lice and ticks. Symptoms of rickettsial infections include rash, fever, and flulike symptoms. African tick bite fever is caused by *rickettsia africae* and tends to be a milder illness, with less prominent rash and little tendency to progress to complicated disease. All rickettsial diseases respond to treatment with antibiotics such as doxycycline and tetracycline

As of 10 May, the Government of South Africa has reported 186 confirmed cases of RVF in humans, including 18 deaths, in Free State Province, Eastern Cape Province, Northern Cape Province, Western Cape, and North West Province. RVF is a viral disease that primarily affects animals (such as cattle, buffalo, sheep, goats and camels). The disease can also affect humans. The main mode of transmission of RVF is via direct or indirect contact with the blood or organs of infected animals. Human infections have also resulted from the bites of infected mosquitoes. There is evidence that humans may become infected by ingesting the unpasteurized or uncooked milk of infected animals.

WHO advises no international travel restriction to or from South Africa. However, WHO recommends that visitors to South Africa, especially those intending to visit farms and/or game reserves, avoid coming into contact with animal tissues or blood, avoid drinking unpasteurized or uncooked milk or eating raw meat.

All travelers should take appropriate precautions against bites from mosquitoes and other blood-sucking insects (including the use of insect repellents, wearing long-sleeved shirts and trousers, and sleeping under mosquito nets). Travel medicine professionals and travel medicine services should be aware of the current RVF situation in South Africa in order to provide advice and care accordingly.

For more information

Department of Health, South Africa

National Institute for Communicable Diseases (NICD)

Robert Koch Institute

Rift Valley fever: WHO fact sheet

Protection against vectors [pdf 5-18kb]
International Travel and Health

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 5. 17	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		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)		Amitai Z, Bromberg M, Bernstein M, Raveh D, Keysary A, David D, Pitlik S, Swerdlow D, Massung R, Rzotkiewicz S, Halutz O, Shohat T. Clin Infect Dis. 2010 Jun 1;50(11):1433-8.	イスラエル

研究報告の概要

○イスラエル中央部の都市の学校における大規模Q熱アウトブレイク
背景:2005年6月28日に、イスラエル中央部の都市部の、全寮制高校の生徒および職員322名に多くの発熱性疾患症例が報告された。その後の調査で、その2週間前のQ熱アウトブレイクが確認された。
方法:Q熱疾患の危険因子を特定するため、症例対照研究を行った。環境サンプルを採取し、*Coxiella burnetii*(*C.burnetii*)の感染源と伝播経路を確認した。
結果:2005年6月15日～7月13日の間に、303名中187名(62%)が体調の不具合を報告した。検査を実施した164名中144名(88%)に、*C.burnetii*感染の血清学的証拠が明らかとなった。学生であること、学校の食堂で定期的に食事をしたこと、6月の宗教上の休日期間ならびにその前の週末に寮生活を行ったことは、いずれもQ熱感染の重大なリスク因子であった。PCR検査により学食の空調から*C.burnetii* DNAが検出され、空調を介して病原体に空気感染したことが示唆された。
結論:インフルエンザのオフシーズンにおいて、インフルエンザ様疾患のアウトブレイクの調査を行う際には、*C.burnetii*感染を強く疑うことが必要である。

報告企業の意見	今後の対応
イスラエル中央部の都市の全寮制高校における大規模Q熱アウトブレイクの原因調査を行ったところ、学食の空気調節システムから*Coxiella burnetii* DNAが検出され、空気調節システムによる空気感染が示唆されたとの報告である。	日本赤十字社では、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。

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

(17)

MAJOR ARTICLE

A Large Q Fever Outbreak in an Urban School in Central Israel

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Background. On 28 June 2005, numerous cases of febrile illness were reported among 322 students and employees of a boarding high school located in an urban area in central Israel. Subsequent investigation identified a large outbreak of Q fever which started 2 weeks earlier. We describe the investigation of this outbreak and its possible implications.

Methods. We conducted a case-control study to identify risk factors for Q fever disease. Environmental sampling was conducted to identify the source and the mode of transmission of *Coxiella burnetii*, the infectious agent.

Results. Of 303 individuals, 187 (62%) reported being ill between 15 June and 13 July 2005. Serological evidence for *C. burnetii* infection was evident in 144 (88%) of the 164 tested individuals. Being a student, dining regularly at the school dining room, and boarding at school during a June religious holiday and the preceding weekend were all significant risk factors for contracting Q fever. *C. burnetii* DNA was detected using polymerase chain reaction on samples from the school dining room's air conditioning system, supporting contribution of the air conditioning system to the aerosol transmission of the infectious agent.

Conclusions. We report a large outbreak of Q fever in an urban school, possibly transmitted through an air conditioning system. A high level of suspicion for *C. burnetii* infection should be maintained when investigating point source outbreaks of influenza-like disease, especially outside the influenza season.

Q fever is a worldwide-distributed bacterial zoonosis caused by *Coxiella burnetii*. The most common reservoirs are domesticated ruminants, but other mammals, birds, and arthropods are also naturally infected [1, 2]. *C. burnetii* is often excreted in milk, urine, and feces of infected animals and is present in high numbers within the amniotic fluid and the placenta during parturition [2]. Viable bacterium may be present in the soil for months or years, and inhalation of contaminated aerosols is the major mode of transmission [2, 3]. In humans, acute infection may present as a self-limited influenza-like illness, hepatitis, and/or atypical pneumonia [4, 5]. About 60% of infections may be asymptomatic [4], especially among female persons [4, 6] and children aged <15 years [7].

Most reports of Q fever outbreaks are from rural areas and are associated directly or indirectly with farms or farm animals [2, 3]. Nevertheless, urban outbreaks have been described after exposure to slaughterhouses [8, 9], animal research laboratories [10], parturient cats [11], contaminated straw [12], and following windborne spread of *C. burnetii* from farmlands [13]. In some urban outbreaks, the source of the infection was never determined [14, 15].

In Israel during 1998–2004, the average annual incidence of Q fever was 0.6 cases 100,000 persons (20–70 cases per year) (Israel Ministry of Health, personal communication). Only a few outbreaks were reported, with the majority occurring in rural or adjacent areas

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following outbreaks of Q fever in livestock, and all were relatively limited in scale [15–17].

We report a very large urban outbreak of Q fever in a boarding high school in Israel. This outbreak is unique in its magnitude and setting, because there was no proximity to livestock or their products.

METHODS

Epidemiologic investigation. On 28 June 2005, 2 reports of a possible outbreak of febrile illness in a religious boarding high school in the center of the largest urban area in Israel were received at the Tel Aviv District Health Department. Initial investigation identified a large outbreak of influenza-like illness which started 2 weeks earlier, had already peaked, and was later confirmed to be due to acute *C. burnetii* infection.

We conducted a case-control study to identify risk factors for contracting Q fever. All school students and employees were asked to fill out a short questionnaire, including demographic characteristics, medical history, school boarding history, in-school dining habits, and contact with pets at school. Those who reported being ill during the previous 2 months were asked to specify the date of onset of illness, duration, symptoms and signs, and use of health services. All students and employees were referred for Q fever testing. In several cases, primary practitioners were contacted for additional information. Regional and reference laboratories were queried about additional Q fever cases from the school surroundings during the same time period.

Human serologic testing. Serum samples were tested for antibodies to *C. burnetii* with use of several laboratory methods. Indirect immunofluorescent assays were performed at the Israeli Reference Laboratory for Rickettsial Diseases in Ness-Ziona [18]. Complement fixation tests were performed by the Tel Aviv Medical Center's Clinical Virology Unit with use of the standard complement fixation microtiter method (Lennette and Schmidt) [19]. Qualitative enzyme immunoassays were performed by Clalit Health Services community laboratories with use of the PANBIO Q fever DIP-S-TICKS test. Quantitative tests were performed in various laboratories in western Europe.

Case definitions. A "clinical case" was defined as a patient with symptoms compatible with Q fever, with illness onset from 1 June through 31 July 2005 and no other likely cause for his/her illness.

A "confirmed case" was defined as anyone with immunoglobulin (Ig) M and IgG indirect immunofluorescent assay titers $\geq$100 to phase II antigen, or IgG titers $\geq$800 and IgM titers <100 in a "clinical case" that was tested at least 4 months after illness [8, 20]. Using complement fixation test, a phase II titer $\geq$256 was considered to represent a confirmed case.

A "probable case" was defined as phase II IgM titer $\geq$100 and IgG titer <100 by indirect immunofluorescent assay, a phase II titer <256 but $\geq$32 by complement fixation test, or a positive or borderline laboratory result of qualitative enzyme immunoassay or other quantitative tests. A "possible case" was defined as a "clinical case" with no serologic testing. A "non-case" (control) was defined as negative serologic results for Q fever.

Environmental and veterinary investigation. A comprehensive environmental inspection of the school grounds was conducted by environmental health inspectors, a veterinarian, and an air-conditioning system specialist for a possible source of infection. Two weeks after the last reported case, environmental samples were collected from the air-conditioning systems. The samples included 8 gauze pads that were used to swab the dining room's and synagogue's air-conditioning systems and 4 samples from the 2 fiberglass filters from the inlet of the dining room's air-conditioning unit. All samples were prepared for DNA extraction.

Serum samples of male and female feral cats trapped in the Tel Aviv area for routine neutering by municipality veterinarians were tested for Q fever by complement fixation test [21]. Samples that reacted nonspecifically were retested by indirect immunofluorescent assay (*C. burnetii* spot IF; BioMérieux). In addition, endometrial tissue proximal to the cervix was collected from each of the spayed female cats and was processed for DNA extraction.

DNA was extracted by use of the DNeasy DNA purification kit (Qiagen). Polymerase chain reaction (PCR) assay was performed as described by Stein and Raoult [22].

All tests were performed in the Kimron Veterinary Institute (Bet Dagan, Israel). Filter samples from the dining room's air-conditioning system were also sent to the Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention.

Data analysis. Data were analyzed with Excel (Microsoft) and SPSS, version 10 (SPSS), software. The prevalence of possible risk factors for contracting Q fever in cases (confirmed cases with and without probable cases) and controls was compared using the Fisher's exact test. Odds ratio (ORs) and 95% confidence intervals (95% CI) were calculated. All significant risk factors were tested for colinearity.

RESULTS

The school setting. The school, a religious boarding high school for boys, is located in central Tel Aviv in a densely populated area. During June 2005, 271 students aged 14–20 years (mean age $\pm$ standard deviation, 16.9 $\pm$ 1.5 years) and 51 employees attended the school. Eighty-four students boarded at the school regularly. Some of the others, who resided in different cities in Israel, stayed over during certain weekends and holidays. A weekend occurred on 10–11 June 2005, and 12–13 June was a special Jewish holiday (Shavuot). The em-

ployees were mainly men (84%) aged 33–92 years (mean age ± standard deviation, 55.4 ± 13.8 years) from various cities in central Israel.

Outbreak description. Of the 322 individuals who attended the school during June 2005, 187 reported being ill from 1 June through 31 July 2005, including 179 (96%) students and 8 (4%) employees (19 individuals were excluded from further analyses because of lack of information). The clinical attack rate was 62% (70.5% and 16% among students and employees, respectively). Attack rates were similar in different grades and ranged between 67% and 74.5%.

Information on date of illness onset was available for 155 (83%) individuals. The epidemic curve (Figure 1) correlates to a point source epidemic. The earliest and the latest date of illness onset were 15 June and 13 July, respectively. The majority of cases reported onset during 19–26 June. Assuming an incubation period of 14–21 days [1, 2], the presumed exposure occurred around 5 June. The reported illness duration was 1–21 days (mean duration ± standard deviation, 7 ± 3 days).

The dominant clinical presentation (Table 1) was fever (98%), headache (90%), and weakness (80%). Only 21% had cough, and none reported symptoms consistent with hepatitis. One hundred forty-one individuals (79%) visited their primary practitioner during their illness. Thirty-one individuals underwent chest radiography examination, and 7 (4%) received a diagnosis of pneumonia. Five patients were hospitalized (2 students and 3 employees) for pneumonia ($n = 2$, 1 of which was a man aged 92 years, the oldest patient in our exposed population), perimyocarditis ($n = 1$), perimyocarditis and pneumonia ($n = 1$), and observation ($n = 1$). Duration of hospitalization ranged between 1–7 days. No deaths occurred. Only 3 individuals were treated with doxycycline during illness. Of note, no additional cases of acute Q fever were diagnosed in the neighborhoods surrounding the school during the same time period.

Serologic results. Results of serologic tests were available for 164 individuals (151 [59%] students and 13 [26.5%] employees). One hundred eight (66%) were "confirmed cases" (103 students and 5 employees), 36 (22%) were "probable cases" (35 students and 1 employee), and 20 (12%) were "non-cases" (13 students and 7 employees). Sixty-five individuals met the criteria for a "possible case" (63 students and 2 employees).

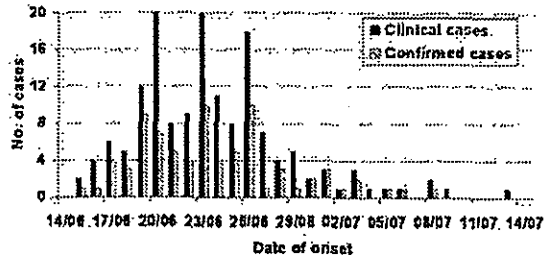

Figure 1. Epidemic curve of all clinical cases and confirmed symptomatic cases. Clinical cases were defined as individuals who reported symptoms compatible with Q fever with illness onset from 1 June through 31 July, with other etiologies ruled out. Confirmed symptomatic cases included any clinical case with positive serologic test results for Q fever.

Table 1. Symptoms of All Clinical Cases and Confirmed Symptomatic Cases

	No (%) of cases	
Symptom	All clinical cases	Confirmed cases
Fever	184 (98)	92 (98)
Headaches	166 (90)	85 (92)
Sweats	81 (49)	45 (53)
Weakness	145 (80)	78 (87)
Chills	60 (35)	36 (42)
Vomiting	30 (17)	22 (24)
Myalgia	39 (23)	22 (26)
Cough	38 (21)	22 (24)
Sore throat	42 (23)	23 (26)
Chest pain	21 (13)	13 (15)

Eighty-six percent and 81% of the confirmed and probable cases, respectively, were clinically ill. All of the non-cases were asymptomatic. The incubation period and the clinical presentation of the confirmed cases resembled that of all clinical cases (Figure 1 and Table 1).

The exact attack rate could not be determined, because everyone was not tested for Q fever; therefore, we estimated a range. The lower limit was 144/303 (47.5%), including confirmed and probable cases. The upper limit was 209/303 (69%), which also included the possible cases. This was based on the observation that all serologically tested clinical cases were either confirmed or probable cases.

The symptomatic to asymptomatic ratio among serologically positive individuals (85:15) is biased, because symptomatic individuals were more likely to be tested. Given that all tested symptomatic individuals had positive results, the numerators were more likely to be near 187 versus 116−20 (all symptomatic individuals vs the asymptomatic minus the seronegative individuals), which translates to a ratio of 66:34 or even higher.

Risk factors. Table 2 summarizes the prevalence of several possible risk factors in confirmed cases and controls. Being a student (OR, 11.09; 95% CI, 3.07–40.07), boarding at school during the June holiday (OR, 13.9; 95% CI, 4.45–43.45), and dining regularly at the school dining room (OR, 8.57; 95% CI, 2.05–35.79) were significantly associated with contracting Q fever. When probable cases were included in the univariate analysis, boarding at school during the weekend before the June holiday was also significantly associated with Q fever infection (OR, 3.18; 95% CI, 1.09–9.22). Because all of the above significant risks factors were statistically associated with each other, we did not perform multiple logistic regression analysis.

Table 2. Risk Factors for Acquiring Q fever

Factor	No (%) of persons		OR (95% CI)
	Cases	Controls	
Status in school (student vs employee)	103 (95)	13 (65)	11.09 (3.07–40.07)
Boarding at school on a regular basis	32 (30)	3 (15)	2.45 (0.67–8.95)
Boarding at school during Shavuot holiday	91 (92)	9 (45)	13.9 (4.45–43.45)
Boarding at school during the weekend before the holiday	48 (59)	6 (35)	2.67 (0.9–7.92)
Boarding at school during the weekend after the holiday	33 (41)	6 (35)	1.29 (0.43–3.83)
Eating at the school dining room (frequently vs seldom or never)	96 (96)	14 (74)	8.57 (2.05–35.79)
Contact with pets on school ground	0 (0)	0 (0)	

NOTE. CI, confidence interval; OR, odds ratio.

Environmental and veterinary investigation. Numerous stray cats were seen in the schoolyard, especially in proximity to the kitchen and the garbage cans which were located outside the dining room. The dining room had its own air-conditioning system, with inlet that drew air from the dining room and outlet that emitted the cooled air back to the room. The air-conditioning ducts were located on the dining room's roof and could be accessed by animal secretions. One of the 4 filter samples, as well as 1 of the 8 gauze swabs taken from the inlet of the dining room's air-conditioning unit, had positive results for Q fever by PCR. Similar positive PCR results were obtained by the Centers for Disease Control and Prevention on filter samples.

Serum samples of 65 feral cats were tested for Q fever serology. Nine cats (14%) had positive results; 2 (10%) of 20 were caught within a 2-km radius of the school, whereas the other 7 (15%) of 45 were from other parts of the city. Forty feline uterine specimens were tested by PCR, and all were found to have negative results.

DISCUSSION

We describe a Q fever outbreak that was unusual in its magnitude and place of occurrence. It represents 1 of the largest outbreaks described in the literature and the largest to occur in a densely populated urban area located far away from livestock farms [3]. The clinical attack rate was remarkably high (62%), with the serological attack rate estimated to be even higher (69%). This is a conservative estimate because asymptomatic individuals, who could have been serologically positive (if tested), were not included and the pre-existing immunity in this particular population was assumed to be very low (based on research that found 14% seropositivity to Q fever among adults residing in the Northern part of Israel, which is a more rural area) (A.K., unpublished data). The symptomatic to asymptomatic ratio was estimated to be 66:34, higher than that reported elsewhere (40:60) [1, 4].

The high attack rate and symptomatic to asymptomatic ratio might be explained by a large inoculum of bacteria and effective modes of transmission. The demonstration of the presence of *C. burnetii* by PCR in the samples from the dining room's air-conditioning system supports an effective aerosol transmission. A similar phenomenon was described in an outbreak in a cosmetics factory where all the exposed workers were symptomatic [23]. The high proportion of symptomatic infection can also be attributed to the male predominance of the exposed population [4, 6] and to the fact that none of the students were aged <14 years [7].

Notable is the low clinical attack rate among the school employees, compared with the students (16% vs 70.5%), which we think is attributable to their lower exposure to the infectious agent. An alternative explanation could be a higher pre-existing immunity among the employees. However, even if the pre-existing immunity was 14% (A.K., unpublished data), this would have changed the calculated clinical attack rate among employees by 2% only (from 16% to 18%).

The dominant clinical presentation was an influenza-like illness, and the working diagnosis of the majority of the primary physicians was a viral infection. Seven patients (4%) received a diagnosis of pneumonia, and none exhibited overt signs of hepatitis. Because of the delayed notification of the Tel Aviv District Health Department and the subsequent delay in the laboratory confirmation of *C. burnetii* infection, the outbreak investigation had little effect on the clinical management during the acute illness. Thus, laboratory and imaging tests were not conducted routinely but were rather conducted on the basis of clinical judgment, and only 3 individuals were treated with doxycycline.

Geographic variation in the clinical presentation of Q fever is well described [2]. In a recent review of 100 hospitalized patients with acute Q fever from Israel [24], the most common presentation was an acute febrile illness with few physical findings. Rare but severe manifestations of the disease are myocarditis and pericarditis, each described in ~1% of patients [1]. Two patients in the present study were hospitalized for myopericarditis. Thus, the clinical presentation in the present study is consistent with that described in the literature.

Most reported large Q fever outbreaks have occurred in or adjacent to rural areas as a result of direct or indirect exposure to infected livestock, especially to parturition products, as is the case in an outbreak in the Netherlands [25]. Urban outbreaks have been typically linked to farm animals that were brought to slaughterhouses [8, 9], animal research laboratories [10], urban farmers' markets [26], contaminated livestock products [23], or windborne aerosols carried long distance from neighboring farms engaged in outdoor lambing and calving [13]. Some urban outbreaks have been linked to parturient dogs [27] and cats [11, 28], and in some the source was never determined [14, 15].

The source of infection in the present outbreak was not clearly defined. However, the findings that being a student, dining at the school's dining room, and boarding during the June holiday were significantly associated with contracting the disease support the hypothesis that the transmission of the infection occurred in the dining room. The positive PCR results from the dining room's air-conditioning system further suggest that the air-conditioning system contributed to the aerosol transmission of the agent, although we could not prove whether the primary source of infection was the dining room or the air-conditioning system. The fact that the environmental samples were taken 2 weeks after the last reported case and mainly from the inlet of the air-conditioning system could explain why only 2 inlet samples of 12 total samples had positive results for *C. burnetii* by PCR. No new cases appeared a month after the initial case (Figure 1), and no other cases were diagnosed in the vicinity of the school, pointing to a limited exposure, both in time and space.

The air-conditioning system could have been contaminated by the numerous stray cats seen in the schoolyard. We were unable to demonstrate that cats from the school vicinity were more likely to be seropositive for Q fever than cats from different areas of the city. Nevertheless, the cat sampling showed that *C. burnetii* is endemic in feral cats in the school's surroundings. To our knowledge, no similar surveys were previously conducted among cats in Tel Aviv.

The magnitude of the present outbreak is impressive, given the yearly incidence of Q fever in Israel (0.6 cases 100,000 persons) and in comparison with other outbreaks described in nonrural areas. It demonstrates that *C. burnetii* can be effectively transmitted to a large number of people through a common exposure.

This outbreak raises the issue of underdiagnosis of Q fever, especially when a primary practitioner treats a sporadic case that manifests as an influenza-like illness. In our study, the working diagnosis of the majority of the physicians was a viral infection. This also implies that there could be a delay in outbreak investigations with implications on the probability of revealing their sources. A high index of suspicion is required when dealing with a relatively prolonged febrile disease, even with no history of exposure to farm animals. A cluster of febrile patients, especially if occurring outside the influenza season, should raise the possibility of Q fever, and rapid investigation into the etiology and source of infection should be made by public health authorities.

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Potential conflicts of interest. All authors: no conflicts.

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 4. 22	該当なし	

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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)			ベネズエラ

研究報告の概要

○カラカス(ベネズエラ)の学校における、経口感染による急性シャーガス病(CD)の大都市でのアウトブレイク

背景:*Trypanosoma cruzi*(*T. cruzi*)は、媒介動物の糞便で汚染された食物によって経口感染する。経口感染による急性CDの小規模流行の疫学的・臨床的な特徴については、ほとんどわかっていない。

方法:学校コミュニティに影響を及ぼした急性CDのアウトブレイク時において、コホート疫学研究を実施した。症状と感染源を特定するため、統一的問診を計画した。すべての患者から心電図データを入手し、免疫酵素的および間接血球凝集検査によって、特異的血清抗体を評価した。一部の症例においては、寄生虫血症を直接的または培養、動物接種試験、PCR法により検査した。

結果:曝露された1000名中103名に感染が確認された。感染者のうち、75%に症状があり、その20.3%は入院を必要とした。また59%は心電図異常を示し、44名に寄生虫血症が認められ、子供1名が死亡した。臨床的な特徴は、ベクターを介した感染で見られるものとは異なった。子供は感染率が有意に高かった。疫学研究では、汚染した生グアバジュースが唯一の感染原因とされた。

結論:当該アウトブレイクは、大都市部で、主に若年齢を中心とした中流層の、健康に問題のない集団に感染するという、先例のない公衆衛生的非常事態を招いた珍しいものであった。迅速な診断と処理により、高い死亡率は回避された。しかし*T. cruzi*の食物を介する感染は、現在認識されるより頻繁に起こる可能性がある。

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
ベネズエラの大都市におけるシャーガス病のアウトブレイクについての疫学研究を行ったところ、*Trypanosoma cruzi*の食物を介する感染は、現在認識されるより頻繁に起こる可能性が示されたとの報告である。	日本赤十字社は、輸血感染症対策として献血時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、シャーガス病の既往がある場合には献血不適としている。日本在住の中南米出身献血者については、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して検討する予定である。今後も引き続き情報の収集に努める。

MAJOR ARTICLE

Large Urban Outbreak of Orally Acquired Acute Chagas Disease at a School in Caracas, Venezuela

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(See the editorial commentary by Miles, on pages 1282–1284.)

Background. *Trypanosoma cruzi* oral transmission is possible through food contamination by vector's feces. Little is known about the epidemiology and clinical features of microepidemics of orally acquired acute Chagas disease (CD).

Methods. A case-control, cohort-nested, epidemiological study was conducted during an outbreak of acute CD that affected a school community. Structured interviews were designed to identify symptoms and sources of infection. Electrocardiograms were obtained for all patients. Specific serum antibodies were assessed by immunoenzimatic and indirect hemagglutination tests. In some cases, parasitemia was tested directly or by culture, animal inoculation, and/or a polymerase chain reaction technique.

Results. Infection was confirmed in 103 of 1000 exposed individuals. Of those infected, 75% were symptomatic, 20.3% required hospitalization, 59% showed ECG abnormalities, parasitemia was documented in 44, and 1 child died. Clinical features differed from those seen in vectorial transmission. The infection rate was significantly higher among younger children. An epidemiological investigation incriminated contaminated fresh guava juice as the sole source of infection.

Conclusions. This outbreak was unique, because it affected a large, urban, predominantly young, middle-class, otherwise healthy population and resulted in an unprecedented public health emergency. Rapid diagnosis and treatment avoided higher lethality. Food-borne transmission of *T. cruzi* may occur more often than is currently recognized.

The burden of illness associated with Chagas disease (CD) remains the second highest among all of the endemic tropical diseases in Latin America and results in an annual loss of >2 million disability-associated life years (DALYs) [1, 2]. Although Chile, Uruguay, and Brazil have been certified as free of vectorial transmission by domiciliary *Triatoma infestans* [1], eradication appears to be an impossible task because of the complexity of the zoonotic life cycle of its causative agent, *Trypanosoma cruzi*. In addition to vectorial transmission, other secondary mechanisms of infection include congenital, transfusional, organ transplantation–related, and oral transmission. A sparse number of outbreaks of orally acquired human CD have been reported from Brazil [3–7], Argentina [8], and Colombia [9].

Venezuela has a successful CD vector control program that is based on the improvement of rural housing and vector control [10, 11]. However, epidemiological data suggest a reemergence of the infection [12–14]. At the capital, Caracas, which is a densely populated cosmopolitan city surrounded by mountains covered by tropical forests, the local sylvatic triatomine vector, *Panstrongylus geniculatus,* has been recorded since 1920 [15]; it was reported inside the houses in 1986 [16] and captured in the wild or within households show-

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ing a high rate (76.1%) of *T. cruzi* infection [17]. However, vectorial transmission has not been reported in this city.

The current study describes the largest known outbreak of orally acquired CD to date in the American continent, which involved numerous children and personnel from an urban school in Caracas.

METHODS

On 6 December 2007, trypomastigotes of *T. cruzi* were detected on peripheral blood smears from a 9-year-old student (index case), who was admitted to the Hospital Universitario de Caracas (Caracas, Venezuela) with a 3-week history of fever of unknown origin (FUO). Twenty persons from the patient's school were hospitalized with similar symptoms and were later found to have circulating trypomastigotes and/or serological test results positive for CD. The municipal health authorities were contacted at once, and they reported an unexpected simultaneous sharp increase in medical consultations and absenteeism among school personnel from 30 October through 25 November 2007.

The center involved (Unidad Educacional "Andrés Bello") is located in the Municipality of Chacao, in the eastern part of Caracas, with predominantly middle-class inhabitants. All of the food and beverages consumed by the students and personnel were supplied by the same caterer that supplied other municipal schools, with the exception of breakfast, which was prepared under unsupervised sanitary conditions, located in a distant slum on the western mountain slopes of the city. A multidisciplinary task force was summoned to analyze the epidemiological situation with the aim of controlling the outbreak [18]. A case-control, cohort-nested, epidemiological outbreak study was designed to assess the extent of the outbreak and to identify possible sources of infection. Cases were classified as "suspected" or "confirmed" in accordance with a consensus document prepared by the interdisciplinary group, based on World Health Organization recommendations [19]. A suspected case patient was any person with an epidemiological link to the institution involved from 10 October through 1 November 2007 who developed FUO of >5 days duration and other clinical manifestations. A confirmed case patient was any suspected case patient or asymptomatic person with the epidemiological link who, in addition, exhibited blood parasites or specific anti–*T. cruzi* antibodies by 2 different serological techniques: enzyme-linked immunosorbent assay (ELISA) and indirect hemaglutination (IH) or ELISA and Western blot (WB) tests.

The study population consisted of all students, teachers, workers from the school, external persons involved with the preparation or transportation of food consumed in the school, and any person considered to be a "school contact" potentially at risk. Blood samples for diagnosis were initially collected from 11 December through 14 December 2007, as an emergency intervention, with the aim of identifying infected persons and immediately starting antiparasitic treatment of any individual affected by a severe, potentially lethal, acute illness in the context of a large outbreak that occurred at a critical time of the year (3 days before a prolonged Christmas and new year vacation). During a second sampling that was performed 6 weeks later, 21 January through 25 January 2008, all participants undertook a detailed clinical and epidemiological questionnaire on CD risk factors (eg, exposure to vectors, transfusions, infected relatives, contact with animal reservoirs, and ingestion of food and/or beverages in the school). Case patients were compared with control subjects from the same cohort of exposed individuals.

The study was performed under the supervision of the Ethical Committee of the Tropical Medicine Institute. Informed written consent was obtained from each participant or from their legal guardians.

For the first 43 symptomatic patients, fresh and Giemsa-stained peripheral blood smears were reviewed for trypomastigotes. In addition, 2 mL of blood were cultured in biphasic medium and checked periodically over at least 3 months. Mice were inoculated intraperitoneally with 300 μL of blood and examined each week [19].

All serum samples were screened for immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies against a crude extract of *T. cruzi* epimastigotes [20] with use of an ELISA developed in house [21] and an IH test [22]. The immunodiagnosis of CD was based on the positivity of at least 2 specific serological tests [19]. Those samples with ELISA results positive for IgG and negative IH results were also tested with WB tests [23].

A representative number of 150 blood samples were randomly evaluated by a polymerase chain reaction (PCR). For the DNA extraction, 5 mL of blood was mixed with an equal volume of 6M guanidine HCl /0.2M EDTA (GE) [24]. The amplification reactions were targeted to the 330–base pair minicircle fragment of the *T. cruzi* kinetoplastid DNA [25].

Conventional 12-lead electrocardiogram (ECG) recordings were obtained from confirmed or suspected case patients and treated with either benznidazole (Rochagan; Roche Laboratories) at a dosage of 6 mg/kg/day for 60 days or nifurtimox (Lampit; Bayer Laboratories) at a dosage of 8 mg/kg/day for 90 days [19, 26].

The dependent variable or main outcome was based on serological status. Epidemiological exposure was evaluated using χ^2 or the Student's t test depending on the binary or continuous independent distribution of the variable. Only variables significantly associated in the univariate regression were included in the multivariate regression, using $P < .05$ as the entry criteria. The relationship between risk factors and final outcome (*T.*

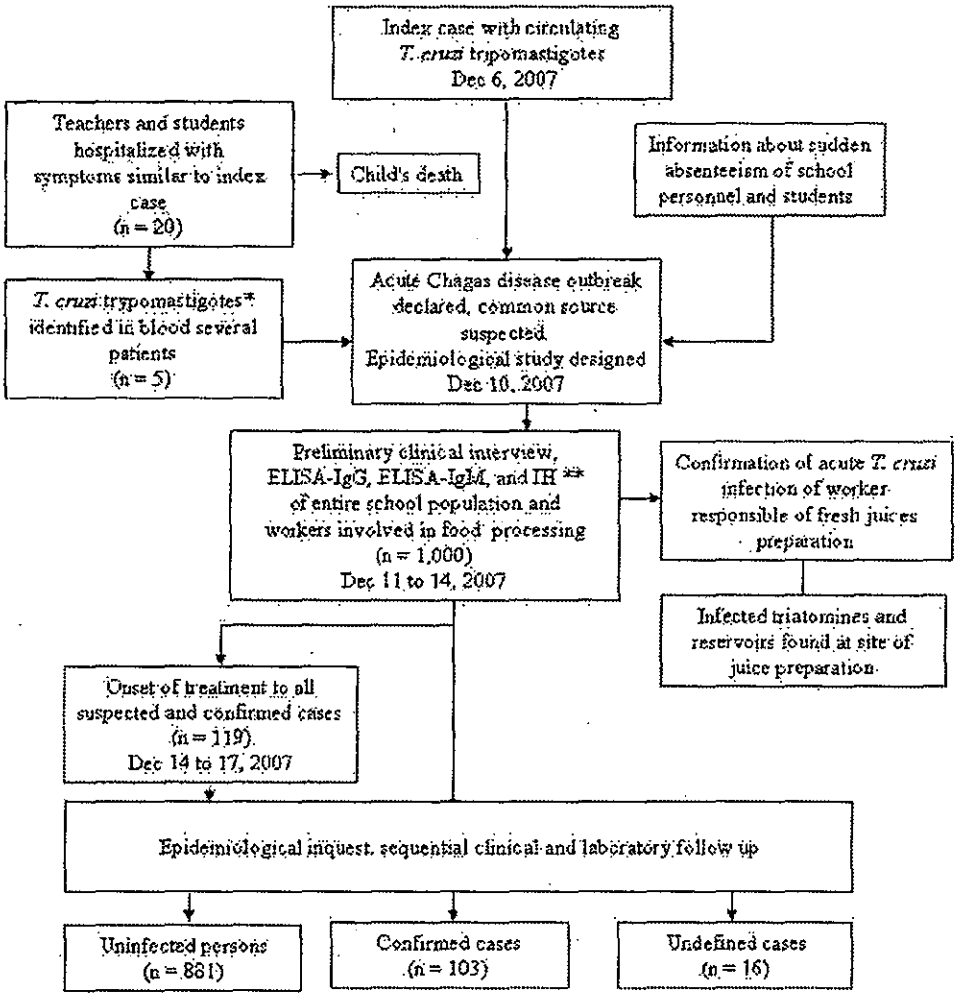

Figure 1. Study profile and major outcomes of the epidemiological investigation of the outbreak of acute Chagas disease, Caracas, Venezuela, 2007. *Parasitemia investigation by direct techniques. **Parasitemia, Western blot, and polymerase chain reaction tests performed on a more limited group of exposed individuals (see Methods). ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IH, indirect hemaglutination; *T. cruzi*, *Trypanosoma cruzi*.

cruzi infection) was estimated by means of the paired odds ratio (OR), with 95% confidence intervals (CIs). Stata, version 6.0 for Windows (Stata), was used as the basic statistical software for all calculations.

RESULTS

Figure 1 depicts the general outline of the study. Because the outbreak occurred in a well-off urban area of the city with no current vectorial transmission, a food-borne mechanism was presumed to be the cause. Date of exposure was estimated to occur between 10 October and 25 October 2007, based on previous reports of orally acquired infections with documented incubation periods of 5–20 days [5].

The demographic characteristics of the entire exposed population ($n = 1000$) are shown in table 1. No statistically significant differences were found in the attack rates among the sexes. Although, as a whole, age was not associated with the main outcome, a more meticulous revision of age distribution of those infected revealed a bimodal distribution curve, with a reverse trend, in which the OR for CD decreased with age for children but increased with age for adults. As depicted in Tables 1 and 2, significantly different attack rates were observed among students and teachers in relation to their school attendance (morning vs afternoon shifts; 65 cases [17.9%] among 363 subjects vs 10 cases [2.6%] among 385 subjects; OR, 3.19 [95% CI, 2.1–4.8; $P < .001$). The difference between the attack rate among students of the morning shift (22.5%) and the attack rate among children of the afternoon shift (2.4%) was statis-

Table 1. Demographic Characteristics and Rates of Infection of 1000 Individuals Exposed to Infection at a Public School Community of Caracas, Venezuela, Affected by a Large Outbreak of Orally Acquired Acute Chagas Disease in December 2007

Variable	No. (%) of exposed individuals (n = 1000)	
	Study population	Infected subjects
Age		
≤18 years old	795 (79.5)	77 (9.6)
>18 years old	205 (20.5)	26 (12.6)
Sex		
Male	455 (45.1)	50 (10.9)
Female	545 (54.9)	53 (9.7)
Students		
Kindergarten	65 (8.7)	15 (23.1)
1st grade	63 (8.4)	13 (20.6)
2nd grade	54 (7.2)	7 (12.9)
3rd grade	61 (8.1)	9 (14.7)
4th grade	66 (8.8)	7 (10.6)
5th grade	92 (12.3)	9 (9.7)
6th grade	82 (10.9)	7 (8.5)
7th grade	96 (12.8)	6 (6.2)
8th grade	89 (11.9)	0 (0)
9th grade	79 (10.5)	4 (5.1)
Subtotal	747 (74.7)	77 (10.3)
Nonstudents		
Personnel	165 (16.5)	25 (15.2)
Food handlers	16 (1.6)	1 (6.2)
Other contact	72 (7.2)	0 (0)
Subtotal	253 (25.3)	26 (10.2)
Shift		
Morning	363 (36.3)	65 (17.9)
Afternoon	385 (38.5)	10 (2.6)
Both	252 (25.2)	28 (11.1)

tically significant ($P < .05$). Although the absolute number of infected children was higher (77 of 103 infected subjects), the maximum infection rate (15.2%) was observed among the school employees. One of the 16 workers who were involved directly in the preparation or transportation of luncheons showed evidence of acute *T. cruzi* infection, with serological test results positive for specific IgM and IgG (Table 1).

A significant positive correlation was found between ingestion of guava juice and risk of infection (OR, 3.5 [95% CI, 1.85–6.7]) (Table 2). The epidemiological interviews revealed that, except for the guava juice, all other beverages were made in the early morning. The guava fruits, in contrast, were boiled the night before and left to cool inside a large uncovered pot before blending in the morning. Once in the school, the juice was delivered to the morning shift, first to school personnel, then to kindergarten students, and then to students in ascending grades. Some personnel and students of the afternoon shift customarily consumed any remaining juice.

Of those infected, 75% were symptomatic, 20.3% required hospitalization, and a 5-year-old child died of acute chagasic myocarditis. Most patients reported fever that lasted >7 days, abdominal pain, headache, dry cough, and myalgia; to a lesser degree, they reported diarrhea, facial edema, malaise, arthralgias, dyspnea, and tachycardia (Table 3). In the univariate regression analysis, the following symptoms showed a significant association with a higher risk of serologically confirmed infection: fever, arthralgias, skin lesions (rash, erythema nodosum, or facial edema), and cardiovascular abnormalities. However, on the multivariate analysis, only fever and cardiovascular abnormalities showed statistical significance.

In 61 (59%) of the 103 confirmed cases, ≥1 abnormality was noticed on the ECG recordings. T wave abnormalities were significantly more common among patients ≤18 years of age, whereas supraventricular arrhythmias and microvoltages were predominant among adults (Table 4), who more frequently developed severe clinical cardiological manifestations that required hospitalization.

Among 1000 persons evaluated, 103 individuals had anti–*T. cruzi* IgG antibodies by ELISA, and 90 (87.3%) were also IgM positive. The specific IH test was concordant in 99 (96.1%) of 103 individuals, whereas the remaining 4 individuals had positive WB results.

Because of logistic constraints, parasitemia could be assessed in only 43 patients by parasitological methods. Of these, 13 (30.2%) had positive fresh-stained blood smear results, in vitro culture, or mice inoculation.

Sixteen individuals with ELISA results positive for anti–*T. cruzi* IgG antibodies but negative IH results nevertheless received a full course of antiparasitic treatment. During follow-up, they became IgG seronegative while remaining persistently negative according to both IH and WB results. Five such patients developed clinical signs, as well as ECG abnormalities. Because these patients did not fulfill World Health Organization criteria for the CD diagnosis, they were considered to have undefined cases (Figure 1).

Samples of 150 persons were randomly chosen to be tested by specific PCR targeted at the *T. cruzi* kinetoplastid DNA. The reaction was positive in 35 (79.5%) of 44 serologically confirmed cases. All 106 seronegative individuals tested were also negative by PCR. A collateral survey performed at the site where the incriminated juice was processed revealed the presence of infected *P. geniculatus* and domestic rats.

As part of an ongoing cooperative study with the Instituto López Neyra in Granada, Spain, 3 parasite isolates obtained from patients, as well as from 1 infected triatomine captured at the juice preparation site, were typed using *T. cruzi* ribosomal and mini-exon gene markers. Preliminary results revealed a great genetic homogeneity, with all of the isolates belonging to the *T. cruzi* I lineage. Furthermore, homology analysis of the

Table 2. Univariate and Multivariate Logistic Regression Analysis of Risk Factors Associated with *Trypanosoma cruzi* Transmission during an Outbreak of Orally Acquired Chagas Disease, Caracas, Venezuela, 2007

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age				
≤18 Years	0.85 (0.79–0.91)	.01	0.7 (0.73–0.87)	.001
>18 Years	1.03 (1.0–1.07)	.02	1.03 (1.1–1.05)	.01
Worker vs student	1.3 (0.83–2.06)	.24	...	...
Shift (morning vs afternoon)	3.19 (2.1–4.8)	.001	4.7 (2.6–8.3)	.001
Any fresh beverage	2.17 (0.77–6.1)	.14	...	...
Guava juice	3.5 (1.85–6.7)	.001	3.2 (1.4–7.1)	.004
Passion fruit juice	0.95 (0.59–1.62)	.95	...	...
Melon juice	1.16 (0.76–1.7)	.47	...	...
Lemon-starch drink	1.03 (0.68–1.52)	.85	...	...
"Chicha"	0.77 (0.51–1.18)	.24	...	...
Oat meal drink	1.37 (0.9–2.0)	.13	...	...
Tamarind juice	0.6 (0.39–0.94)	.60	...	...
Mango juice	0.79 (0.5–1.1)	.26	...	...
Papaya juice	1.32 (0.8–2.0)	.19	...	...
Pineapple juice	0.72 (0.4–1.9)	.12	...	...

NOTE. CI, confidence interval; OR, odds ratio.

sequence of an amplified polymorphic mini-exon from *T. cruzi* RNA confirmed that all parasite isolates from the patients were identical, which was consistent with a common source of infection.

DISCUSSION

Thanks to a coordinated program in the Southern Cone countries, the transmission of CD has been successfully interrupted in Uruguay and Chile, as well as in at least 8 of the 12 states of Brazil in which CD is endemic [19, 27]. However, the persistence of numerous sylvatic foci and the wide distribution of vectors and reservoirs, together with a progressive reduction in the availability of the vector's natural source of blood (birds and mammals) in intervened forested areas, is driving originally wild triatomines to invade human dwellings [28, 29]. Once domiciliation has occurred, *P. geniculatus* may feed abundantly on domestic reservoirs, as well as on humans. As part of their nocturnal activity, vectors circulate widely inside the house and can thereby eventually contaminate unprotected food and beverages with their feces. There is also the possibility of trans-

Table 3. Univariate and Multivariate Logistic Regression Analysis According to Symptoms and Serological Test Results for 1000 Individuals Exposed during an Outbreak of Orally Transmitted Acute Chagas Disease in Caracas, Venezuela, 2007

		Serological test results		Univariate analysis		Multivariate analysis	
Symptom	No. (%) of subjects (n = 1000)	Percent positive/percent negative	P^a	OR (95% CI)	*P*	OR (95% CI)	*P*
Fever	190 (19.0)	46.6/15.7	.001	4.6 (3.0–7.1)	.001	5.4 (3.9–9.6)	.001
Artralgias	18 (1.8)	6.6/1.2	.001	5.7 (2.1–15.4)	.001	3.3 (0.4–26.2)	.250
Skin lesions[b]	30 (3.0)	11.4/2.0	.001	6.2 (2.9–13.4)	.001	2.2 (0.7–6.9)	.140
Cardiovascular	4 (0.4)	1.9/0.2	.001	8.6 (1.2–62.0)	.030	4.3 (1.2–12.8)	.040
Gastrointestinal	84 (8.4)	11.4/8.0	.230	1.4 (0.7–2.8)	.240	...	...
Respiratory	49 (4.9)	7.6/4.5	.170	1.7 (0.7–3.7)	.170	...	...
Unspecific	26 (2.6)	4.7/2.3	.140	2.0 (0.7–2.8)	.150	...	...

NOTE. CI, confidence interval; OR, odds ratio.

[a] By χ^2 analysis.

[b] Rash, erythema nodosum, and facial edema.

Table 4. Basal Electrocardiogram (ECG) Abnormalities by Age Group for 61 Infected Patients from an Outbreak of Orally Acquired Acute Chagas Disease in Caracas, Venezuela, 2007

ECG abnormality	Age group ≤18 Years (n = 48)	Age group >18 Years (n = 13)	Total	P[a]
ST abnormality	30	4	34	.028
T abnormality	39	1	40	<.001
Supraventricular arrhythmia	3	6	9	.002
Ventricular arrhythmia	2	0	2	.897
Microvoltage/decrease amplitud QRS	0	3	3	.007
QTc prolongation	2	0	2	.897
Fascicular block	3	2	5	.621
AV block	2	0	2	.897

[a] Yates corrected χ^2 analysis.

mission by food contamination with urine or anal secretions of infected marsupials [30].

The genetic homogeneity and lack of significant genetic intralineage polymorphism observed in all of the isolates thus far typed from the current outbreak is consistent with a common source of infection. Moreover, the confirmation of an acute infection in the woman responsible for the preparation of the juice lends further support to evidence that indicates short-term exposure, as do the logistic regression analysis results, which incriminated the guava juice as the possible source of contamination. We therefore postulate that, during the night, infected triatomines might have contaminated the unprotected pot where the guava juice was left before being blended in the early morning. Once the juice arrived at the school, it was first served to the teachers and afterwards served to the students, progressing from the lower to the higher grades of the morning shift. Any remaining juice was later shared by the teachers and students of the afternoon shift. This sequence of events could explain the relatively high attack rate observed among school personal (15.2%) and the significant decrease in the attack rate among students in the ninth grade (5.1%), compared with that among kindergarten students (23.1%). The significant difference in the attack rates found between students of the morning (22.5%) and afternoon shifts (2.4%) suggests that the concentration of the inoculum may have been different for both groups, perhaps reflecting a steady decrease in the survival of infecting metacyclic trypomastigotes [31].

Orally transmitted CD episodes have been described previously, all of which have been reported in South America [3–9, 32–34]. Distinctive epidemiological features included a lower number of infected persons (37 cases being the maximum number reported in any outbreak); relatively high lethality (up to 35.2%, with an average rate of 7.1%); a preponderance of cases occurring among adults; and occurrence in remote rural areas or in urban communities where fruits obtained from areas of endemicity, such as açai *(Euterpe oleracea)*, piassava *(Leopoldinea piaçaba)*, and sugar cane, were consumed. The present outbreak is unique in that it affected a large, predominantly young, healthy urban population and was associated with high rates of parasitemia and morbidity but a very low mortality rate (0.97%). The latter probably relates to prompt diagnosis and treatment. It is the first time that contaminated guava juice has been incriminated as the source of infection. Moreover, this represents a genuine urban oral CD outbreak, because the *T. cruzi* strain that was involved in the outbreak originated from an inner-city household, where peridomestic triatomines and rodent reservoirs allowed the maintenance of transmission.

One crucial problem was the overwhelming amount of clinical cases that required diagnostic confirmation. Serological testing with the ELISA was very useful for this purpose, and the assessment of both IgG and IgM anti–*T. cruzi* antibodies for all members of the exposed population enabled us to demonstrate the infection in the early phase. The concurrent onset of symptoms in most cases and the fact that specific IgM antibodies were demonstrated in a high percentage of cases (87.3%) further suggests that exposure to the infecting inoculum was recent [35] and singular or short-lived.

Of the 103 individuals in whom *T. cruzi* parasitemia was determined by parasitological methods and/or PCR, 44 (40.7%) had positive test results. This is probably one of the highest rates of parasitemia ever documented in any orally transmitted CD outbreak.

Although 75% of the infected individuals were symptomatic, the predominant clinical manifestations observed (fever, headache, and myalgias) are all highly unspecific. Indeed, dengue, mononucleosis, hepatitis, and intoxications were among the causes contemplated initially. Clinical findings such as facial edema, gingivitis, and dry cough are probably the consequence of the penetration of the parasite throughout the oral cavity, lips or pharyngeal mucosa. These latter manifestations, along

with other unexpected findings, such as erythema nodosum, anasarca, and lower limbs edema, are not described in vectorial transmission and even in prior reports of orally-acquired CD. They may be related to the host's immune inflammatory response conditioned by the genetics of each individual or by a high parasite load [36]. On the other hand, the findings of acute myocarditis were observed in an unusually high proportion (59%) of confirmed cases.

The diagnosis of acute CD requires a high index of suspicion by the clinician, especially when patients are seen away from the traditional areas of endemicity. In countries in which CD occurs, this condition must be considered in the differential diagnosis of FUO, because food-borne acute CD may occur more often than is currently recognized.

Progressive environmental changes that affect the ethology and ecology of potential *T. cruzi* reservoirs and vectors, together with an increase in human populations surrounded by intervened forests, have favored the urbanization and domiciliation of the cycle maintained by *P. geniculatus*, thus affecting the poor populations of the misery belts around most Latin American cities and middle-class populations, under the concept of the "edge-mediated effects" [37]. This new situation imposes necessary changes in the strategy of CD control programs, which until now have been limited to vector control activities in rural Latin American communities in areas of endemicity.

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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 2010年8月18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	①②③乾燥抗HBs人免疫グロブリン ④⑤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	Agence France-Presse /2010/08/14	公表国 パキスタン
販売名 （企業名）	①ヘブスブリン筋注用200単位　（ベネシス） ②ヘブスブリン筋注用1000単位　（ベネシス） ③ヘブスブリン　（ベネシス） ④ヘブスブリンIH静注1000単位　（ベネシス） ⑤静注用ヘブスブリン-IH　（ベネシス）			

研究報告の概要

ベルギーの男性が南アジア起源の薬剤耐性いわゆるスーパー細菌で死亡した。新たな健康の脅威からの最初の死亡報告である。
2番目のベルギー人はモンテネグロに旅行中に事故に遭い、入院後感染したが、ベルギーで治療をうけ回復した。
最初の犠牲者はパキスタンへの旅行中に交通事故に遭い、脚を負傷し、パキスタンの病院で治療している間に耐性菌に感染したベルギー人で、帰国後の6月に死亡した。
彼は、最近同定されたNew Delhi metallolactamase-1(NDM-1)という、例えばE.coliのような通常のバクテリアを抗生物質耐性にする遺伝子を有するバクテリアに感染した。このバクテリアは昨年、インドで入院していたスウェーデン人の患者で最初に同定された。
このバクテリアの流行の中心はインドとパキスタンのようである、しかし、接触と旅行を通して伝播は広がっている。

使用上の注意記載状況・その他参考事項等

代表としてヘブスブリンIH静注用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ウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
NDM-1産生多剤耐性菌による死亡例の初めての報告である。 万一、ニューデリーメタロ-β-ラクタマーゼ-1(NDM-1)を産生する細菌が原料血漿に混入したとしても、除菌ろ過等の製造工程で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。

Belgian man dies of South Asian superbug, hospital reports

AGENCE FRANCE-PRESSE AUGUST 14, 2010

A Belgian man died from a drug-resistant so-called superbug originating in South Asia, a doctor said Friday, the first reported death from the new health threat.

A second Belgian was infected after being hospitalized after an accident during a trip to his native Montenegro, but recovered following treatment in Belgium, another expert said.

The first victim was infected while being treated in a hospital in Pakistan and died in June, Denis Pierard, a microbiologist from AZ VUB hospital in Brussels where the man had been treated, told Belgian media.

"He was involved in a car accident during a trip to Pakistan. He was hospitalized with a major leg injury and then repatriated to Belgium, but he was already infected," the doctor said.

Despite being administered colistin, a powerful antibiotic, the patient died, Pierard said.

He was infected by a bacteria that carried the newly identified gene New Delhi metallolactamase-1 (NDM-1) that makes ordinary bacteria such as E. coli resistant to antibiotics. It was first identified last year in a Swedish patient admitted to hospital in India.

Scientists fear the gene could easily migrate to other bacteria, making them antibiotic-resistant.

"The epicentre of the presence of this bacteria seems to be India and Pakistan, but it appears through contact and travel, its spread is becoming wider," said Youri Glupczynski from the University of Leuven.

British medical journal The Lancet reported this week that bacteria containing the NDM-1 gene had been found in 37 Britons who had received medical treatment in South Asia, and three cases have been reported in Australia. There have been two cases in Canada, one of them in B.C.

別紙3

番号2

研　究　報　告　調　査　報　告　書

識別番号・報告回数				第一報入手日 ：平成22年8月18日	新医薬品等の区分 ：該当なし	総合機構処理欄
一　般　的　名　称	－		研究報告の公表状況	－	公表国： 英国	
販　売　名　（企　業　名）	－					
研究報告の概要	インド、パキスタン、英国の多剤耐性腸内細菌におけるNDM－1の流行を調査した。その結果、チェンナイで44件、ハリヤナで26件、英国で37件、その他のインドとパキスタンで73件のNDM－1が検出された。ほとんどが大腸菌（36件）と肺炎桿菌（111件）で見つかり、tigecyclineとcolistin以外の抗生物質に耐性化していた。ハリヤナから分離された肺炎桿菌は同一だったが、英国とチェンナイの株は多様化していた。大部分が分離株のプラスミド上にNDM－1があった。NDM－1陽性だった多くの英国人が、1年以内にインドかパキスタンに旅行したか、あるいはこれらの国と関連があった。					使用上の注意記載状況等・その他参考事項等
報告企業の意見			今後の対応			
本報告は，当該生物由来製品による感染症情報ではない． 本報告を“新規感染症”および“重大な感染症情報”と考え，報告する．			今後も感染症情報の収集に努め，当該生物由来製品に係る情報を入手した場合には速やかに調査・報告を行い安全性の確保に努める．			

MedDRA/J Ver. 13.1J

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Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

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Summary

Background

Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-β-lactamase 1 (NDM-1) are potentially a major global health problem. We investigated the prevalence of NDM-1, in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK.

Methods

Enterobacteriaceae isolates were studied from two maior centres in India—Chennai (south India), Harvana (north India)—and

those referred to the UK's national reference laboratory. Antibiotic susceptibilities were assessed, and the presence of the carbapenem resistance gene bla_{NDM-1} was established by PCR. Isolates were typed by pulsed-field gel electrophoresis of XbaI-restricted genomic DNA. Plasmids were analysed by S1 nuclease digestion and PCR typing. Case data for UK patients were reviewed for evidence of travel and recent admission to hospitals in India or Pakistan.

Findings

We identified 44 isolates with NDM-1 in Chennai, 26 in Haryana, 37 in the UK, and 73 in other sites in India and Pakistan. NDM-1 was mostly found among *Escherichia coli* (36) and *Klebsiella pneumoniae* (111), which were highly resistant to all antibiotics except to tigecycline and colistin. *K pneumoniae* isolates from Haryana were clonal but NDM-1 producers from the UK and Chennai were clonally diverse. Most isolates carried the NDM-1 gene on plasmids: those from UK and Chennai were readily transferable whereas those from Haryana were not conjugative. Many of the UK NDM-1 positive patients had travelled to India or Pakistan within the past year, or had links with these countries.

Interpretation

The potential of NDM-1 to be a worldwide public health problem is great, and co-ordinated international surveillance is needed.

Funding

European Union, Wellcome Trust, and Wyeth.

別紙3

研　究　報　告　調　査　報　告　書

識別番号・報告回数				第一報入手日 ：平成22年8月18日	新医薬品等の区分 ：該当なし	総合機構処理欄
一般的名称	－		研究報告の公表状況	－	公表国： 日本	
販売名（企業名）	－					
研究報告の概要	インド、パキスタンが発生源とみられ、ほとんどの抗生物質が効かない新種の細菌に感染した患者が欧州などで増えており、ベルギーで16日までに最初とみられる死者が確認された。欧州メディアによると、英国、フランス、ベルギー、オランダ、ドイツ、米国、カナダ、オーストラリアで感染が確認され、今後さらに拡大する恐れがあるという。英国では約50件の感染が確認されている。感染者の多くは、医療費の安いインドやパキスタンで美容整形手術などを受けており、感染源は両国との見方を示している。					使用上の注意記載状況等・その他参考事項等
報告企業の意見			今後の対応			
本報告は，当該生物由来製品による感染症情報ではない． 本報告を“新規感染症”および“重大な感染症情報”と考え，報告する．			今後も感染症情報の収集に努め，当該生物由来製品に係る情報を入手した場合には速やかに調査・報告を行い安全性の確保に努める．			

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NMP 2010-0001

毎日jp

サイエンス

細菌:新種の感染が拡大 ベルギーで初の死者

インド、パキスタンが発生源とみられ、ほとんどの抗生物質が効かない新種の細菌に感染した患者が欧州などで増えており、ベルギーで16日までに最初とみられる死者が確認された。欧米メディアによると、英国、フランス、ベルギー、オランダ、ドイツ、米国、カナダ、オーストラリアで感染が確認され、今後さらに拡大する恐れがあるという。

英医学誌ランセット最新号によると、何種類かの細菌が特定の抗生物質を分解する酵素「NDM1」を作り出す遺伝子を持ち、ほとんどすべての抗生物質に対して耐性を持つようになった。こうした細菌に感染すると死亡率が非常に高くなるため、感染への監視強化と新薬の開発が必要だとしている。

同誌によると、英国では約50件の感染が確認されている。感染者の多くは、医療費の安いインドやパキスタンで美容整形手術などを受けており、同誌は感染源は両国との見方を示している。

ベルギー・メディアによると、新たな細菌に感染した男性が死亡したのは今年6月。男性は旅行中にパキスタンで交通事故に遭い、現地の病院で手当てを受けた。ベルギーに戻った時には既に感染しており、投与した抗生物質も効かなかったという。

インド保健省は、感染源をインドと関連づけることに反発し「インドへの医療目的の観光は安全だ」と主張している。(ブリュッセル共同)

毎日新聞 2010年8月17日 19時06分

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
				2010. 4. 27	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	Byrnes EJ 3rd, Li W, Lewit Y, Ma H, Voelz K, Ren P, Carter DA, Chaturvedi V, Bildfell RJ, May RC, Heitman J. PLoS Pathog. 2010 Apr 22;6(4):e1000850.	公表国 米国
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社) 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

○米国北西部に現れた高病原性*Cryptococcus gattii* (*C.gattii*)
*C.gattii*は、免疫抑制状態にある患者のみならず健常人へも感染し、致死性の疾病を引き起こす。この真菌は従来、熱帯・亜熱帯性真菌と考えられていたが、1999年にカナダのバンクーバー島の気温の上昇により流行したと考えられ、隣接するカナダ本土ブリティッシュコロンビアや米国本土にも拡大している。この大流行は*C.gattii type* VGII、特に、VGIIa/majorが原因であったが、新しい遺伝子型(VGIIc型)の*C.gattii*の感染が出現し、数人が死亡している。オレゴンで見つかった新たなVGIIcは免疫細胞あるいはマウスに対して病原性が高いことが示された。新たな気候の中で疾病を引き起こすために、病原体がこれらの地域に適応する方法を確立し、高病原性になっていく可能性を示唆する。

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
米国北西部で見つかり、致死性の疾病を引き起こす高病原性*Cryptococcus gattii* は、従来、熱帯・亜熱帯性真菌と考えられていたが、新しい気候の中でその土地に適応していった可能性があるとの報告である。	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。

OPEN ACCESS Freely available online PLoS PATHOGENS

Emergence and Pathogenicity of Highly Virulent *Cryptococcus gattii* Genotypes in the Northwest United States

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Abstract

Cryptococcus gattii causes life-threatening disease in otherwise healthy hosts and to a lesser extent in immunocompromised hosts. The highest incidence for this disease is on Vancouver Island, Canada, where an outbreak is expanding into neighboring regions including mainland British Columbia and the United States. This outbreak is caused predominantly by *C. gattii* molecular type VGII, specifically VGIIa/major. In addition, a novel genotype, VGIIc, has emerged in Oregon and is now a major source of illness in the region. Through molecular epidemiology and population analysis of MLST and VNTR markers, we show that the VGIIc group is clonal and hypothesize it arose recently. The VGIIa/IIc outbreak lineages are sexually fertile and studies support ongoing recombination in the global VGII population. This illustrates two hallmarks of emerging outbreaks: high clonality and the emergence of novel genotypes via recombination. In macrophage and murine infections, the novel VGIIc genotype and VGIIa/major isolates from the United States are highly virulent compared to similar non-outbreak VGIIa/major-related isolates. Combined MLST-VNTR analysis distinguishes clonal expansion of the VGIIa/major outbreak genotype from related but distinguishable less-virulent genotypes isolated from other geographic regions. Our evidence documents emerging hypervirulent genotypes in the United States that may expand further and provides insight into the possible molecular and geographic origins of the outbreak.

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Introduction

Newly emerging and reemerging diseases have become a major focus of infectious disease research in the 21st century. Reemerging diseases are classified as those that have been previously documented, but are now rapidly increasing in incidence, geographic range, or both [1]. Emerging disease events have been occurring at higher than average rates in the United States due to several factors such as wildlife diversity, environmental change, international travel, and increases in host susceptibility [2,3]. An additional factor contributing to increases in morbidity and mortality for many infectious diseases involves genetic recombination events or gene/pathogenicity island acquisitions. These events can occur via either horizontal gene transfer or conjugation/introgression, leading to novel pathogenic genotypes. This form of virulence evolution has been well characterized in bacterial, viral, fungal, and parasitic human diseases [4,5,6,7,8,9]. The ability to cause damage to mammalian hosts is a common theme among all microbial pathogens, making it a key aspect of host-pathogen studies [10].

In the genomic era, it is now possible to combine conventional epidemiological approaches with newly developed molecular typing techniques to gain insight into the emergence and molecular epidemiology of pathogens. These approaches can improve understanding of population dynamics during an outbreak, and may lead to novel methods for the rapid identification, treatment, and diagnosis of emerging infections [11]. In addition, molecular typing serves as an initial approach to classify isolates into distinct genotypes for analysis. Further investigations may include the examination of virulence and phenotypic traits that may be common or distinct between genotypes [6,12,13]. Gaining insights into the molecular epidemiology and virulence of newly emerging diseases has considerable potential for the rapid assessment and management of newly emerging infections.

Over the past decade, *Cryptococcus gattii* has emerged as a primary pathogen in northwestern North America, including both Canada and the United States [6,13,14,15,16,17,18]. In the past, *C. gattii* has often been associated with *Eucalyptus* trees in tropical and subtropical climates, causing disease in immunocompetent

Author Summary

Emerging and reemerging infectious diseases are increasing worldwide and represent a major public health concern. One class of emerging human and animal diseases is caused by fungi. In this study, we examine the expansion on an outbreak of a fungus, *Cryptococcus gattii*, in the Pacific Northwest of the United States. This fungus has been considered a tropical fungus, but emerged to cause an outbreak in the temperate climes of Vancouver Island in 1999 that is now causing disease in humans and animals in the United States. In this study we applied a method of sequence bar-coding to determine how the isolates causing disease are related to those on Vancouver Island and elsewhere globally. We also expand on the discovery of a new pathogenic strain recently identified only in Oregon and show that it is highly virulent in immune cell and whole animal virulence experiments. These studies extend our understanding of how diseases emerge in new climates and how they adapt to these regions to cause disease. Our findings suggest further expansion into neighboring regions is likely to occur and aim to increase disease awareness in the region.

hosts at low incidences [19,20,21]. *C. gattii* is distinct from its sibling species *Cryptococcus neoformans* [22], which more commonly infects immunosuppressed hosts and infects almost one million people annually with over 620,000 attributable mortalities [23,24,25]. *C. gattii* can be classified into four discrete molecular types (VGI-VGIV), which represent cryptic species as no nuclear allelic exchange between groups has been observed [6]. This molecular classification is significant because VGII is responsible for approximately 95% of the Pacific Northwest infections in Canada and the United States [12,15]. The appearance of *C. gattii* in North America is alarming because this is the first major emergence in a temperate climate, indicating a possible expansion in the endemic ecology of this pathogen [26,27].

Several significant questions persist regarding the outbreak and its expansion within the United States. As the global collection of *C. gattii* isolates expands, the molecular epidemiology of the species has become increasingly informative, particularly through multilocus sequence typing (MLST), which allows data to be readily compared between groups within the research community [6,15,28,29,30]. The increase in global and regional isolates that have been typed at the molecular level allows detailed analysis of *C. gattii*. The analysis of both conserved coding regions, and diverse noncoding regions provides insight into the genotypes responsible for the outbreak. A major finding in this study is a level of underlying diversity within the VGIIa/major genotype in the region of expansion and other geographic locales.

Prior studies documented that the *C. gattii* VGIIa/major genotype isolates from Vancouver Island are highly virulent in experimental murine infection assays [6]. Here we expanded this analysis to examine clinical VGIIa genotype isolates from Vancouver Island, the United States, and Brazil, in addition to an environmental VGIIa isolate from California. Our findings are consistent with recent macrophage intracellular proliferation studies, demonstrating that United States isolates from the recent Pacific NW outbreak exhibit high virulence [31]. The enhanced virulence of isolates from the outbreak region, when compared with those from other regions, suggests that the genotypes circulating in the Pacific NW are inherently increased in their predilection to cause disease in mammalian hosts.

In addition to the detailed examination of the VGIIa/major genotype clade, we report that the novel VGIIc genotype is highly virulent in a murine inhalation model. Moreover, the VGIIc genotype was found to have high intracellular proliferation rates in macrophages and a significantly increased percentage of mitochondria with tubular morphology after macrophage exposure, and thus VGIIc isolates share virulence attributes with the VGIIa/major genotype isolates from the Vancouver Island outbreak. These results extend the molecular and phenotypic understanding of the recently discovered VGIIc/novel genotype and help shed light into its possible geographic and molecular origins.

These studies provide insights into both the evolutionary history and virulence characteristics of this unique and increasingly fatal fungal outbreak in the temperate climate of the North American Pacific Northwest and highlight the importance of a collaborative interdisciplinary approach to the analysis of emerging pathogens. Application of these approaches may increase awareness of disease risks in the expansion zone, lead to more rapid diagnoses and, as a result, accelerate the implementation of appropriate therapy.

Materials and Methods

Isolate Identification

Human and veterinary cases of confirmed or suspected *C. gattii* infections in the states of Washington and Oregon were identified by referring physicians and veterinarians, and subsequently isolates were purified and examined. Melanin production was assayed by growth and dark pigmentation on Staib's niger seed medium, and urease activity was detected by growth and alkaline pH change on Christensen's agar. These tests established that isolates were *Cryptococcus* (*C. neoformans* or *C. gattii*). Isolates were concomitantly examined for resistance to canavanine and utilization of glycine on L-canavanine, glycine, 2-bromothymol blue (CGB) agar. Growth on CGB agar indicates that isolates are canavanine resistant, and able to use glycine as a sole carbon source, triggering a bromothymol blue color reaction indicative of *C. gattii*, whereas *C. neoformans* is sensitive to canavanine, and cannot use glycine as a sole carbon source, resulting in no growth or coloration in this selective indicator medium. All CGB positive isolates were then grown under rich culture conditions prior to storage at −80°C in 25% glycerol and genomic DNA extraction. For genomic DNA isolation, a modified protocol of the MasterPure Yeast DNA purification kit from Epicentre Biotechnologies was used. Briefly, 500 µl of glass beads (425–600 nm) were added into the combination of cells and 300 µl cell lysis solution. The rest of the method followed the protocol provided by the manufacturer.

Molecular Epidemiology

For multilocus sequence typing analysis (MLST) [32], each isolate was analyzed with a minimum of eight and in some cases sixteen loci. For each isolate, genomic regions were PCR amplified (Table S1), purified (ExoSAP-IT), and sequenced. All primers used for the analysis were designed specifically to amplify open reading frame (ORF) gene sequence regions including those with noncoding DNA regions to maximize discriminatory power. Sequences from both forward and reverse strands were assembled, and manually edited using Sequencher version 4.8 (Gene Codes Corporations). Based on BLAST analysis of the GenBank database (NCBI), each allele was assigned a corresponding number. GenBank accession numbers with corresponding allele numbers are listed in the supplementary information (Table S2). To determine that the nine VGIIc/novel isolates are clonally related, given the level of diversity in the loci and the number of isolates that have been examined, we applied an equation to measure the probability of a genotype occurring more than once in the dataset

[33,34]. For the variable number of tandem repeat (VNTR) analysis, the Tandem Repeat Finder (TRF) version 4.00 software package was employed for marker development, using the genomic sequence of *C. gattii* isolate R265 (http://www.broadinstitute.org/annotation/genome/cryptococcus_neoformans_b.2/Home.html) [35]. The identified tandem repeat sequences and 400 bp of the flanking region were extracted from the genomic sequence and ranked according to the number of total repeats and the size of repeat units using an in-house Perl script (available upon request). Markers were examined for stability and those with high variability and stability were chosen for the analysis. Sequences were assembled and edited using Sequencher version 4.8 (Gene Codes Corporations) and aligned using the Clustal W web based software package (http://www.ebi.ac.uk/Tools/clustalw2/index.html).

Mating Conditions

Mating analysis was conducted on V8 media (pH 5). Isolates were incubated at room temperature in the dark for 2–4 weeks in dry conditions. All strains were crossed with the VGIII mating type a isolate B4546 and the VGIII mating type α isolate NIH312, both of which are fertile and commonly used for mating studies [36]. Fertility was assessed by microscopic examination for hyphae, fused clamp cells, basidia, and basidiospore formation.

Clustering and Haplotype Analyses

For each VNTR marker, a sequence type was defined as a sequence exhibiting a unique mutation. Each sequence type was confirmed to be unique by BLAST analysis of the NCBI GenBank database [37]. A concatenated VNTR sequence type (CVST) was defined as unique combinations of sequence types from the VNTR markers. A multiple alignment of the sequences was carried out using Clustal W software [38]. Analysis of the sequences was conducted using the Neighbor-Joining and Maximum Parsimony methods within the MEGA 3.1 software [39]. In addition, the use of the maximum likelihood method (PhyML 3.0) with SH-like approximate likelihood-ratio test and HKY85 substitution model was applied [40,41]. For this purpose, sequences of the selected VNTR markers were concatenated. We additionally concatenated all of the strain-typing markers including the housekeeping genes used in MLST and VNTR loci for clustering analysis. The haplotype mapping analysis was carried out using TCS software version 1.21 (http://darwin.uvigo.es/software/tcs.html) [42].

Intracellular Proliferation Rate (IPR) Determination

A proliferation assay was previously developed to monitor the intracellular proliferation rate (IPR) of individual strains for a 64-hour period following phagocytosis [31]. For this assay, J774 macrophage cells were exposed to cryptococcal cells that were opsonized with 18B7 antibody for 2 hr as described previously [43]. Each well was washed with phosphate-buffered saline (PBS) in quadruplicate to remove as many extracellular yeast cells as possible and 1 ml of fresh serum-free DMEM was then added. For time point T = 0, the 1 ml of DMEM was discarded and 200 µl of sterile dH_2O was added into wells to lyse macrophage cells. After 30 minutes, the intracellular yeast were released and collected. Another 200 µl dH_2O was added to each well to collect the remaining yeast cells. The intracellular yeast were then mixed with Trypan Blue at a 1:1 ratio and the live yeast cells were counted. For the subsequent five time points (T = 16 hrs, T = 24 hrs, T = 40 hrs, T = 48 hrs and T = 64 hrs), intracellular cryptococcal cells were collected and independently counted with a hemocytometer. For each strain tested, the time course was repeated at least three independent times, using different batches of macrophages. The IPR value was calculated by dividing the maximum intracellular yeast number by the initial intracellular yeast number at T = 0. We confirmed that Trypan Blue stains 100% of the cryptococcal cells in a heat-killed culture, but only approximately 5% of cells from a standard overnight culture. Compared to a conventional colony counting method, this method was shown to be more sensitive in detecting the clustered yeast population or yeast cells undergoing budding. IPR values were used to assess how consistent the different VGII genotype subgroups were. For this statistical analysis the medians of each population were compared with the non-parametric Mann-Whitney U-test and values of $p<0.025$, after controlling for multiplicity, and were accepted as statistically significant (http://elegans.swmed.edu/~leon/stats/utest.cgi).

Mitochondrial Morphology

The mitochondrial morphology assays were conducted in a similar way to those in previous studies, with modifications [31]. *C. gattii* cells, grown overnight at 37°C in DMEM in a 5% CO_2 incubator without shaking for 24 hr, or isolated from macrophages 24 hr after infection, were harvested, washed with PBS twice and re-suspended in PBS containing the Mito-Tracker Red CMXRos (Invitrogen) at a final concentration of 20 nM. Cells were incubated for 15 min at 37°C. After staining, cells were washed in triplicate and re-suspended in PBS. For each condition, more than 100 yeast cells per replicate for each of the tested strains were chosen randomly and analyzed. For quantifying different mitochondrial morphologies, images were collected using a Zeiss Axiovert 135 TV microscope with a 100× oil immersion Plan-Neofluar objective. Both fluorescence images and phase contrast images were collected simultaneously. Images were captured with identical settings on a QIcam Fast 1394 camera using the QCapture Pro51 version 5.1.1 software. All Images were processed identically in ImageJ and mitochondrial morphologies were analyzed and counted blindly.

Three individual experiments were performed for each condition and the data were tested for normality using the Shapiro-Wilk test. For homogeneity of variances we used the Levene statistic. For statistically significant differences among the mean data we applied a One-Way ANOVA. Multi-comparisons using Tukey Honestly Significant Differences tests were performed to identify statistically significant differences between pairs. A p-value of $p<0.05$, after controlling for multiplicity, was considered to be statistically significant. Regression analysis was used to measure the correlation between tubular mitochondrial morphology and IPR values; an F-value of $P<0.05$ was considered to be a significant correlation.

Murine Virulence Tests and Histopathology

To examine the virulence potential of global VGII isolates, with a specific emphasis on the Pacific NW VGII outbreak genotypes, two independent murine virulence experiments were conducted at two facilities (Duke University Medical Center and the Wadsworth Center). The murine virulence assays at Duke University Medical Center and the Wadsworth Center used a similar protocol to previous *C. gattii* and *C. neoformans* experimental infections [6,44,45].

At the Duke University Medical Center Animal Facility, virulence was assessed using female A/Jcr mice (NCI, 18–24 g). Strains were cultured in YPD broth for 18–20 h at 30°C, harvested, washed three times with sterile PBS and counted using a hemocytometer to determine cell concentrations. Inocula for both murine experiments were confirmed by plating on YPD and counting colony-forming units (c.f.u.). Nine to ten A/Jcr mice per strain were anesthetized with pentobarbital and infected via intranasal instillation with 5×10^4 c.f.u. in 50 µl of sterile 1× PBS.

Animals that displayed severe morbidity, based on twice-daily examinations, were euthanized. Time to mortality was evaluated for statistical significance using Kaplan–Meier survival curves within the Prism software package (GraphPad Software), and P values were obtained from a log-rank test. Survival data was plotted for graphical analysis using the Prism software package.

At the Wadsworth center animal facility, all assays were conducted using male BALB/c mice (approximately 6 weeks old, 15–20 g, Charles River Laboratories, Inc.). Strains were grown overnight in YPD broth at 30°C with shaking. The cells were harvested, washed in PBS, and counted using a hemocytometer. Five mice per strain were anesthetized with a mixture of xylazine–ketamine, and allowed to inhale 10^5 (30 µl) cryptococcal cells per mouse, via intranasal instillation. Mice were given food and water *ad libitum* and monitored twice daily. At the first sign of poor health or discomfort, infected animals were euthanized. Brain and lung tissues from the dead animals were cultured on Niger seed agar for *C. gattii* recovery to confirm infections were due to this pathogen. Time to mortality was evaluated for statistical significance as described above.

Two animals from each strain assayed in the study conducted at Duke University were selected for histopathology analysis either at the time of sacrifice or at the conclusion of the experiment for the more attenuated isolates. For each animal, lung samples were collected and stored in 10% neutral buffered formalin. Samples were paraffin embedded and hematoxylin and eosin (H&E) stained at the Duke University Research Histology Laboratory. After staining and slide preparation, each sample was examined microscopically for analysis of cryptococcal cell burden and immune responses. Images were captured using an Olympus Vanox microscope (Duke PhotoPath, Duke University Medical Center).

Ethics Statement

The animal studies conducted at the Wadsworth Center were in full compliance with all of the guidelines set forth by the Wadsworth Center Institutional Animal Care and Use Committee (IACUC) and in full compliance with the United States Animal Welfare Act (Public Law 98–198). The Wadsworth Center IACUC approved all of the vertebrate studies. The studies were conducted in facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

The animal studies at Duke University Medical Center were in full compliance with all of the guidelines of the Duke University Medical Center Institutional Animal Care and Use Committee (IACUC) and in full compliance with the United States Animal Welfare Act (Public Law 98–198). The Duke University Medical Center IACUC approved all of the vertebrate studies. The studies were conducted in Division of Laboratory Animal Resources (DLAR) facilities that are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

Results

Molecular Analysis of *C. gattii* VGII Outbreak vs. Global Isolates

To examine the *C. gattii* outbreak isolates collected from 2005 to 2009 (Figure 1), an in-depth stepwise molecular analysis was applied to each isolate, and the genotypes were compared with other global genotypes. In total, 20 markers were selected for analysis. These markers include both coding and noncoding genomic regions and range in size and allelic diversity (Table 1). Additionally, all of the markers are randomly distributed among the chromosomes in the most recent assembly of the reference *C. gattii* VGI genome, WM276 (Figure 2). Initially, all isolates were sequenced at a total of eight MLST markers, and four variable number of tandem repeats (VNTR) markers (Figure 3, Table 2). Next, global isolates were selected for diversity, and several isolates from each of the primary genotypes in the expansion region were chosen for sequence analysis at eight additional MLST loci, bringing the total number of genetic markers analyzed for these isolates to 20 (Figure 4A). As expected, the MLST markers were less variable and more conserved, while the VNTR markers allowed for higher-resolution differentiation between isolates that appeared identical by MLST analysis. The generated datasets were then concatenated both without and with VNTR data (Figure 4B, Figure 4C).

The combined analysis of the results presented here, and a 30 marker MLST analysis conducted previously [6,18], reveal several findings of interest in relation to VGII genotypes in the region. From the analysis of 34 markers (30 MLST/4 VNTR), we show that the Vancouver Island VGIIa/major isolates are fully identical at all loci to several recent isolates from Washington and Oregon, as well as a historical clinical isolate (1970's), NIH444, from Seattle. Additionally, the VGIIb/minor isolates from Australia and Vancouver Island are identical at 34 total loci, and also identical to VGIIb/minor isolates from Oregon at 20 loci (16 MLST/4 VNTR). Furthermore, all VGIIc isolates to date are identical across all 20 loci examined (Figure 4A). However, we also are able to discriminate the outbreak VGIIa genotype from an environmental VGIIa isolate from California, CBS7750, and clinical VGIIa isolates CA1014 and ICB107 from California and Brazil, respectively, at one or more MLST/VNTR loci. It is clear from prior studies that the VGIIa/major and VGIIb/minor isolates are clonal lineages [6,12,15,46], and here we confirmed that this is the case for the nine VGIIc/novel isolates, based on 7-loci MLST analysis of the global VGII population (Figure S1) ($p<0.0001$).

The largest and most comprehensive dataset arose from the combined analysis of seven MLST and four VNTR loci, resulting in a total of 41 sequence types (STs). This dataset was generated from clinical, veterinary, and environmental *C. gattii* isolates (Figure 3, Figure S1, Table S3). From the analysis, it is clear that the VGIIa/b/c clusters are all related to each other, but also distinct. In addition, the data show that the VGIIa/major clade is closely clustered to VGIIc, further validating prior reports that examined a more limited number of loci [13,47]. In addition, VGIIc (ST21) shares high sequence identity to ST34, represented by a mating type a clinical isolate from Colombia, suggesting that the VGIIc genotype may have resulted from a-α mating, even though all isolates related to the Pacific NW outbreak are exclusively α mating type. Additionally, Vancouver Island isolates from our collection that had not been fully typed by MLST were sequenced at two loci to determine if any were unrecognized VGIIc isolates ($n=56$) (Figure S2). Of these, 51 were found to be VGIIa, five were VGIIb, and none were VGIIc, consistent with previous data from the region. Thus, VGIIc appears to remain exclusive to the United States, specifically Oregon, and has never been reported from Vancouver Island, the mainland of Canada, Washington State, or elsewhere globally.

Within the VGIIa/major cluster, based on the initial MLST analysis of 30 loci, only a single isolate (ICB107) could be distinguished from the other VGIIa isolates, and this was at only one locus [18]. To further investigate this homogeneous population causing the vast majority of the outbreak-related morbidity and mortality, we expanded the molecular analysis to include highly variable regions of the genome. The application of these VNTR markers, in combination with the MLST markers,

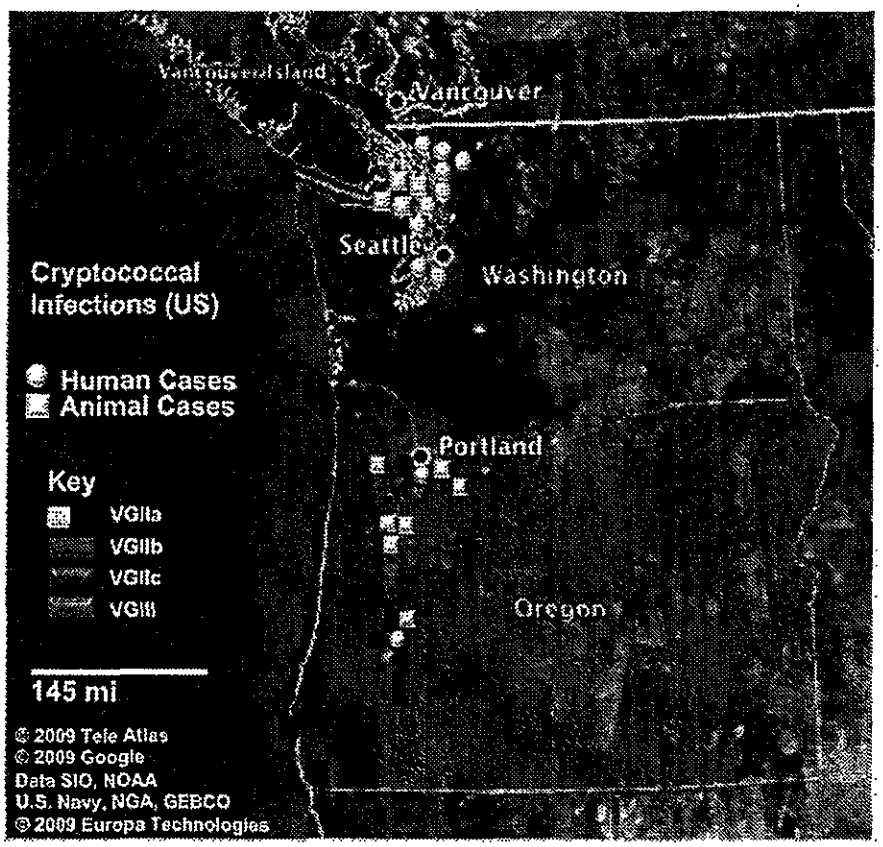

Figure 1. Geographic dispersal of pathogenic *C. gattii* genotypes in the United States. Circles represent human cases and squares represent animal (non-human mammalian) cases. All cases shown have been reported from 2005 to 2009. Isolates are color coded by genotype, in which yellow and blue correspond to VGIIa/major genotype cases (yellow ST1, blue ST30), red corresponds to VGIIb/minor, green corresponds to the novel VGIIc genotype, and orange corresponds to two cases determined to be molecular type VGIII. In total, there were 39 cases (18 human, 21 animal) that have been confirmed by phenotypic and genotypic profiling.
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allowed us to generate five independent STs from within the VGIIa/major genotype and related isolates (Figure 3).

These five sequence types (ST1, ST2, ST3, ST13, ST30) contained a total of 44 isolates (Figure 3, Table S3). The canonical VGIIa/major outbreak genotype, ST1, contained the vast majority of the 44 isolates (n = 38). As expected based on previous models of the *C. gattii* outbreak expansion [13], ST1 consisted of isolates exclusively from the initial outbreak and expansion zones, including British Columbia, Washington, and Oregon (Table S3). These results further validate the hypothesis that the epicenter of the outbreak was on Vancouver Island, beginning in the late 1990's, with a direct expansion into neighboring mainland British Columbia and subsequently into the United States [13]. The only exception in this dataset is isolate NIH444, an older isolate from the region that was isolated from a patient sputum sample in Seattle in the early 1970's [18], which is also identical at all 34 markers examined. This suggests that the VGIIa/major genotype responsible for most of the outbreak cases may have been circulating in the region prior to the outbreak. The possible travel history of this patient is unknown, and could therefore have involved exposure on Vancouver Island. Overall, this analysis provides increased evidence that the outbreak genotype is unique to the region thus far, and molecularly distinct from closely related isolates from both California and South America.

While the homogeneous nature of the VGIIa/major isolates based on robust molecular typing validated previous models, an underlying diversity within this group was also discovered. First, we further validated that the isolate ICB107 (ST13), from Brazil, was indeed distinct from the ST1 VGIIa/major clade. This isolate differs at one MLST marker (*LAC1*), and three VNTR markers (VNTR3, VNTR15, VNTR34). Additionally, the high-resolution sequence analysis was able to discriminate other VGIIa isolates that were collected from California. These include isolate CBS7750 (ST3), collected from the environment in San Francisco in 1990 [48], and isolate CA1014 (ST2), which was isolated from a patient with HIV infection in southern California. Each of these two isolates differs from ST1 due to unique mutations within the VNTR7 and VNTR34 loci, respectively. This shows that similar VGIIa genotype isolates have been found elsewhere, but that none are identical to those circulating as part of the ongoing Vancouver Island outbreak. Whether these isolates are a result of drift from ST1, or if ST1 arose from one of these related genotypes is not known.

In addition to discriminating VGIIa isolates that were not from the outbreak region, we also found a novel ST, ST30, which is highly similar to ST1, but divergent at a unique region of VNTR34. Interestingly, all three of the ST30 isolates are exclusively from Oregon, including two human clinical cases and one marine mammal case (Figure 1, Figure 3, Table S3).

Table 1. Markers used in this study.

Marker	Length (bp)	Chromosome (WM276)	Alleles
SXI1α	1,354	9	10
SXI2a	2,529	N/A*	2
IGS1	740	2	15
TEF1	700	13	5
GPD1	547	6	10
LAC1	554	7	5
CAP10	568	11	4
PLB1	600	13	9
MPD1	677	7	1
HOG1	564	3	11
BWC1	587	4	7
CNB1	571	10	6
TOR1	574	6	5
CRG1	575	2	9
FHB1	535	3	5
FTR1	545	3	7
CAP59	557	1	9
VNTR3	334	1	13
VNTR7	270	4	21
VNTR15	364	6	19
VNTR34	526	2	32

* *SXI2a* is an idiomorphic allele, and therefore not present in the α mating type isolate WM276.

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These results are consistent with an expansion followed by genetic drift in the highly variable VNTR loci. Isolates of ST30 have not been detected on Vancouver Island, indicating that this divergence is recent, and likely occurred after the expansion of ST1 into the United States. Alternatively, both ST1 (VGIIa/major) and ST30 may have been present for a long period, with only ST1 having been transferred to Vancouver Island.

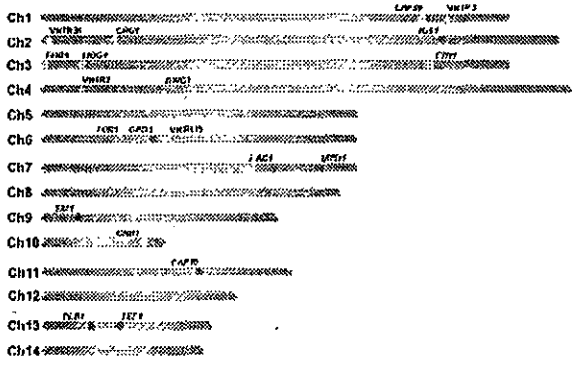

Figure 2. Markers used in the study are dispersed in the genome. A map of each chromosome is represented, illustrating the locations of each marker based on the genomic sequence of the *C. gattii* isolate WM276. MLST markers (n = 16) are indicated on the map by hexagons, with pink denoting the standard set used, blue the expanded set of loci, and red the *MAT* linked locus that is specific to α isolates. Green triangles represent the four VNTR loci that were examined.

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To gain insights into the potential origins of the VGIIc genotype, and to assess its position within the overall VGII clade, clustering analysis was applied. Analysis of the combined dataset including 41 sequence types generated from 115 *C. gattii* isolates shows that the VGIIc genotype is independent, but similar to VGIIa (Figure 3). The closest relationship determined from the analysis was to ST34, an isolate from Colombia, which is also of the opposite a mating type. Moving beyond the direct branch, it appears that the VGIIc genotype shares sequence similarities to global isolates from South America, Africa, and also European isolates with likely African origins based on collected clinical case histories. Additionally, the VGIIc group also shares the *IGS1* allele with isolates from Australia, further obscuring the possible origins and necessitating a more thorough analysis (Figure 4A).

When the clustering analysis was expanded to include additional MLST loci (Figure 4A), both with and without the VNTR markers, the relationships of VGIIc to other global genotypes was further elucidated, with close relationships observed with global isolates from South America, Africa, Europe (Greece), and Australia (Figure 4B, Figure 4C, Table S4). These results increase the comprehensiveness of the analysis, and allow predictions of the relationship of this genotype to global isolates. Examination of alleles illustrates that, when the analysis is expanded, the VGIIc group appears to be more diverse from VGIIa and VGIIb. Each allele represented in green was initially denoted as an allele that was unique to the VGIIc genotype, with a total of seven such alleles (Figure 4A). To further elucidate the possible origins of these alleles, isolates selected based on their global diversity were sequenced at these loci (Figure 4A). Identical matches for four of the seven VGIIc-unique alleles were identified in isolates from Brazil, Australia, Europe, and European isolates with likely African origins, while three alleles (*SXI1α*, *HOG1*, and *CRG1*) remain unique to this novel genotype and only seen in Oregon thus far (Figure 4A).

To further characterize the genetic relationships among the global isolates in relation to the outbreak isolates, maximum likelihood (ML) analysis was applied. Initially, the isolates were characterized at 15 MLST loci, excluding the *MAT* locus so that both α and a isolates could be included. This analysis indicates that VGIIc may be more distantly related to the VGIIa/major genotype than initially observed. In addition, analysis of the 15 MLST loci shows a possible relation of VGIIc with isolates from South America, Africa, Europe, and Australia (Figure 4B). When this analysis was expanded to also include the four VNTR loci, similar results for the global comparisons of all genotypes and the relation of VGIIc to global isolates were observed (Figure 4C). For these reasons, additional sampling and analysis will be necessary to more precisely elucidate if this novel virulent genotype originated locally, or originated in an under-sampled region.

In addition to clustering analyses, TCS haplotype-mapping software was applied to establish the evolutionary histories of the MLST alleles examined during the analysis (Figure 5, Figure 6, Figure S3). From the sequence results, all of the VGIIc isolates were determined to be 100% identical, indicating that there was likely a recent emergence in which all of the isolates are clonally derived. To test this hypothesis, the TCS analysis allowed for the examination of individual loci to determine which alleles are likely ancestral, intermediate, or recently derived. Of the sixteen loci examined, eight were consistent with VGIIc possessing the ancestral allele, six of the alleles were distal nodes at the terminal end of the respective haplotype networks, and two loci were of intermediate allele positions.

Alleles with ancestral genotypes are less informative because these alleles may not have diversified over time in the VGIIc

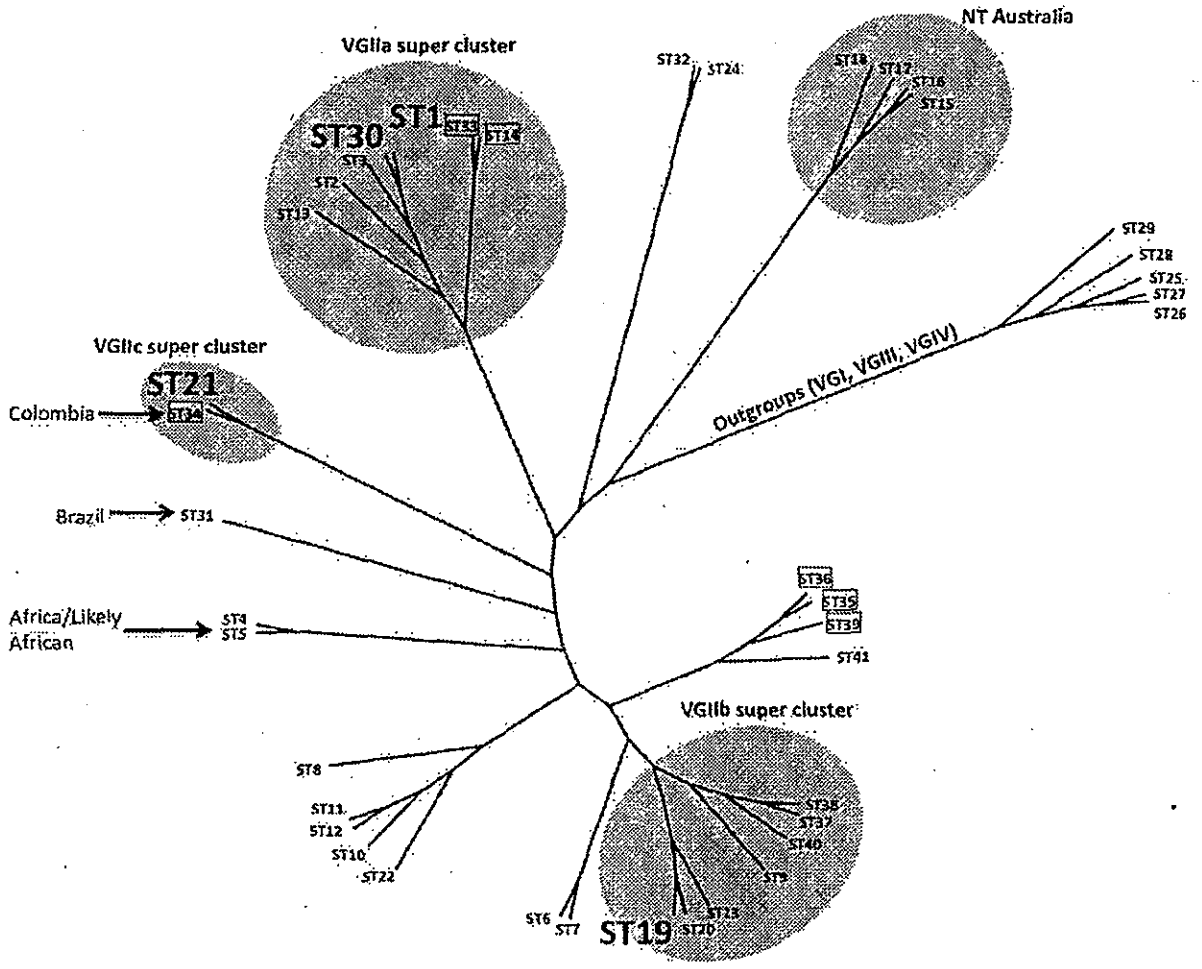

Figure 3. Clustering analysis of global VGII isolates shows high global diversity. This dendrogram, based on seven MLST loci and four VNTR loci, illustrates the global divergence seen in this molecular type. Major clusters are highlighted accordingly to illustrate the placements of the VGIIa/b/c super clusters as well as a unique NT cluster that has been found only in Australia thus far. Sequence types 1, 30, 19, and 20 are enlarged and represent the primary genotypes responsible for the Pacific NW outbreak. Boxed isolates represent those of the a mating type and all other sequence types represent the genotypes observed for mating type α isolates. Several genotypes are also combined with geographic information to illustrate the diversity surrounding several sequence types. Isolates from the VGI, VGIII, and VGIV molecular types serve as out-group sequence types.
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lineage for various reasons, including selection pressures and overall lack of diversity at the allele. When only non-ancestral alleles were examined, 75% lay at the distal ends of their haplotype maps. Intriguingly, the three VGIIc alleles unique to the genotype (*SXI1α*, *HOG1*, and *CRG1*) all have distal placements (Figure 5A–C). Additionally, the most recent ancestor to VGIIc in all three cases can be shown to derive from isolates that are from South America and Australia, indicating that VGIIc may have emerged out of one of these regions (Figure 5). While other regions including Europe and North America can be seen, no other regions are observed for all three of these alleles. These distal placements are consistent with a recent divergence of the unique VGIIc lineage. The haplotype analysis, in combination with the lack of any underlying diversity within the nine VGIIc isolates analyzed, indicates a recent emergence of this novel virulent genotype in Oregon.

To examine the role that recombination may have played in the population structure of the VGII molecular type, we conducted paired allele analysis for 25 representative global isolates (Figure 6, Figure S4). The discovery of all four possible allele combinations between two unlinked loci (AB, ab, Ab, aB) serves as evidence for likely recombination [49]. From this analysis, we show that isolates collected from South America, Africa, and Australia appear to be involved in recombination events. Representative VGIIa/major, VGIIb/minor, and VGIIc/novel isolates were found among groups of recombinant isolates. A group of ten isolates, all α, from South America and Africa (Figure S4) appeared most commonly as recombinant partners, although several a mating type isolates were also less frequently involved. In further support, when we examined the number of genotypes present by region and compared this data to the total number of genotypes represented (Figure S1), it is clear that South America and Africa populations are more diverse when compared with isolates from North America, which are more clonal. Additionally, while the observed diversity in Australia was lower than South America and Africa, this may be attributable to sampling bias of clonal regions as prior studies have shown that this continent is a region with high levels of recombination due to both same-sex and opposite-sex mating

Table 2. Isolates collected from cases within the United States, 2005–2009 (n = 40).

Isolate	Host	Residence	Molecular Type*
T67707	Human	Washington	VGIIa/major
W15209	Human	Washington	VGIIa/major
EJB4	Human	Washington	VGIIa/major
EJB5	Human	Washington	VGIIa/major
EJB6	Human	Washington	VGIIa/major
EJB7	Human	Washington	VGIIa/major
EJB8	Human	Washington	VGIIa/major
EJB9	Human	Washington	VGIIa/major
EJB13	Human	Washington	VGIIa/major
KB11632	Human	Oregon	VGIIa/major
EJB3	Human	Oregon	VGIIa/major
EJB19	Human	Oregon	VGIIa/major
MMC08-1042	Human	Oregon	VGIIa/major
EJB16	Alpaca	Oregon	VGIIa/major
EJB17	Dog	Oregon	VGIIa/major
3700 (1)	Porpoise	Washington	VGIIa/major
3700 (2)	Porpoise	Washington	VGIIa/major
3635	Porpoise	Washington	VGIIa/major
3059	Porpoise	Washington	VGIIa/major
EJB21	Porpoise	Oregon	VGIIa/major
EJB22	Dog	Oregon	VGIIa/major
EJB51	Alpaca	Oregon	VGIIa/major
EJB54	Cat	Oregon	VGIIa/major
EJB77	Dog	Oregon	VGIIa/major
EJB79	Alpaca	Oregon	VGIIa/major
A6MR38	Human	Oregon	VGIIc/novel
EJB12	Human	Oregon	VGIIc/novel
EJB18	Human	Oregon	VGIIc/novel
EJB14	Cat	Oregon	VGIIc/novel
EJB15	Alpaca	Oregon	VGIIc/novel
EJB52	Cat	Oregon	VGIIc/novel
EJB55	Ovine	Oregon	VGIIc/novel
EJB74	Cat	Oregon	VGIIc/novel
EJB75	Dog	Oregon	VGIIc/novel
EJB10	Human	Oregon	VGIIb/minor
MMC08-896	Dog	Oregon	VGIIb/minor
EJB53	Elk	Oregon	VGIIb/minor
EJB76	Cat	Oregon	VGIIb/minor
EJB11	Human	Washington	VGIII
MMC08-897	Cat	Oregon	VGIII

* The Molecular type designation is based on 8-loci MLST analysis.

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events [50]. In addition to the paired allele analysis, allele diagrams were constructed to observe possible recombination within individual MLST loci (Figure S5). The most parsimonious explanation for allelic diversity in 11 of the MLST loci analyzed is as a result of consecutive and/or independent mutations within the population. Within the four remaining loci, there exists at least one hybrid allele that may be the result of a recombination event between two hypothesized parental alleles in the global VGII population (Table 3, Figure S5). Phenotypic mating results were conducted and illustrate that the VGIIa/major (α), VGIIc/novel (α), VGII mating type **a** genotypes, as well as several of the proposed parental contributors from the allelic and genotypic recombination analysis show fertility with the production of spores when mated with fertile VGIII isolates (Table S5). Taken together, this suggests that both α-α and **a**-α mating events may be contributing to the formation of recombinant genotypes as well as *the production of infectious spores. There were no examples of* alleles introgressed into VGII from VGI, VGIII, or VGIV, in accord with findings that the four VG molecular types likely represent cryptic species [6,29]. In summary, these results suggest that recombination events may be critical driving forces in the evolution of *C. gattii* VGII diversity, which may in part contribute to the generation of genotypes displaying increased virulence.

VGIIc/novel and VGIIa/major Outbreak Isolates Are Hypervirulent

It has recently been shown that intracellular proliferation rate (IPR) values for cryptococcal cells within macrophages are positively correlated with virulence in the murine model for cryptococcosis [31]. To further elucidate the potential virulence of outbreak isolates collected from the United States, proliferation rates of selected isolates were tested and compared to other isolates for which proliferation data had been previously obtained. In total, IPR values for eight of the nine VGIIc isolates were measured (Figure 7A). In addition, the type strains for VGIIa/major (R265) and VGIIb/minor (R272) were included as controls, and previously published data for other VGIIa and VGIIb isolates were included for comparisons [31]. On the basis of individual strains, seven of the eight VGIIc/novel isolates showed high IPR levels, with only a single outlier (EJB52) that had a low IPR value (0.97). Taken together, the median IPR value for VGIIc is significantly closer to that of VGIIa/major than to VGIIb/minor (Figure 7A). These results indicate that the VGIIc genotype has a similar intracellular phenotype, and thus virulence profile to the VGIIa/major genotype. This is noteworthy because previous analysis showed that the VGIIa/major genotype isolates from the outbreak had unusually high IPR values, and the VGIIc isolates from the same outbreak are here shown to have similarly high IPR values.

Another unique feature of the outbreak VGIIa/major isolates is the ability to form highly tubular mitochondria after intracellular parasitism, a characteristic that correlates with both IPR and murine virulence [31]. To explore the morphology of VGIIc isolates, we examined selected isolates in DMEM media and after exposure to macrophages. This analysis included two VGII environmental isolates (CBS8684, CBS7750) and four of the VGIIc/novel isolates. As expected, the vast majority of the mitochondria for all six isolates were non-tubular after exposure to DMEM media alone (Figure 7B). However, after exposure to macrophages, three of the four VGIIc isolates tested showed significantly higher percentages of tubular morphology (Figure 7C). The lone VGIIc isolate that did not exhibit this morphology (EJB52) was the same isolate that also had a low IPR value, and is thus an overall outlier for the VGIIc genotype.

When the results of IPR versus percentage of cells exhibiting tubular morphology were plotted, the graph showed a statistically significant correlation of the two measures with an R^2 value of 0.85 (Figure 7D). These results further indicate that the VGIIc genotype is phenotypically similar to the Vancouver Island VGIIa/major outbreak strains. Our results also support evidence for similar mechanisms regulating the increased virulence seen in the novel VGIIc genotype. The exact roles that the mitochondrial

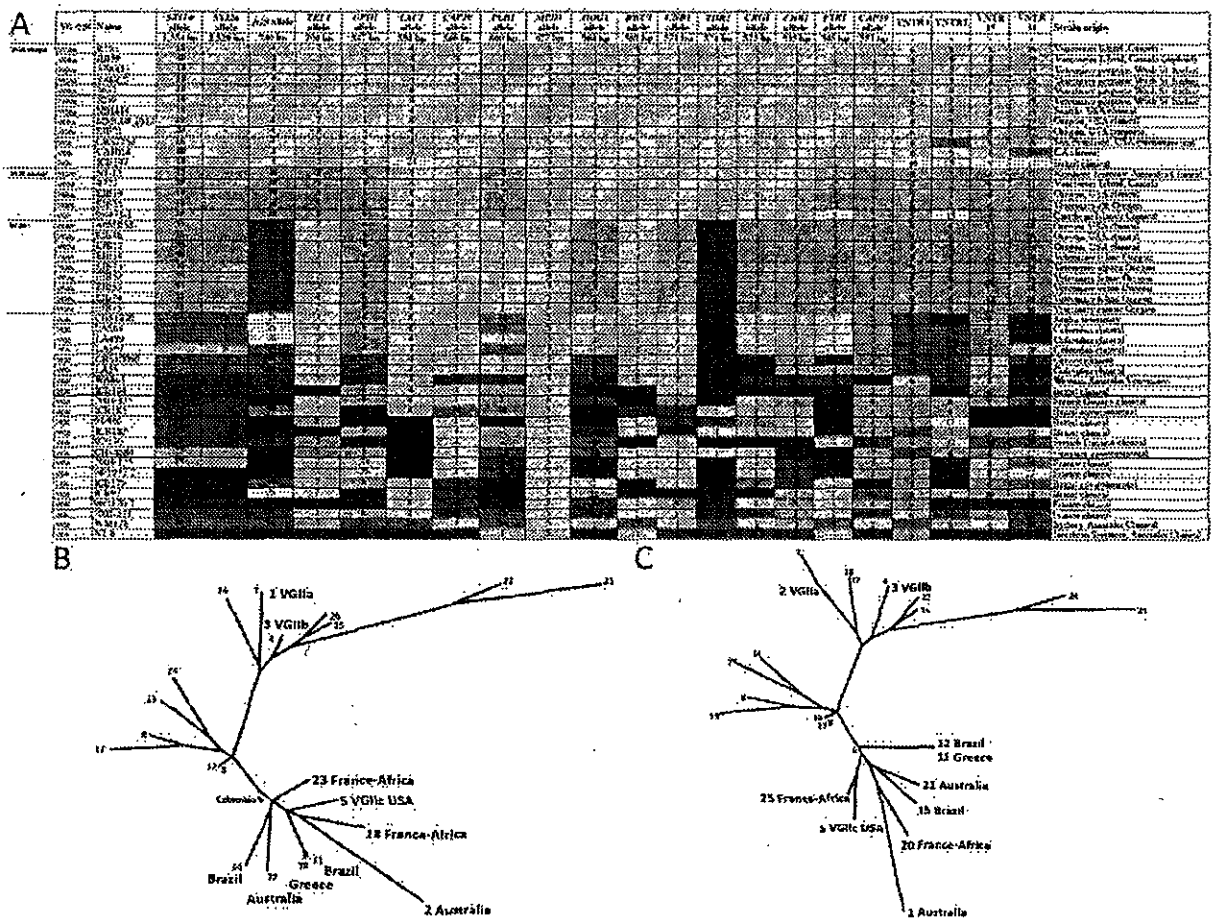

Figure 4. Expanded molecular analysis reveals increased divergence in VGIIc. A) Multilocus sequence typing analysis of 16 loci. Selected isolates from the outbreak in addition to global genotypes were selected for the expanded MLST analysis, including all nine of the VGIIc isolates available. Each unique allele is colored for each marker for visual discrimination, and each number represents a GenBank accession number (Table S2). B) A representation (ML) of the sequence data from panel A, with the exclusion of *MAT* locus linked markers (*SXI1α*/*SXI2a*). C) A combination of the sequence data from panel B, with the addition of the four highly variable VNTR markers.
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tubular morphology might play in virulence are not yet known. However, the distinct phenotype is clearly unique to the outbreak isolates and is correlated with an increased ability to grow and divide within host innate immune cells.

The VGIIc isolates were found to be highly virulent in the murine inhalation model of infection. Two studies were conducted to examine virulence. In the first murine experiment a total of six isolates (n = 5 animals/isolate), were examined including two VGIIc isolates (Figure 8A). The VGIIa/major isolate R265 served as a positive control for high virulence, based on prior studies [6], and the VGIIc isolates EJB15 and EJB18 showed similar virulence with this well characterized virulent isolate. Additionally, two VGIIa isolates that are not hypothesized to be from the current Vancouver Island outbreak, including NIH444, which is fully identical across 34 markers, and isolate CA1014, which differs from R265 at VNTR34, show a significant reduction in virulence compared to the high virulence isolates ($P<0.05$). Finally, in accordance with previous studies, the VGIIb/minor type strain R272 from Vancouver Island was avirulent in this model.

The analysis of virulence within the VGII genotype was extended in a second experiment, in which 12 isolates (n = 9–10 animals/isolate) were examined. This study included two VGIIa/major isolates from the outbreak zone, two VGIIb/minor isolates from the outbreak zone, five of the novel VGIIc isolates, two VGIIa-related isolates that are not part of the outbreak, and the *C. neoformans* var. *grubii* type strain, H99. The H99 isolate used (H99S) has been shown to be highly virulent in the murine model of infection [44,51].

As expected, all five of the VGIIc isolates from Oregon as well as the VGIIa/major isolates from Vancouver Island and Oregon, and the highly virulent H99 isolate exhibited a high level of virulence (median survival = 20.6 days). The VGIIb/minor isolates tested were significantly decreased in virulence compared to the more virulent VGIIa and VGIIc genotypes ($P<0.005$). The VGIIb isolate R272 was avirulent whereas the VGIIb isolate EJB53 from Oregon exhibited significantly less virulence compared to the VGIIa/major and VGIIc isolates ($P<0.005$, median survival = 46 days). Similar to the first animal study, two VGIIa isolates that differ at one or more molecular markers from the major VGIIa outbreak genotypes were also tested. The environmental isolate CBS7750 and a clinical isolate from South America ICB107 were significantly attenuated ($P<0.005$) (Figure 8B). These results

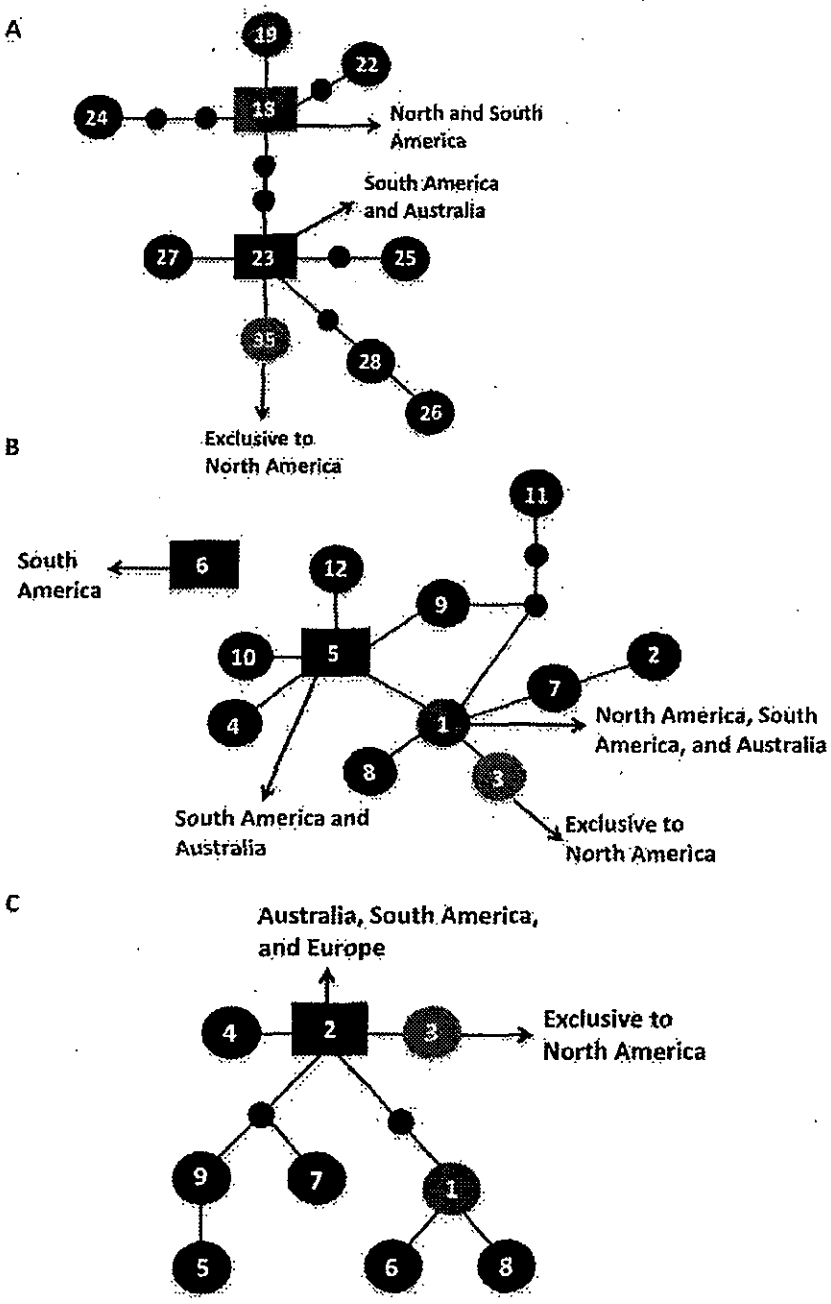

Figure 5. Haplotype networks define allele ancestry. Allele placements are indicated numerically, with the VGIIa/major genotype also represented by blue coloration, the VGIIb/minor genotype by purple coloration, and the VGIIc/novel genotype by green coloration. Large circles represent alleles extant in the population, and the small circles represent alleles that have not been recovered, or which may no longer be extant in the population. Each connecting line represents one postulated evolutionary event, with the squared allele representing the posited ancestral allele (two possible ancestral alleles depicted for *SXI1α*). A–C) Haplotype networks of the unique VGIIc alleles, *SXI1α*, *HOG1*, and *CRG1*, respectively, with geographic origins indicated.
doi:10.1371/journal.ppat.1000850.g005

provide further evidence that these are related to but distinguishable from isolates that are specific to the Vancouver Island outbreak, and subsequent United States expansion, and are decreased in ability to mount fatal infections in a mouse intranasal instillation model of infection.

The cause of infection was further evaluated by histopathological analysis of lung sections recovered from two infected animals per isolate at sacrifice. Harvested organs were processed and sectioned for slides with H&E staining. The lungs from the virulent isolates showed significant inflammation and numerous crypto-

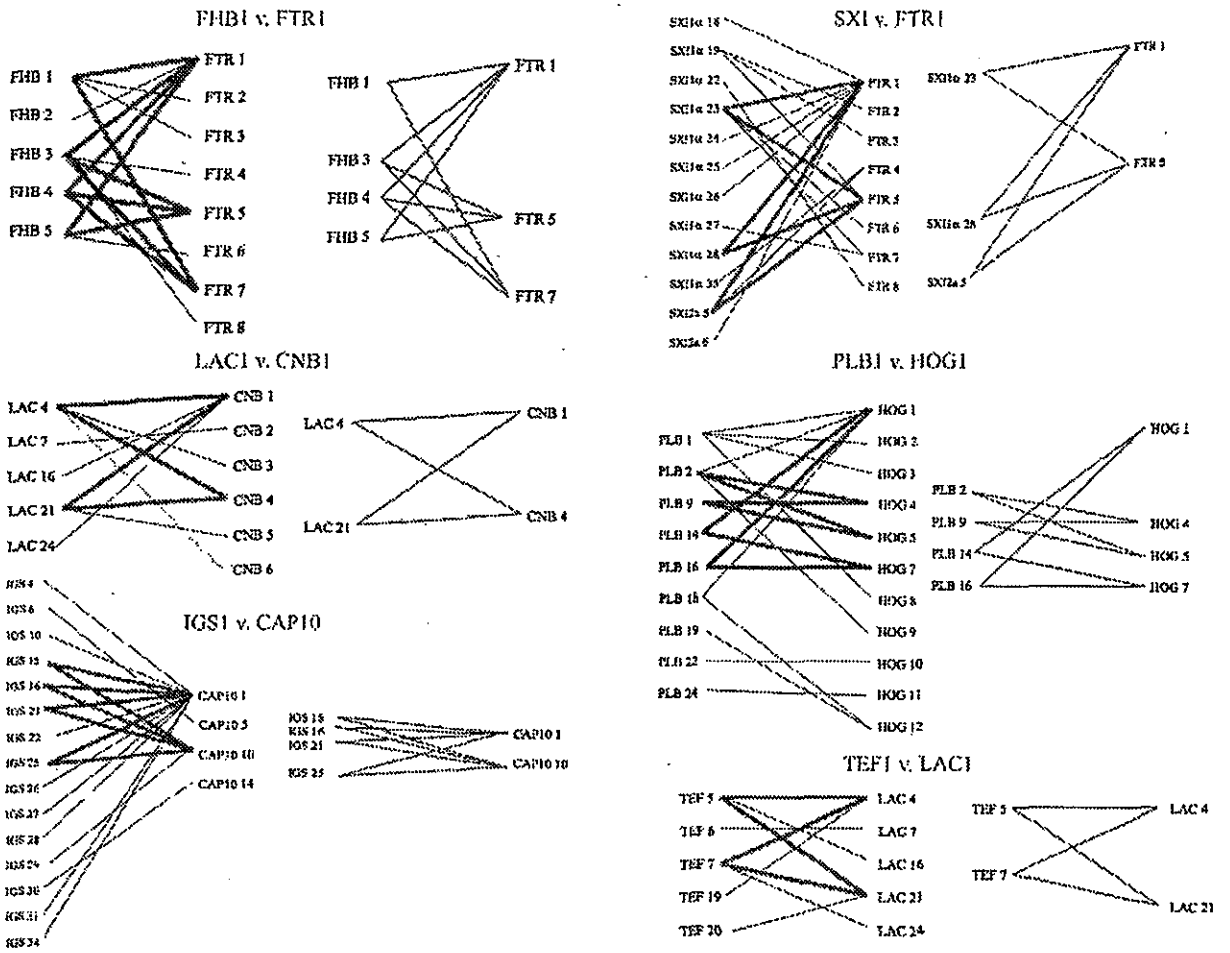

Figure 6. Evidence for recombination within the VGII molecular type. Informative paired allele graphs from VGII global isolates. An hourglass shape indicates the presence of all four possible pairs of alleles and serves as evidence for recombination. A total of 56 graphs with at least one possible recombining allele pair were generated from a set of 25 representative genotypes within the VGII molecular type, including isolates of both mating type **a** and α (see also Figure S4).
doi:10.1371/journal.ppat.1000850.g006

coccal cells dispersed throughout the alveoli, in accordance with severe pulmonary infection. Our findings show that there are no major clinical differences between pulmonary infections with the infectious genotypes VGIIa/major (Figure 8C), and the novel VGIIc genotype (Figure 8D). These results further support similar disease progression caused by these two highly virulent outbreak genotypes.

Discussion

The findings presented here document that the outbreak of *C. gattii* in Western North America is continuing to expand throughout this temperate region, and that the outbreak isolates in the United States of both the VGIIa/major genotype and the novel VGIIc genotype are clonally derived and highly virulent in host models of infection. These conclusions are based on an extensive molecular analysis of isolates collected from the United States (Table 2) and a comprehensive global collection of VGII isolates of diverse geographic origin (Figure S1), examining both conserved and divergent regions of the genome. The virulence analysis is based on assays in both murine derived macrophages and mice. These findings demonstrate that this emerging and fatal outbreak is continuing to expand, and that the virulence of these isolates is unusually high when compared to isolates of closely related but distinguishable genotypes found in other non-outbreak regions.

The continued expansion of *C. gattii* in the United States is ongoing, and the diversity of hosts increasing. Cases have been observed in urban and rural areas, and have occurred in a range of mammals [16,52]. On Vancouver Island and the mainland of British Columbia, cases have been documented in marine and terrestrial mammals including cats, dogs, porpoises, ferrets, and llamas [15,52,53]. This trend has continued in the United States, with several cases in agrarian, domestic, and wild terrestrial mammals, as well as marine mammals, adding elk, alpacas, and sheep to the aforementioned list (Table S1) [13,14,17]. The co-expansion of the outbreak among mammals and humans is significant for several reasons. Non-migratory mammals serve as sentinels for disease expansion, particularly given that isolation of *C. gattii* from the environment is difficult, and not yet successful at all in Oregon. Additionally, the threat to agricultural and domestic animals is significant and thus the need for cooperation among

Table 3. Proposed recombinant alleles and hypothesized parental contributors.

Hypothesized recombinant alleles	isolate/genotype	Hypothesized Parental alleles	Hypothesized parental isolates/genotypes*
IGS1-4	*VGIIa*	IGS1-15	*VGIIc*, WA861, ICB184
		IGS1-16	ICB179, WM178
IGS1-30	ICB183	IGS1-22	*2004/335*
		IGS1-26	*CBS8684*, 2003/125, 98/1037-2
HOG1-2	*NT-8*	HOG1-1	*VGIIa*, VGIIb, *99/473-1*, *La499*, La567, *La584 CBS1930*, ICB179, WM178
		HOG1-3	*VGIIc*
		HOG1-7	*96/1120-1*, 2001/571
		HOG1-4	ICB184, 2003/125, 98/1037-2
HOG1-11	ICB97	HOG1-1	*VGIIa*, VGIIb, *99/473-1*, *La499*, La567, *La584 CBS1930*, ICB179, WM178
		HOG1-3	*VGIIc*
		HOG1-7	96/1120-1, 2001/571
		HOG1-9	97/170
CRG1-5	WA861	CRG1-1	*VGIIa*, VGIIb, *99/473-1*, *La499*, La567, *La584 CBS1930*, *2004/335*, ICB183, ICB182, *CBS8684*, 2003/125, 98/1037-2, *96/1120-1*, WM178
		CRG1-6	*93/980*
		CRG1-8	ICB179
		CRG1-9	2001/571
CAP59-5	2001/571	CAP59-3	WA861, *NT-8*
		CAP59-6	ICB179
CAP59-9	97/170	CAP59-2	VGIIb, *99/473-1*, *La55*, *La499*, La567, *La584*, *CBS1930*, *CBS10090*, ICB184, 2003/125, 98/1037-2
		CAP59-7	*CBS8684*
		CAP59-3	WA861, *NT-8*

* Bold indicates MATa, Italics indicates fertile representative.
doi:10.1371/journal.ppat.1000850.t003

health officials is critical. Finally, the widespread spectrum of disease illustrates that the organism is likely to be pervasive in the environment, and that physicians and veterinarians should be well informed of symptoms to facilitate early diagnoses, and successful isolate collection and tracking.

A major question in the study of this outbreak is whether sexual recombination, either within or between mating types, is occurring or has occurred in the region. The possibility of meiosis is important for two reasons. The first is that sexual recombination is postulated to be a driving force for the increased virulence of the VGIIa/major genotype, supported by the discovery of a diploid VGIIa/major isolate, an intermediate in unisexual mating (all nine VGIIc/novel isolates are haploid) [6,36]. *C. gattii* has also been shown to undergo opposite sex mating in the laboratory, although this has not yet been observed to occur between two isolates of the VGII molecular type [36,54,55]. Studies in *C. neoformans* have shown that this related pathogen completes a full **a**-α sexual cycle in association with plants [56]. Additionally, a recent study of environmentally sampled Australian VGI isolates demonstrated evidence for recombination via both opposite and same-sex mating [50]. Taken together, available evidence indicates that both opposite and same-sex mating are naturally occurring in populations. This evidence lends support to the hypothesis that meiosis might be a factor in the forces that are driving high virulence in the outbreak region.

The second major event that results from sexual processes in the pathogenic *Cryptococcus* species is the formation of spores. Small spores ranging from 1–2 μm in diameter have been observed to be produced in large numbers as the result of opposite sex mating in both *C. neoformans* and *C. gattii* [57,58]. Studies by Lin and colleagues showed that sexual spores can be produced as the result of a meiotic process occurring between cells of the same mating type, a process referred to as unisexual or same-sex mating [59]. Several studies have shown spores to be pathogenic in animal models of infection. Two previous studies both showed evidence for virulence of *Cryptococcus* spores, and in one case provided evidence for enhanced virulence compared to yeast cells [60,61]. More recently, studies have shown that *Cryptococcus neoformans* spores are indeed virulent in the murine intranasal instillation model of infection [44,62], providing evidence that spores should be considered as infectious propagules in models examining infections, expansion, and emergence of both *C. neoformans* and *C. gattii*. Given that all of the Pacific NW isolates are α mating type, and particles small enough to be spores are present in the air [26,63], the most parsimonious model is that if these are spores, they are produced via α-α unisexual reproduction.

Our findings further indicate that mitochondria may play a significant role in the increased virulence seen in the outbreak isolates [31]. Tubular morphology and the increased ability to proliferate within immune cells indicate that the ability to proliferate and survive within host cells is fundamental to virulence. The possible role of mitochondrial involvement is intriguing and also increasingly relevant based on studies that have shown mitochondrial inheritance and recombination may impact *C. gattii* evolution, with the inheritance of the mitochondrial genome from the **a** mating type parent in opposite-sex mating [64,65]. Future studies in this area should address the roles that mitochondrial genes, or nuclear genes that regulate mitochondria

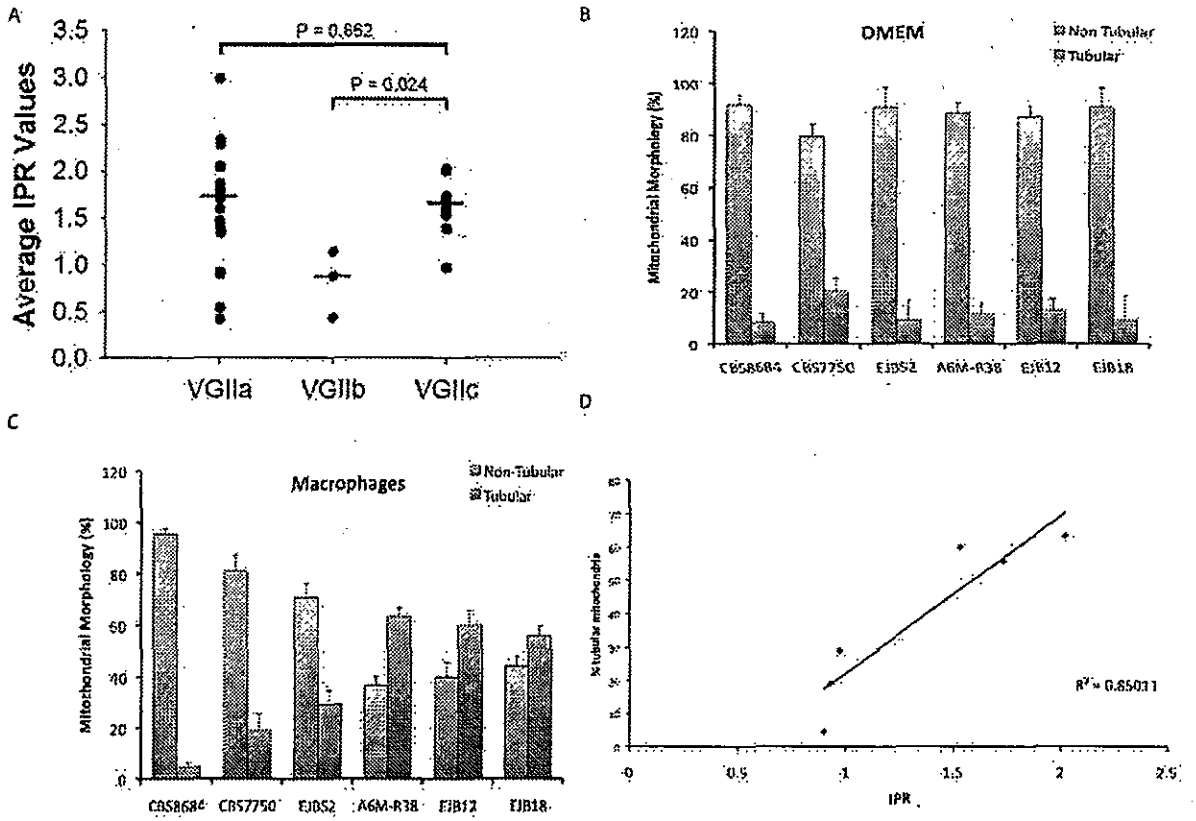

Figure 7. In vitro analyses of intracellular proliferation and mitochondrial morphology provide evidence the VGIIc genotype is hypervirulent. A) IPR rates of VGIIc isolates are similar to those from the VGIIa/major genotype and higher than those seen in the less-virulent VGIIb/minor genotype. Eight VGIIc isolates were tested individually, with the overall averages for the three primary outbreak genotypes presented. B) Percentage of cells with tubular mitochondrial morphology in DMEM. C) Percentage of cells with tubular mitochondrial morphology in macrophages. D) Linear correlation of IPR and percentage of tubular mitochondria after macrophage exposure.
doi:10.1371/journal.ppat.1000850.g007

may play in the hypervirulence observed in the outbreak isolates. Furthermore, it may be that cell-cell fusion events via mating and mitochondrial exchange without meiosis or nuclear genetic exchange have played roles in recombination and virulence acquisition in naturally occurring *C. gattii* populations [64,65].

A central question in the field lies in the possible origins of the virulent genotypes. For the VGIIa and VGIIc lineages, it is clear that those are unique to the Pacific NW, and either arose there locally, or were transferred from an under-sampled region (Australia, South America, Africa). Isolates that are related to, but distinct at one or more molecular marker from VGIIa have been identified in San Francisco (CBS7750), southern California (CA1014), and South America (ICB107). However, in each of these cases, the isolates are not identical with the VGIIa/major isolates from the Pacific NW. Whether the outbreak isolates are derived from these isolates, or alternatively that these isolates are derived from the outbreak lineage is at present unclear. In the VGIIb/minor outbreak lineage, isolates from Australia are identical at all 30 MLST loci and four VNTRs analyzed, and the most parsimonious model is that the two are directly related. While it is conceivable that both the Australian and the Vancouver Island VGIIb/minor genotype isolates were dispersed independently from another geographic locale, until isolates are identified conclusively from another locale the most parsimonious model is transfer from Australia to the Pacific NW. We note that a single isolate with a related but distinct genotype (isolate 99/473) from the Caribbean has been identified; and other isolates have been reported to share the VGIIb genotype but have been analyzed at a limited number of MLST markers (n = 7) which is insufficient to establish how closely related these isolates are to the outbreak VGIIb/minor genotype strains [29]. The origins of VGIIc are unclear, with the genotype possibly arriving in the Pacific NW from South America, Africa, Europe, or Australia. Alternatively, this novel unique genotype may have arisen locally.

As for the geographic origins of VGII diversity, this also remains to be established and may involve populations in Australia, South America, and Africa. It is clear that there is considerable diversity among isolates from South America. As we originally proposed as an alternative model [6], and has been independently presented by other investigators (W. Meyer, T. Boekhout, JP Xu, pers. comm.), South America may represent a source of diversity and ongoing generation of novel isolates. Analysis of 8 MLST loci in this study indicates that in South America and the Caribbean there are 14 genotypes seen in 21 isolates, while in North America only 3 genotypes have been observed through the analysis of 64 isolates (Figure S1). Additionally, there is accumulating evidence that fertile isolates of both **a** and α mating type are present in South America [29], and thus ongoing **a**-α opposite sex mating may be occurring there. It is also clear that a unique set of VGII isolates are circulating in Australia, and there is evidence for ongoing

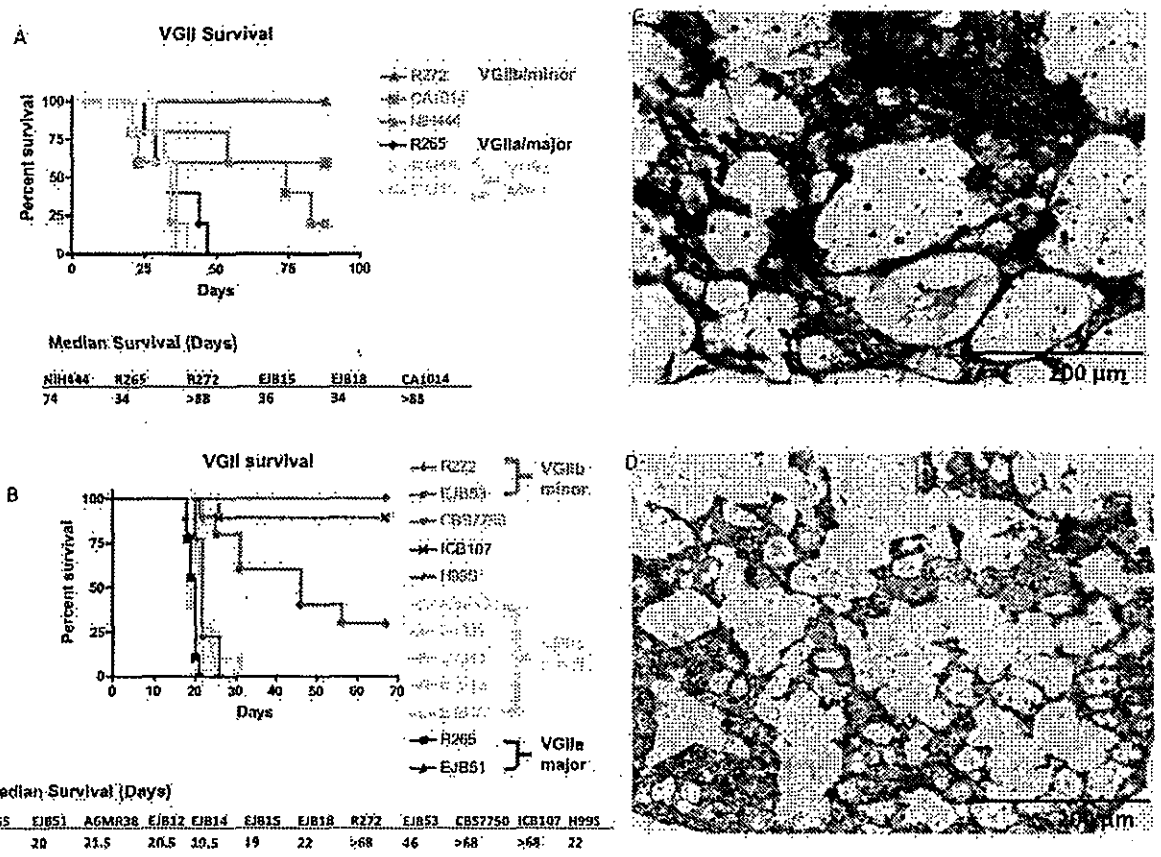

Figure 8. Isolates from the United States outbreak are hypervirulent. A) Groups of five animals were each infected with an infectious inoculum of 1.0×10^5 cells of VGIIa isolates R265, CA1014, or NIH444, VGIIb isolate R272, or VGIIc isolates EJB15 or EJB18. B) Groups of nine or ten animals were each infected with an infectious inoculum of 5.0×10^4 cells of VGIIa isolates R265, EJB51, CBS7750, or ICB107, VGIIb isolates R272 or EJB53, VGIIc isolates A6MR38, EJB12, EJB14, EJB15, or EJB18, or *C. neoformans* var. *grubii* isolate H99. C–D) Representative H&E stained histopathology slides from lung sections of severely morbid sacrificed animals from the VGIIa/major (R265) (C) and VGIIc (EJB18) (D) genotypes (sections from animals in panel B of this Figure).
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recombination in α only and **a**-α populations, suggesting that mating contributes to the generation of diversity in Australia [36,49,54,55,66,67]. Finally, the analysis of global VGII isolates reveals genetic diversity in Africa, and given the recent findings that *C. neoformans* likely originated in sub-Saharan Africa (A. Litvintseva and T. Mitchell, pers. Comm.), further analysis of African *C. gattii* isolates is clearly warranted.

It remains possible that South America, Africa, or both represent the ancestral populations of *C. gattii*, and that more recent dispersal events from other established populations (for example, from Australia to the Pacific Northwest) have occurred to contribute to the outbreak. As yet, all of the isolates found in the Pacific Northwest are α mating type. Thus, if sexual reproduction is occurring in the Pacific Northwest, it would appear to involve same-sex mating occurring under environmental conditions. Recent studies have documented that *C. neoformans* and *C. gattii* are stimulated to undergo opposite-sex mating in laboratory conditions that simulate environmental niches (pigeon guano medium, co-culture with plants) and thus similar conditions may be necessary in nature [56,68]. Overall, both the VGIIa/major and the VGIIc/novel genotypes contain a number of MLST loci that are thus far restricted to these lineages, and their origins remain to be identified.

Independently of the variables leading up to and influencing this outbreak, the major concern is and continues to be the inexorable expansion throughout the region. From 1999 through 2003, the cases were largely restricted to Vancouver Island. Between 2003 and 2006, the outbreak expanded into neighboring mainland British Columbia and then into Washington and Oregon from 2005 to 2009. Based on this historical trajectory of expansion, the outbreak may continue to expand into the neighboring region of Northern California, and possibly further.

The rising incidence of cryptococcosis cases in humans and animals highlights the need for enhanced awareness in the region, and those regions that may potentially become involved. While rare, little is currently known about how or why specific humans and animals become infected. Increased vigilance may decrease the time from infection to diagnosis, and thus lead to more effective treatment and a reduction in mortality rates. The potential dangers of travel-associated risks should be noted, as a growing number of cases attributable to travel within the Pacific NW region have been documented [69,70]. Northern California has similar temperate climates to endemic regions within Oregon, leading to the hypothesis that the emergence may expand there, while expansion eastward may be limited by winters with average temperatures often below freezing [17].

The expansion of the outbreak into California is plausible based on several studies documenting the presence of *C. gattii* throughout the state and in Mexico. *C. gattii* molecular type VGII was environmentally isolated in the San Francisco area in 1990 (isolate CBS7750) [48], and there have also been two confirmed and one travel-associated case of *C. gattii* molecular type VGI in California. Of the VGI cases, one occurred in a male Atlantic bottlenose dolphin in San Diego, one was isolated from a liver transplant recipient in San Francisco, and the other from an otherwise healthy patient in North Carolina with travel history to the San Francisco region [71,72,73]. In addition *C. gattii* has been reported in southern California among a cohort of HIV/AIDS patients [74]. Recently, studies of clinical isolates from Mexico revealed all four molecular types of *C. gattii* to be present [75]. Taken together, the hypothesis that the virulent isolates from the Pacific NW will expand into California must be considered by both physicians and public health officials.

During the coming years, monitoring and researching the outbreak expansion as a multidisciplinary effort will be critical. The ability to bring diverse groups of professionals interested in *C. gattii* expansion has been greatly facilitated through the formation of the *Cryptococcus gattii* working group of the Pacific Northwest [17]. From a research standpoint, further examination of the molecular mechanisms underlying the increased virulence in both VGIIa/major and VGIIc/novel will be useful for the development of aggressive treatments that may be needed. Furthermore, increased efforts to determine the ecology and population dynamics of *C. gattii* in the region, and elucidating the evolutionary history of the VGIIc genotype will be critical to gain further insights into the origins of this unprecedented and frequently fatal fungal outbreak.

Supporting Information

Figure S1 MLST of all VGII isolates used in the study and the four out-group isolates used in the phylogenetic analysis.
Found at: doi:10.1371/journal.ppat.1000850.s001 (0.07 MB PDF)

Figure S2 MLST analysis of Vancouver Island isolates at 2 loci. These were chosen to determine if any of the isolates might have belonged to the VGIIc group.
Found at: doi:10.1371/journal.ppat.1000850.s002 (0.02 MB PDF)

Figure S3 TCS haplotype networks for the thirteen alleles not represented in Figure 5 of the main text.
Found at: doi:10.1371/journal.ppat.1000850.s003 (0.15 MB PDF)

Figure S4 All paired allele graphs from VGII global isolates generated during the analysis. Isolates of both mating type a and α were included. In addition, a group of ten isolates, all α, from South America and Africa appeared most commonly as recombinant partners and are illustrated.
Found at: doi:10.1371/journal.ppat.1000850.s004 (0.12 MB PDF)

Figure S5 Allelic recombination analysis for 15 loci indicates that 11 are likely derived from consecutive and/or independent mutations within the population. The four other loci show at least one hybrid allele that may be the result of a recombination event between two proposed parental alleles in the global VGII population. Squared alleles represent likely recombinants, while circled alleles indicate proposed parental contributors. Each of the possible contributors is indicated by a respective color.
Found at: doi:10.1371/journal.ppat.1000850.s005 (1.34 MB PDF)

Table S1 Primers used in the study.
Found at: doi:10.1371/journal.ppat.1000850.s006 (0.03 MB XLS)

Table S2 GenBank accession numbers for all of the MLST and VNTR alleles represented in the text and figures.
Found at: doi:10.1371/journal.ppat.1000850.s007 (0.05 MB XLS)

Table S3 Detailed sequence type information from Figure 3.
Found at: doi:10.1371/journal.ppat.1000850.s008 (0.03 MB DOC)

Table S4 Detailed sequence type information from Figure 4B and Figure 4C.
Found at: doi:10.1371/journal.ppat.1000850.s009 (0.02 MB XLS)

Table S5 Mating properties of selected VGII isolates.
Found at: doi:10.1371/journal.ppat.1000850.s010 (0.02 MB XLS)

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Author Contributions

Conceived and designed the experiments: EJB WL YL DAC VC RCM JH. Performed the experiments: EJB WL YL HM KV PR. Analyzed the data: EJB WL YL HM KV PR DAC RJB RCM JH. Contributed reagents/materials/analysis tools: VC RJB JH. Wrote the paper: EJB WL YL JH.

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研究報告の概要

目的：「プロテアーゼ感受性プリオン症(PSPr)」の 2 つの新しい遺伝子型を報告する。これは 2008 年に記載され新型のプリオン病で、被験者 11 人はプリオン蛋白質(PrP)遺伝子のコドン 129 が全員バリン同型接合(129VV)だった。2 つの新しい PSPr は、メチオニン同型接合(129MM)とメチオニン/バリン異型接合(129MV)の個人である。

方法：129MM、129MV、129VV の被験者 15 人は国立プリオン病病理監視センターで臨床、組織病理学的、免疫組織化学、遺伝子型、PrP 特性で比較評価を受けた。

結果：罹病期間(22 から 45 ヶ月の間)は、129VV と 129MV の被験者で有意に異なった。PrP 電気泳動プロフィルと共に他の殆どの表現型の機能は同様だったが、3 つの 129 遺伝子型で区別できる。主な違いは、疾患関連 PrP のプロテアーゼ消化の感受性にあり、129VV では高度であるが、129MV と 129MM では遙かに低いか、全くない。この違いは本来の命名を変え、「可変プロテアーゼ感受性プリオン症(VPSPr)」になった。被験者は誰も PrP 遺伝子コドン領域の変異はなかった。

解釈：3 つの 129 遺伝子型が全員関係し、区別でき、表現型として関係するので、VPSPr は二番目の孤発性プリオン蛋白質疾患になる。この特徴は 1920 年に報告したクロイツフェルト・ヤコブ病によく似ていた。しかし、異常プリオン蛋白質の特性は VPSPr は典型的なプリオン病とは異なることを示唆している。おそらく、ゲルストマン・ストロイスラー・シャインカー疾患の亜型と類似している。

使用上の注意記載状況・その他参考事項等

代表としてノイアート静注用 500 単位の記載を示す。
2. 重要な基本的注意
(1)略
1)略
2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病(vCJD)等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
「可変プロテアーゼ感受性プリオン症(VPSPr)」という、新規の孤発性プリオン病についての報告である。 血漿分画製剤は理論的なvCJD伝播リスクを完全には排除できないため、投与の際には患者への説明が必要である旨を2003年5月から添付文書に記載している。2009年2月17日、英国健康保護庁(HPA)はvCJDに感染した供血者の血漿が含まれる原料から製造された第Ⅷ因子製剤の投与経験のある血友病患者一名から、vCJD異常プリオン蛋白が検出されたと発表したが、弊社の原料血漿採取国である日本及び米国では、欧州滞在歴のある献（供）血希望者を一定の基準で除外し、また国内でのBSEの発生数も少数であるため、原料血漿中に異常型プリオン蛋白が混入するリスクは1999年以前の英国に比べて極めて低いと考える。また、製造工程においてプリオンが低減される可能性を検討するための実験を継続して進めているところである。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

ORIGINAL ARTICLE

Variably Protease-Sensitive Prionopathy: A New Sporadic Disease of the Prion Protein

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Objective: The objective of the study is to report 2 new genotypic forms of protease-sensitive prionopathy (PSPr), a novel prion disease described in 2008, in 11 subjects all homozygous for valine at codon 129 of the prion protein (PrP) gene (129VV). The 2 new PSPr forms affect individuals who are either homozygous for methionine (129MM) or heterozygous for methionine/valine (129MV).
Methods: Fifteen affected subjects with 129MM, 129MV, and 129VV underwent comparative evaluation at the National Prion Disease Pathology Surveillance Center for clinical, histopathologic, immunohistochemical, genotypical, and PrP characteristics.
Results: Disease duration (between 22 and 45 months) was significantly different in the 129VV and 129MV subjects. Most other phenotypic features along with the PrP electrophoretic profile were similar but distinguishable in the 3 129 genotypes. A major difference laid in the sensitivity to protease digestion of the disease-associated PrP, which was high in 129VV but much lower, or altogether lacking, in 129MV and 129MM. This difference prompted the substitution of the original designation with "variably protease-sensitive prionopathy" (VPSPr). None of the subjects had mutations in the PrP gene coding region.
Interpretation: Because all 3 129 genotypes are involved, and are associated with distinguishable phenotypes, VPSPr becomes the second sporadic prion protein disease with this feature after Creutzfeldt-Jakob disease, originally reported in 1920. However, the characteristics of the abnormal prion protein suggest that VPSPr is different from typical prion diseases, and perhaps more akin to subtypes of Gerstmann-Sträussler-Scheinker disease.

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Human prion diseases are prominently heterogeneous. In sporadic Creutzfeldt-Jakob disease (sCJD), the most prevalent prion disease, heterogeneity is largely predicated on the common methionine (M)/valine (V) polymorphism at codon 129 of the prion protein (PrP) gene and the disease-associated PrP (PrP^{Dis}) that are

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distinguished in types 1 and 2 based on the electrophoretic mobility of their protease-resistant regions.[1]

However, despite this remarkable heterogeneity, all well-established sporadic prion diseases (here operationally defined as nonacquired prion diseases free of mutations in the PrP gene coding region) have been shown to share the same basic pathogenetic mechanism; PrP^{Dis} interacts with the normal or cellular PrP and converts it into PrP^{Dis}, triggering an autocatalytic process that leads to the accumulation of PrP^{Dis} and ultimately to the clinical disease.[2]

In 2008, we described 11 cases affected by a new disease involving PrP; we named this disease protease-sensitive prionopathy (PSPr).[3] Subsequently, 2 additional cases of PSPr have been independently reported.[4,5] PSPr differed from known sporadic prion diseases in the clinical presentation, in the histopathologic and immunohistochemical features, and in the basic characteristics of the PrP^{Dis}. Furthermore, all 11 cases had the 129VV genotype and no mutation in the PrP gene open reading frame (ORF).

We now report 15 additional cases, all of which bear features of the PSPr as originally reported. However, the new cases also include, in addition to new 129VV subjects, individuals who are 129MV heterozygous and 129MM homozygous. Although the affected subjects belonging to the 3 genotypes share several important characteristics, they also display basic variations that allow the 3 corresponding phenotypes to be distinguished. Therefore, the new cases show that the disease originally described as PSPr, like sCJD, affects all 3 129 genotypes and to some extent mimics the 129-related phenotypic heterogeneity of sCJD, although the PSPr characteristics underline basic differences from sCJD and similarities with Gerstmann-Sträussler-Scheinker disease (GSS), a rare phenotype, which to date has been reported as exclusively associated with PrP gene mutations. In view of the increased protease-resistance of the PrP^{Dis} associated with the new 129 genotypes compared to that of the 129VV cases, we propose to revise the original PSPr label to VPSPr or "variably protease-sensitive prionopathy." Parts of these findings have been presented previously.[6–9]

Subjects and Methods

Subjects

A total of 15 affected subjects, including 3 129MM, 6 129MV, and 6 previously unreported 129VV, were examined. Thirteen affected subjects were referred to the National Prion Disease Pathology Surveillance Center (NPDPSC) (Cleveland, OH) between 2002 and 2010. All cases were symptomatic except 1 of the 129MM subjects, who died suddenly of heart problems while participating in a dementia study as a negative control, underwent autopsy, and was referred to the NPDPSC because it was noted to have spongiform degeneration (SD) on histological examination. One 129MM subject was received by Dr Fabrizio Tagliavini[10] (National Neurological Institute, Instituto Nazionale Neurologico Carlo Besta, Milan, Italy), and 1 129MV subject was received by Dr Piero Parchi (Department of Neurological Sciences, University of Bologna, Dipartimento di Scienze Neurologiche, Università di Bologna, Bologna, Italy). All the subjects including those serving as positive control as indicated were examined at autopsy following analyses of fixed and frozen tissues. Consent was obtained for using tissues for research, including genetic analyses.

Tissue Processing

Fixed and frozen brain tissues were processed as previously described; a different procedure was followed for the case received from Dr Tagliavini.[3,10–12]

Histopathology and Immunohistochemistry

Samples obtained from up to 18 brain regions were processed according to previously described procedures.[3,12] Lesion profiles were constructed using semiquantitative evaluation of SD and astrogliosis in 11 brain regions from 10 subjects, including the 3 129 genotypes. SD and astrogliosis were scored (Fig 1), and the scores from each of the brain regions were summed for each subject separately; values were averaged, their standard deviations determined, and they were plotted according to the brain region.[3,12] Vacuoles with >4μm diameter were measured individually on random photomicrographs of frontal neocortex (10/subject, ×180) using Spotsoftware version 4.6 after calibration (Diagnostic Instruments, Sterling Heights, MI).[3]

Sections from the frontal and occipital neocortices, hippocampus, basal ganglia, thalamus, cerebellar hemisphere, and midbrain were processed for PrP immunohistochemistry with the monoclonal antibody (mAb) 3F4 or 1E4 (Cell Sciences, Canton, MA).[11–17] Selected brain regions were also immunostained with the mAbs 4G8 to amyloid β or PHF1 to the tau protein.[3]

Molecular Genetics

The entire PrP ORF was amplified by polymerase chain reaction using genomic DNA (extracted from unfixed brain tissue or blood) and the primers 42F (CATAACTTAGGGTCACATTT GTCC) and 45R (CCAGATTAACCAATGGTTATTTGC); sequencing was done directly or after cloning into plasmid pSTBlue 1 (Novagen, Madison, WI) by automated sequencing.[13]

Prion Protein Characterization

REAGENTS AND ANTIBODIES. Phenylmethylsulfonyl fluoride was purchased from Sigma Chemical Co. (St. Louis, MO). Peptide N-glycosidase F (PNGase F) was purchased from New England Biolabs (Beverly, MA) and used following the

manufacturers protocol. Reagents for enhanced chemiluminescence (ECL Plus) were from Amersham Pharmacia Biotech (Piscataway, NJ). Antibodies to various sequences of human PrP included anti-C, a rabbit antiserum (220–231), 3F4, a mouse mAb (106–110), and 1E4, a mAb (97–108).[3,14–17]

BRAIN HOMOGENIZATION. The 10% (weight/volume) brain homogenates were prepared in 9 volumes of lysis buffer (100mM Tris, 150 mM NaCl, 0.5% Nonidet P40, 0.5% deoxycholate, 5mM ethylenediaminetetraacetic acid, pH 8.0) on ice using pestles with Eppendorf tubes driven by a cordless motor as previously described.[14] When required, brain homogenates were centrifuged at 1,000 × *g* for 10 minutes at 4°C to collect supernatant.

IMMUNOBLOT ANALYSIS. Samples were resolved on 15% Tris-HCl Criterion precast gels (Bio-Rad Laboratories, Hercules, CA) for gel electrophoresis, and Western blotting as described previously.[15] The proteins on the gels were transferred to Immobilon-P membrane polyvinylidene fluoride (Millipore, Billerica, MA) for 2 hours at 70V. For probing PrP, the membranes were incubated for 2 hours at room temperature with anti-PrP antibodies. Following incubation with horseradish peroxidase-conjugated sheep antimouse immunoglobulin G (IgG) or donkey antirabbit IgG at 1:3,000, the PrP bands were visualized on Kodak film (Eastman Kodak, Rochester, NY) by ECL Plus as described by the manufacturer.

Results

Clinical Features

The cases, grouped according to the 129 genotype, demographics, and clinical data and tests, along with the previous 129VV cases, are summarized in the Table.

In 129VV cases, the presentation was characterized by 1 or more components of a triad comprising psychiatric signs, in the form of behavior and mood changes, speech deficit, and cognitive impairment. Behavior and mood changes, expressed as disinhibition, euphoria, and impulsivity or loss of interest and apathy, were the most frequent (80% of the cases). Language deficits, observed in half of the cases, were characterized by anomic or semantic aphasia, or by dysarthria. Cognitive impairment, mostly of the frontal lobe type, was present at onset in 50% of the cases, alone or together with the behavioral changes and language deficits.

In the 129MV subtype, psychiatric signs were often associated with parkinsonism, followed by ataxia and myoclonus, whereas aphasia was rare; in these cases, the mean age at onset (72 years) and duration (45 months) of the disease were the most advanced and the longest, respectively, of the 3 subtypes and the duration was significantly different from those of the 129VV genotype ($p < 0.017$).

Both symptomatic 129MM subjects (1 died apparently before clinical onset of disease) presented with Parkinsonism and ataxia followed by progressive diffuse cognitive impairment and myoclonus; aphasia was reported in 1 case, but neither showed psychiatric symptoms.

As for the diagnostic tests, just 1 VV case showed signal changes consistent with CJD on magnetic resonance imaging and electroencephalography; all the other cases revealed various degrees of brain atrophy and diffuse slowing of cerebral electrical activity.

Familial occurrence of dementia was reported in about 50% (7/14 available family histories) of the 129VV cases (1 case in the present series), and in 1 129MM, but not in the 129MV genotype.

Histopathology

The hallmark common to all 129 genotypes was the presence of moderate SD comprising vacuoles in the major cerebral regions, which were relatively larger than those observed in sCJDMM1 but overall smaller than those of sCJDMM2 (see Fig 1A–E and Fig 1A-C of Gambetti et al[3]). Occasionally, the molecular layer of the cerebellum contained small homogeneous formations, with the appearance of microplaques in the 129VV and 129MV cases (see Fig 1F, G). On average, all these lesions were more severe in the 129VV and 129MV than in the 129MM cases (see Fig 1E).

The pattern of PrP immunostaining was slightly different in the 3 genotypes.

In the 129VV cases, the PrP immunostaining, as originally described, was targetlike in the cerebrum (Fig 2A) and dotlike in the cerebellar molecular layer (see Fig 2B).

In the 129MV genotype, the targetlike pattern was less recognizable (see Fig 2C). The cerebellar molecular layer showed a more plaquelike immunostaining pattern (see Fig 2D).

In the 129MM subjects, the predominant immunostaining pattern was plaquelike (see Fig 2E). The cerebellum occasionally showed small plaquelike formations (see Fig 2F).

With mAb 1E4, the patterns of PrP immunostaining were similar to those revealed by 3F4 (data not shown).

Various degrees of amyloid β immunostaining, apparently age-correlated, were also observed (data not shown).

Characterization of PrP^{Dis} in the 3 129 Genotypes

PRP^{DIS} ELECTROPHORETIC PROFILE AND PROTEINASE K RESISTANCE. The ladderlike electrophoretic profile of the proteinase K (PK)-resistant PrP^{Dis} fragments, the

TABLE: Summary of Cases

Codon 129	Distribution, % (No.)	Onset, yr ± SD (range)	Duration, mo ± SD (range)	Main Neurological Signs: Psychiatric,[a] %	Aphasia, %	Parkinsonism, %	Ataxia, %	Myoclonus,[b] %	Frontal Type Dementia	Diagnostic Tests: 14.3.3, Positive/ Total or %	EEG, Typical/ Total or %	MRI,[c] Typical/ Total or %	Family History of Dementia
VPSPr													
MM	12 (3)[d]	64 & 78[e]	41 & 50	0	50	100	50	100	0	1/2	1/2	0/2	1/2
MV	23 (6)	72 ± 7[f] (65–81)	45 ± 24[g] (7–72)	83	17	67	67	40	50	0/2	0/2	0/6	0/5
VV	65 (17)[h]	65 ± 8[e,f] (48–77)	23 ± 17[g] (10–60)	71	47	30	71	5	60	1/7	0/14	1/17	7/13
Total % distribution	100	67 ± 10 (48–81)	30 ± 21 (7–72)	68	48	48	64	20	52	2/12	1/18	1/25	8/20
sCJD[i]													
MM1	68	65 (42–91)	4(1–18)	28	23	7	33	97	NA	95%	80%	75%	—
MV1	2	62 (51–72)		12	25	0	75	100	NA		71%		
VV1	1	37 (19–55)	21(10–49)	0	33	33	0	67	NA	100%	0%	100%	—
MM2	2	64 (49–77)	16 (9–36)	0	33	33	17	67	NA	75%	0%	43%	—
MV2	9	60 (41–81)	17 (5–72)	34	11	22	81	77	NA	80%	7%	86%	—
VV2	16		6 (3–18)	19	0	6	100	66	NA		7%	70%	—
Totals	98[j]	63	6	26	18	8	49	87	NA	89%	56%	72%	

[a]Psychiatric symptoms include depression, psychosis, and personality/behavioral changes.
[b]Generally appeared late in the disease.
[c]Twenty-one of 25 VPSPr patients showed significant cerebral atrophy.
[d]One of the 3 129MM subjects who died of accidental causes before onset of clinical disease has been excluded.
[e]$p < 0.025$;
[f]$p < 0.045$;
[g]$p < 0.03$ (statistical analysis by GraphPad [La Jolla, CA] Prism 5 software).
[h]Including the 11 129VV cases previously published.[3]
[i]Data adapted from Gambetti et al,[1] Parchi et al,[12] and Zou et al[17]; cases with co-occurrence of disease-associated prion protein type 1 and 2 have been omitted.[14,18,19]
[j]Does not include sporadic fatal insomnia (2%).[20]
SD = standard deviation; EEG = electroencephalogram; MRI = magnetic resonance imaging; VPSPr = variably protease-sensitive prionopathy; M = methionine; V = valine; sCJD = sporadic Creutzfeldt-Jakob disease.

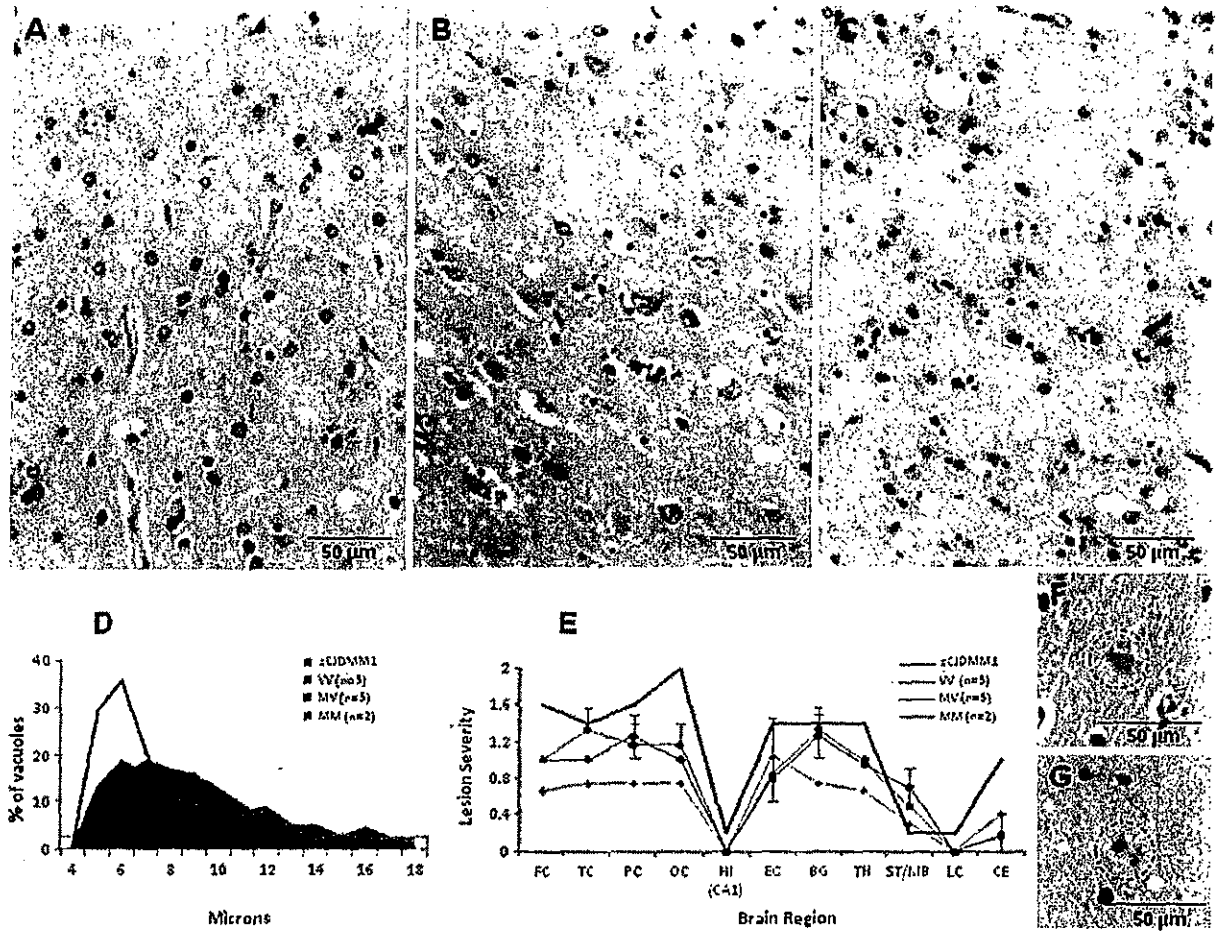

FIGURE 1: Histopathology with vacuole size and lesion profiles in the cases belonging to the 3 129 genotypes of variably protease-sensitive prionopathy (VPSPr). The spongiform degeneration is qualitatively similar in all 3 129 genotypes (A, 129VV; B, 129MV; C, 129MM). (D) As originally shown in the 129VV cases,[3] the spongiform degeneration is made of a significant percentage of relatively large and midsize vacuoles on average significantly larger than those of common sporadic Creutzfeldt-Jakob disease (sCJD) subtypes (diameters: VPSPr [combined] 9.3 ± 3.4μ vs sCJDMM1 5.8 ±1.2μ; $p < 0.0001$ [Student t test]), resulting in an elongated vacuole size distribution in the vacuole size histogram. (E) The lesion profiles are very similar in the 3 129 genotypes, but show less severe lesions in the 129MM genotype than in the 129VV and 129MV genotypes. FC, TC, PC, and OC= frontal, temporal, parietal, and occipital cortices; HI = CA1 of hippocampus; EC = entorhinal cortex; BG = basal ganglia; TH = thalamus (medial-dorsal nucleus); ST/MB = striatum/midbrain; LC = pons (locus coeruleus); CE = cerebellar cortex. The vertical bars refer to standard deviations. Spongiform degeneration was scored on a 0 to 4 scale (0, not detectable; 1, mild; 2, moderate; 3, severe; and 4, confluent), and astrogliosis on a 0 to 3 scale (0, not detectable; 1, mild; 2, moderate, and 3, severe). (F, G) Homogeneous micro deposits with the appearance of plaques were observed in the molecular layer of the cerebellum in some cases associated with the 129VV (F) and 129MV (G) genotypes, but not in the 3 129MM cases. (A–C, F, G) Hematoxylin & eosin. M = methionine; V = valine.

distinctive feature of the PSPr 129VV cases, was shared by all the affected subjects belonging to the 129MM and 129MV genotypes, although, due to the higher PK resistance, the representation of most PrP^{Dis} fragments was greater in 129MM and 129MV than in 129VV (Fig 3A).[3] The ladderlike profile demonstrated with 1E4 consisted of 5 major bands migrating at approximately 26kDa, 23kDa, 20kDa, 17kDa, and 7kDa (hereafter identified as VPSPr26, VPSPr23, VPSPr20, VPSPr17, and VPSPr7) (see Fig 3A). In contrast, PrP^{Dis} types 1 and 2 from sCJD formed the classical pattern of 3 bands migrating at 32/30kDa, 28/26kDa, and 21/19kDa (see Fig 3A).

PrP^{Dis} preparations from the 3 genotypes were probed with mAb 1E4 or 3F4 after treatment with various amounts of PK. When PrP^{Dis} fragments were considered all together, both 1E4 and 3F4 confirmed the relatively high PK resistance of PrP^{Dis} in the 129MM cases, intermediate in the 129MV cases, and low or entirely lacking in the 129VV cases (see Fig 3). However, both mAbs also showed the heterogeneous resistance of the individual fragments to PK, which was confirmed with

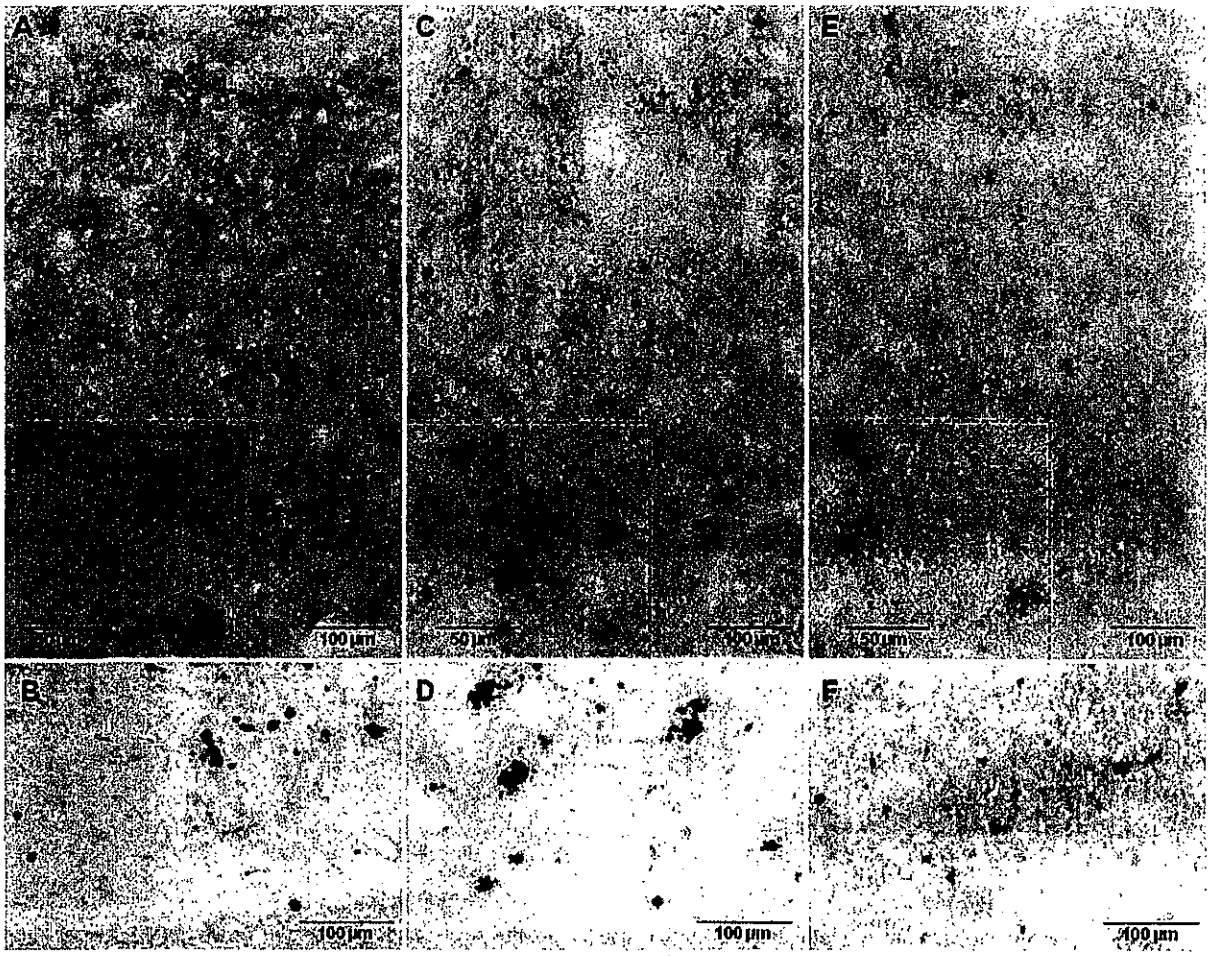

FIGURE 2: Prion protein immunohistochemistry in the 3 variably protease-sensitive prionopathy 129 genotypes. The cerebral cortex (A, C, E) and cerebellar molecular layer (B, D, F) best exemplify the predominant immunostaining patterns. (A) The pattern in the 129VV genotype is often targetlike, with a larger stained granule or clusters of granules surrounded by smaller granules in a focal or more diffuse background of punctate or synaptic staining (*inset:* higher magnification of the same cortical region). (B) The molecular layer of the cerebellum shows relatively large granules that are often compact and intensely stained. (C) In the 129MV genotype, the targetlike pattern is generally less obvious, as large granules are more often isolated; focal or larger areas of synaptic staining are also present (*inset:* as above). (D) In the cerebellum, the granules are fewer, are more loose, and have a plaquelike appearance. (E) The 129MM genotype often shows a plaquelike immunostaining pattern (*inset:* as above). (F) The cerebellum shows small formations. Immunostaining was done with monoclonal antibody 3F4. M = methionine; V = valine.

PK titration experiments. These analyses showed that the VPSPr7 fragment was highly PK-resistant in all 3 genotypes. In contrast, the other 4 fragments appeared to follow 2 distinct patterns, which were similar and involved pairs of the same fragments in both 129MV and 129MM; VPSPr26 and VPSPr20 increased and decreased rapidly in amount peaking at 10μg/ml of PK and generated fairly narrow bell-shaped curves. In contrast, both PSPr23 and PSPr17 increased at a lower rate, peaked between 25 and 50μg/ml of PK, and remained relatively well represented even at 100μg/ml of PK. The representations of the 2 pairs of fragments were significantly different at 100μ/ml PK concentration in both 129 genotypes (129MM, $p < 0.02$; 129MV, $p < 0.005$). As expected, the PK resistance of the 129VV fragments was much lower, except for VPSPr7. Combined, the immunoblots and quantitative analyses argue that VPSPr23 and VPSPr17 have the strongest resistance to PK and likely form secondarily from VPSPr26 and VPSPr20 following treatment with high PK concentrations. It has to be noted, however, that the PK sensitivity of the 129VV preparations was in part related to the mAb used. When probing with 1E4 instead of 3F4, all fragments present in the VPSPr-129MM and -129MV preparations were also detectable in the preparations from the 129VV genotype, even if they displayed different ratios. Therefore,

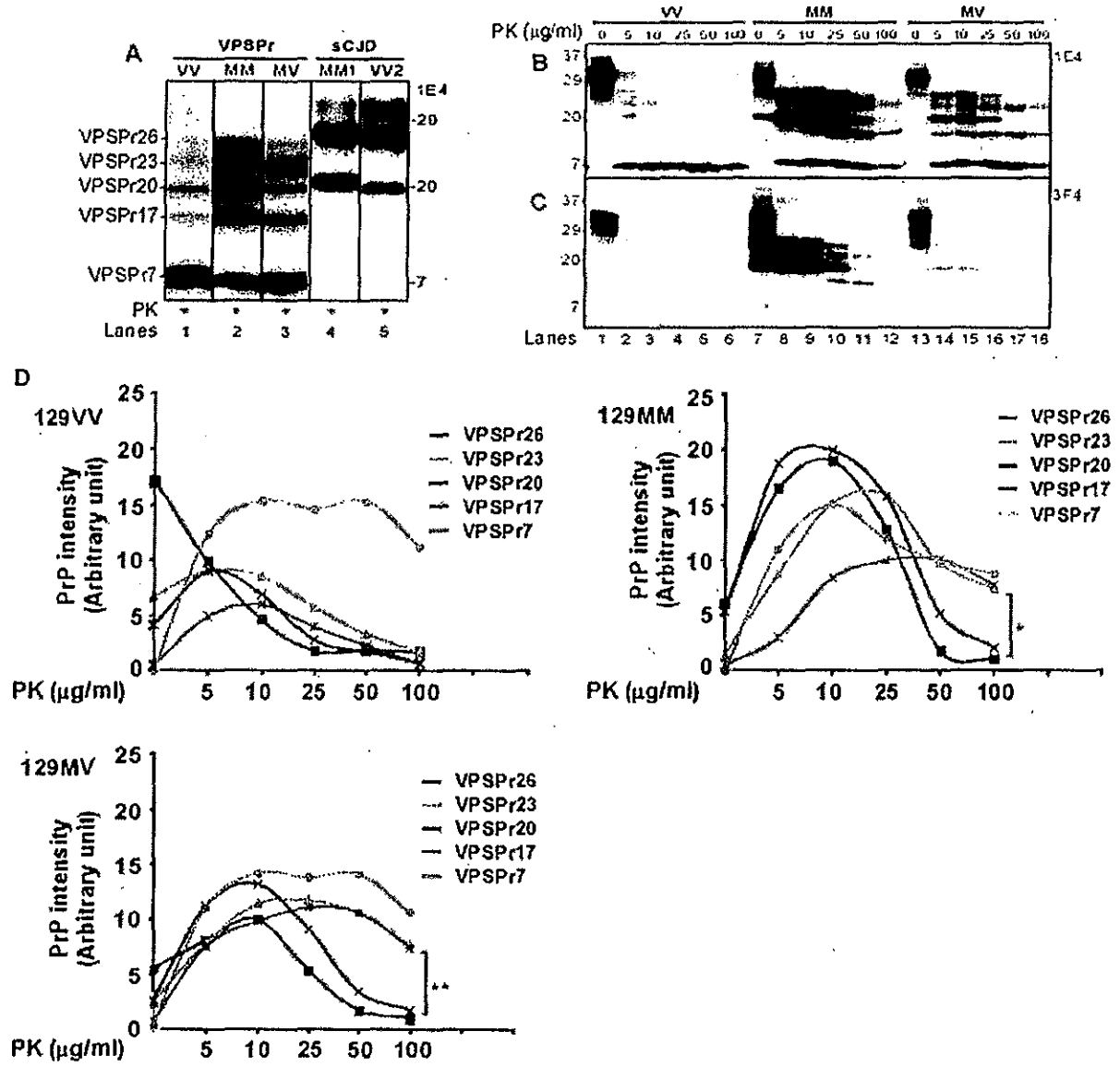

FIGURE 3: Electrophoretic profiles and proteinase K (PK) titration of PK-resistant disease-associated prion protein (PrP^{Dis}) from variably protease-sensitive prionopathy (VPSPr) associated with the 129VV, 129MM, or 129MV genotype. (A) The Western blots of the total brain homogenates (BHs) treated with 25µg/ml of PK and probed with the monoclonal antibody 1E4 reveal 5 PrP bands migrating approximately to 26kDa, 23kDa, 20kDa, 17kDa, and 7kDa, forming a ladderlike pattern in all 3 (129VV, 129MM, and 129MV) genotypes of VPSPr (VPSPr26, VPSPr23, VPSPr20, VPSPr17, and VPSPr7) *(lanes 1–3)*. The faint band that migrates at approximately 30kDa in VPSPr-129VV *(lane 1)* likely represents the incomplete PK digestion of the normal diglycosylated, N-terminus truncated PrP fragment or associated monoglycosylated full-length PrP. In contrast, BHs from sporadic Creutzfeldt-Jakob disease (sCJD) associated with the 129MM genotype and the PrP^{Dis} type 1 (sCJDMM1) or sCJDVV2 (sCJD with the 129VV genotype and PrP^{Dis} type 2) show the typical 3 PK-resistant PrP fragments of type 1 and 2 migrating between 31kDa and 19kDa (lanes 4 and 5). (B, C) PK titration of PrP^{Dis}. Brain homogenates from 129VV, 129MM, and 129MV genotypes were treated with PK at various concentrations between 0 and 100µg/ml. (B) Probed with 1E4. (C) Probed with 3F4. (D) PK titration with quantitative analysis of the individual VPSPr fragments. The curves represent the relative amounts of the individual VPSPr fragments at increasing PK concentrations (0–100µg/ml) after probing the immunoblots with 1E4 in each of the 3 129 genotypes. The relative representations of the bands corresponding to the VPSPr fragments were determined by densitometry and expressed as averages of 129VV (n = 3), 129MM (n = 2), and 129MV cases (n = 3). Comparative analysis of the curves from each of the 3 129 genotypes confirms the PK sensitivity of all the fragments in 129VV cases, with the exception of VPSPr7, which is resistant to PK in all 3 genotypes. The remaining 4 fragments follow similar patterns in both the 129MM and 129MV genotypes; VPSPr26 and VPSPr20 form rapidly but are digested at PK concentrations >10µg/ml; VPSPr23 and VPSPr17 are resistant up to 100µg/ml of PK (*$p < 0.02$; **$p < 0.005$). M = methionine; V = valine.

the PK treatment might not only break down the PrP^{Dis} associated with the 129VV genotypic form, but also generate fragments relatively undetectable by the mAb 3F4. Alternatively, PrP^{Dis} associated with VPSPr-129VV might have a low immunoreactivity with 3F4, even without PK treatment.

IDENTIFICATION OF THE PRP^{DIS} CORE FRAGMENTS AND THEIR COMPARISON WITH THOSE OF THE GSS VARIANT LINKED TO THE A117V MUTATION. Various amounts of VPSPr20, VPSPr17, and VPSPr7 were demonstrated by 1E4 in all 3 129 genotypes after deglycosylation and up to 50μg/ml of PK treatment (Fig 4A). Because the deglycosylation eliminated VPSPr26 and VPSPr23, these 2 fragments likely are the glycosylated isoforms of VPSPr20 and VPSPr17, respectively. This would explain the shared level of PK resistance of these 2 fragments (see Fig 3D). Of notice, the same PK-resistant fragments were well represented also without deglycosylation, suggesting that VPSPr20 and VPSPr17 are present as both glycosylated and unglycosylated isoforms (see Fig 3A, B). With 3F4, only VPSPr20 and VPSPr17 were detectable in the 129MM and 129MV cases, whereas again the 129VV genotype showed no PK-resistant PrP (see Fig 4B). The combined and individual resistance of the deglycosylated fragments to PK was comparable to that of the glycosylated isoforms.

Further characterization of the core fragments with the antibody anti-C (C-terminal residues 220–231) demonstrated 4 PrP bands migrating at approximately 20kDa, 18kDa, 12–13kDa, and 8kDa, of which only the 20kDa band matched VPSPr20 detected with 1E4 and 3F4 (see Fig 4C). The 3 fragments undetected by 1E4 and 3F4 must comprise the C-terminal region (reactive with anti-C) and must lack the 97–112 sequence

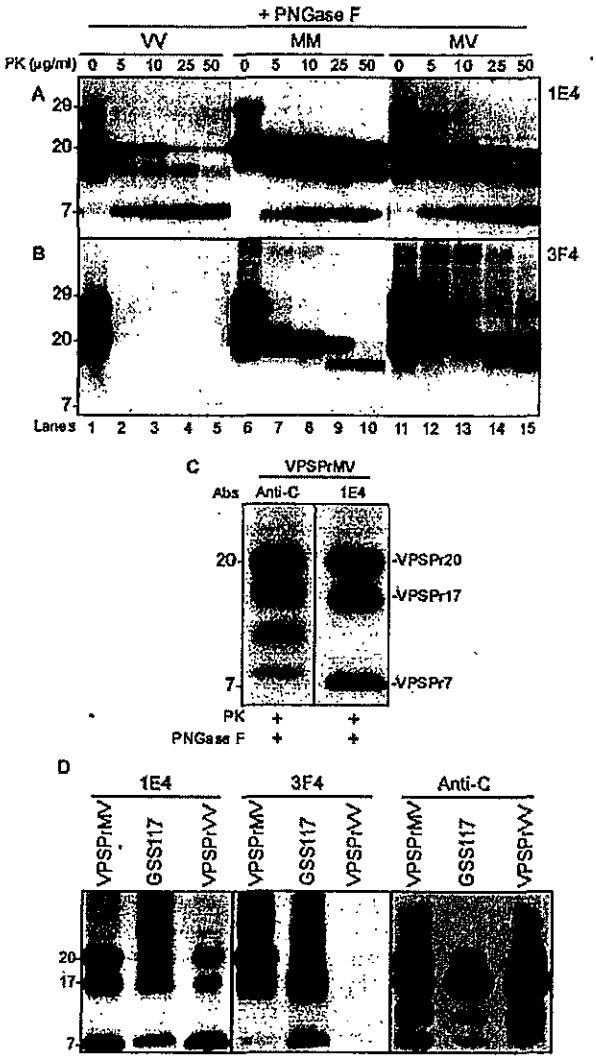

FIGURE 4: Proteinase K (PK)-resistant core fragments of variably protease-sensitive prionopathy (VPSPr) and their comparison with the disease-associated prion protein (PrP^{Dis}) fragments associated with Gerstmann-Sträussler-Scheinker disease (GSS)-A117V. All brain homogenates were treated with increasing concentrations of PK and with peptide N-glycosidase F (PNGase F). (A) With 1E4, all immunoblots from cases with the 129VV,129MM, and 129MV genotypes essentially show variably protease-sensitive prionopathy (VPSPr)-20, VPSPr17, and VPSPr7. However, the PK resistance of these bands varies according to the 129 genotype and the individual bands within the same genotype in a way roughly similar to that shown in Figure 3. (B) The immunoblots probed with 3F4 reveal 2 major bands in the 129MM and 129MV genotypes, which, however, exhibit a quite different pattern of resistance to PK in the 2 genotypes. As expected, no PK-resistant PrP bands are detected in the 129VV genotype. (C) Additional analysis of the core fragments following treatment with 25μg/ml of PK and PNGase, using the antibody anti-C to the PrP C-terminal residues 220–231. Compared to 1E4, anti-C demonstrates 4 bands of 20kDa, 18kDa, 12–13kDa, and 8kDa, respectively, of which only the 20kDa band has the same gel mobility as VPSPr20 detected with 1E4. The other 3 bands, including 18kDa, 12–13kDa, and 8kDa, do not match the bands detected with 1E4. (See text for explanation). (D) Brain homogenates from VPSPr-129MV, GSS117, and VPSPr-129 were treated with PK and PNGase F prior to Western blotting and probed with 1E4 *(left panel)*, 3F4 *(middle panel)*, and anti-C *(right panel)* antibodies. With monoclonal antibody 1E4, bands matching VPSPr20, VPSPr17, and VPSPr7 are detected in the GSS-A117V preparations, but the GSS-V117V bands immunoreact much less with 1E4 than the bands of VPSPr-129MV and VPSPr-129VV. The 23kDa band is seen more prominently in GSS-A117V. With 3F4, the VPSPr17 and VPSPr7 bands are shared by GSS-A117V and VPSPr-129MV, but the 20kDa band is missing in GSS-A117V. The VPSPr7 band is much less reactive in 129MV. As previously, the 129VV is not reactive with 3F4. Anti-C reveals apparently the same bands in all 3 preparations, but with significantly different ratios. M = methionine; V = valine.

containing the 1E4 and 3F4 epitopes. Therefore, 6 core fragments of relative molecular weights between 20kDa and 7kDa were identified by the combined use of 1E4 and anti-C. Several PrP C-terminal fragments of similar relative molecular weight have been previously reported.[18–20] Considerable similarities were observed in the electrophoretic mobilities of the PK-resistant core fragments from the 129MV, 129VV, and 129MM genotypes and GSS-A117V (see Fig 4D). Also in GSS-A117V, the mAb 1E4 demonstrated the presence of 3 bands of 20kDa, 17kDa, and 7kDa described in VPSPr, which, however, displayed different immunoreactivities. Comparable variations in antibody immunoreactivity and band representation were seen with 3F4 and anti-C (see Fig 4D). Therefore, most of the PK-resistant PrP^{Dis} fragments appeared to have similar sizes in VPSPr and GSS-A117V, but different ratios and antibody reactivities.

Discussion

At variance with the series of 11 cases of PSPr described in 2008 and 2 cases subsequently published by others—all 13 of which were 129VV homozygous at the PrP gene—the 15 cases reported here also include affected subjects who are 129MV and 129MM, in addition to new 129VV subjects.[3–5] Comparative analyses indicated that all these cases are affected by the same disease process, and that most of the heterogeneity that we observed results from distinct 129 genotypes.

These cases are likely to be affected by the same disease because of the overall similarity in major phenotypical characteristics, including the clinical features, which prominently exhibit aphasia, ataxia, and parkinsonian signs; SD, displaying vacuoles comparable in size in the 3 genotypes but otherwise different from the vacuoles of other common prion diseases; and finally PrP immunostaining patterns, which also display comparable general features in all these cases. However, the 2 most striking similarities reside in the ladderlike electrophoretic pattern of the PK-resistant fragments and in the unique immunoreactivity of PrP^{Dis} with mAb 1E4. Cumulatively, these findings suggest that all these cases share a similar molecular mechanism of PrP^{Dis} formation.

Significant clinical differences among the 129VV and 129MV groups (only 2 129MM symptomatic subjects were available) occurred in the mean age at onset and in disease duration (see Table). PrP immunostaining patterns were also distinguishable in the 3 groups. An additional difference might lay in disease prevalence, which appeared to be highest in 129VV subjects (65% of the cases), followed by the 129MV (23%) and 129MM subjects (12%) (see Table). However, 2 distinctive features were evident among the 3 groups; these were: (1) the apparent resistance to PK digestion, which was generally much lower in the 129VV cases than in the 129MM and 129MV cases; and (2) the immunoreactivity of the PK-resistant PrP^{Dis} with mAb 3F4, which was strong in the 129MM cases, weak in the 129MV cases, and lacking in the 129VV cases. Cumulatively, these findings argue that, although PrP^{Dis} may be formed by a similar mechanism in the 3 genotypes, the conformation or aggregation is likely different, and this difference results in variable resistance to PK, variable accessibility by 3F4, or both.

These findings also indicate that, in the present series of cases, it is the 129 genotype that modifies the phenotypic characteristics, including PK resistance and antibody immunoreactivity of PrP^{Dis}. However, the possibility that phenotypic heterogeneity is caused by other variations in PrP^{Dis} among the 3 groups or by a combination of different 129 genotypes and PrP^{Dis} characteristics, as is the case with sCJD, cannot be excluded.

The variations in prevalence are likely to be associated with the 129 genotype as well. This also is a feature of sCJD, in which 129MM cases account for about 70% of the total, 129MV for 11%, and 129VV for 17%.[1,12] It is remarkable that the effect of the 129 genotype on disease prevalence in our series of cases appears to be the opposite of that in sCJD. The high percentage of 129VV subjects described to date (20 of 28 known subjects, including the 2 cases reported elsewhere) and the apparent rarity of 129MM subjects (only 3 of 28 subjects) suggest that the prevalence of VPSPr is directly related to the presence of the 129V allele.[3–5] Indeed, at least 1 129V allele is present in 25 of the 28 known cases of VPSPr. The prevalence of the 3 129 genotypes in VPSPr is quite different from that in normal Caucasian populations, in which the 129MM genotype accounts for 43% of subjects, the 129MV for 49%, and the 129VV for 8%.[21]

The present findings raise a number of questions concerning the nature of VPSPr and its place within the group of known prion diseases.

In our series of 26 VPSPr cases collected to date, 8 subjects apparently had familial dementia; they were all 129VV except for 1 129MM. One of the 2 VPSPr-129VV cases reported by others also had a definitive family history of neurodegenerative disease.[4] This raises the possibility that VPSPr is a familial disease with a locus other than the ORF of the PrP gene (which is free of mutations), a condition analogous to that of familial Alzheimer disease.[3,22] Whether the VPSPr subjects reported to date also include inherited cases belonging solely to the 129VV and 129MM genotype remains to be determined.

Well-recognized prion diseases, which are associated with the classic PrP^{Dis} commonly identified as PrP27-30, such as all sCJD subtypes and several subtypes of familial CJD and sporadic and familial fatal insomnia, are transmissible with relative ease to receptive animals.

Inoculated animals develop a full-blown disease with clinical signs, SD, and presence of a PrP27-30 that generally reproduces the characteristics of the PrP27-30 present in the inoculum.[1,23,24] In contrast, other prion diseases, especially GSS, a rare phenotype that to date has been reported as exclusively associated with PrP gene mutations, have been more difficult to transmit or have been reported not to be transmissible at all.[25–28] For example, inoculation of brain homogenate from a subtype of GSS linked to the P102L mutation and characterized by the immunoblot presence of only a PK-resistant fragment of 7kDa similar to that present in VPSPr did not cause a symptomatic disease in recipient transgenic mice, but elicited the formation of PrP amyloid deposits in the absence of abnormal PrP.[26] Similarly, inoculation of PK-sensitive recombinant PrP polymerized into amyloid fibers generated a prion disease in PrP overexpressing transgenic mice that was apparently asymptomatic but caused SD and deposition of PK-sensitive abnormal PrP, 2 features shared by the 129VV genotype of VPSPr, only late in the life of the inoculated animals, consistent with very long incubation times.[29] Furthermore, similar transmission patterns on inoculation of brain homogenates from affected animals or humans have been observed in other neurodegenerative diseases, such as Alzheimer disease and diseases of the tau protein or tauopathies.[30,31] Experiments on the transmissibility of VPSPr are ongoing. Preliminary data indicate that VPSPr transmissibility, if it occurs at all, is not efficient, and it could be more like that of GSS-P102L associated with PrP^{Dis} 7kDa or of PK-sensitive PrP amyloid fibers, which require long incubation times and do not shorten the life span of the affected animals.[26,29]

It is intriguing that GSS also shows characteristics of the phenotype and of the PrP^{Dis} associated with some of the mutations that resemble those of VPSPr.[25] They include long disease duration, multiple PK-resistant fragments, and variable PK resistance of PrP^{Dis}. Our comparative analysis of the electrophoretic profiles in VPSPr and GSS-A117V reveals provocative similarities. This finding raise the issue of whether VPSPr might be viewed as the sporadic form of GSS.

Regardless of its relationship with GSS, the finding that VPSPr affects all 3 129 genotypes, resulting in distinct disease phenotypes and PrP^{Dis} characteristics, establishes VPSPr as the second "sporadic" prion protein disease, after sCJD.

Acknowledgment

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Potential Conflicts of Interest

Nothing to report.

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識別番号・報告回数			報告日	第一報入手日 2010 年 7 月 29 日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	乾燥濃縮人血液凝固第Ⅷ因子		研究報告の公表状況	European Medicines Agency/2010/07/24	公表国 欧州	
販売名（企業名）	コンコエイト-HT（ベネシス）					

研究報告の概要

この文書は、2003 年 2 月に公表され、2004 年 6 月と 2010 年 XXX に改訂された「クロイツフェルト-ヤコブ病と、血漿由来医薬品および尿由来医薬品」についての CPMP(脚注 2)の見解表明書(position statement) (EMEA/CPMP/BWP/2879/-02)の第 2 改訂版であり、1998 年 2 月に公表された「新しい変異型 CJD と血漿由来医薬品」についての CPMP の見解表明書に置き換わるものである。

要約

疫学的なエビデンスが集積してきたが、それらのエビデンスは血漿由来医薬品によってクロイツフェルト-ヤコブ病(CJD)の伝播が起こるとの考え方を裏付けるものではない。あるドナーがドネーション後に孤発性、家族性、もしくは医原性 CJD であることが確認された場合に、血漿由来医薬品のリコールを求めることは妥当ではない、とのこれまでの CHMP の立場には変化はない。

変異型 CJD(vCJD)は新たに出現してきた疾患であり、症例数が最終的にどの程度となるのかは不確かである。vCJD は孤発性 CJD と比較すると末梢組織中への分布がより広く感染性/異常プリオンタンパク質のレベルがより高い。英国で輸血によるヒトへの医原性 vCJD 感染が明確な 4 例から vCJD が輸血を介して伝播しうるものである、ということの強力なエビデンスが得られた。2009 年に、中程度の純度の第 VIII 因子の投与を受けた血友病 A 患者で感染性物質が検出されたが。この製剤は英国で 1998 年より前に採取されたプール血漿から調製されたものであった。

英国に居住していることは vCJD の危険因子とされており、そのことから英国は英国起原の血漿から分画を今後行わないことを決定するに至った。危険期間中に英国に長期間滞在したドナーから血液/分画用血漿のドネーションを受けないようにすることはこの英国の決定と一貫した措置である。1980 年初頭から 1996 年末までの間に英国に累積で 1 年間以上滞在したドナーを、血液/分画用血漿のドネーションから排除することを勧告する。

あるドナーについて英国での滞在に基づけば排除すべきであったことがドネーション後に判明した場合に、当該バッチを回収することは勧告されていないが、それは、このような排除が非常に慎重を期した予防措置だからである。

現在得られているデータでは、ヒト血漿中に vCJD の感染性が仮に存在していたとしても、血漿由来医薬品の製造工程で vCJD の感染性は低減されることが示されている。製造者にはその製造者の用いている製造工程で感染性を低減させる能力がどの程度あるか、ステップごとに調べて推定することが求められている。製造者がこの推定を行う際には、マイルストーンの各々でこの分野の専門家と相談することを勧告する。CHMP とそのバイオテクノロジー作業部会(BWP:Biotechnology Working Party)は、これらの勧告事項と取るべきアクションについて検討を続けるつもりである。

この勧告事項のサポートとして、CHMP と BWP は、外部の専門家の関与も依頼して、vCJD の危険性に関して製造工程の調査方法に関するガイダンスを作成したが、CHMP と BWP は生ずる可能性のある問題点について討議する用意がある。

このような立場を取る理由は、仮に将来、血液および血漿由来医薬品製造のための血漿を採取し集めている国々においてさらに vCJD の症例が発生したならば、以前に TSE 感染性を低減しうることが示されていた製造工程は、過去の製剤の安全性の再保証を与えることとなり、分画を継続することを妥当とすることの助けとなろう。

スクレイピーに感染したげっ歯類の尿中、および慢性消耗性疾患のシカの尿中に低レベルの TSE 感染性物質が検出されている。しかし、尿由来の医薬品による CJD もしくは vCJD の伝播の疫学的証拠はない。尿由来医薬品の製造工程の総合的レビューでは、ある製剤が比較

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	的少数で特徴のよく分かっているドナー集団由来のものである場合には、ドナー選択基準を適用することが可能であることを指摘している。さらに、そのレビューでは、TSE 感染性が出発材料中に存在していたとした場合でも、理論的にはその感染性を低減することができると考えられるステップを、少なくとも 1 つ製造工程中に有していることを指摘している。尿由来医薬品は英国で採取された尿を原料とはしないこととなっている。 　このレビューおよびその他の考慮事項に基づいて、可能であれば、尿ドナーパネルを選択するための除外基準の使用が、予防的措置として勧められる。血漿由来医薬品の製造のための出発材料を提供する血液/血漿ドナーに用いるものとして CJD および vCJD に関しても同じ除外基準が適用されるべきであるが、血液/血漿ドナーとは異なり、それらの判定基準は各ドネーションごとにはチェックされない。尿由来医薬品の製造者が、血漿由来医薬品のためのアプローチと類似のものに従って、製造工程の TSE 感染性物質の低減/排除能を評価することを勧告する。	2. 重要な基本的注意 (1)略 1)略 2)略 3)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
これは血漿由来と尿由来製品（EMEA/CPMP/BWP/2879/02)のクロイツフェルトーヤニブ病に関する CPMP の見解表明書の第２改訂(案）である。 血漿分画製剤は理論的なvCJD伝播リスクを完全には排除できないため、投与の際には患者への説明が必要である旨を2003年5月から添付文書に記載している。2009年2月17日、英国健康保護庁(HPA)はvCJDに感染した供血者の血漿が含まれる原料から製造された第Ⅷ因子製剤の投与経験のある血友病患者一名から、vCJD異常プリオン蛋白が検出されたと発表したが、弊社の原料血漿採取国である日本及び米国では、欧州滞在歴のある献（供）血希望者を一定の基準で除外し、また国内でのBSEの発生数も少数であるため、原料血漿中に異常型プリオン蛋白が混入するリスクは1999年以前の英国に比べて極めて低いと考える。また、製造工程においてプリオンが低減される可能性を検討するための研究を継続して進めているところである。	本報告は本剤の安全性に影響を与えるものではないと考えるので、特段の措置はとらない。

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 London, 24 June 2010
2 EMEA/CPMP/BWP/2879/02/rev 2
3 Committee for Medicinal Products for Human Use (CHMP)

4 CHMP position statement on Creutzfeldt-Jakob disease 5 and plasma-derived and urine-derived medicinal products 6 Draft[1]

Draft Agreed by Biologics Working Party	May 2010
Adoption by CHMP for release for consultation	24th June 2010
End of consultation (deadline for comments)	30th September 2010
Agreed by Biologics Working Party	<Month YYYY>
Adoption by CHMP	<DD Month YYYY>

7

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Keywords	Creutzfeldt-Jacob disease, human Transmissible Spongiform Encephalopathies, plasma-derived medicinal products, urine-derived medicinal products, sporadic CJD, genetic CJD, iatrogenic CJD, variant CJD, blood infectivity, transmissibility

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[1] Delete once the reflection paper is adopted.

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CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products

Table of contents

This is the second revision of the CPMP[2] Position Statement on "Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products" (EMEA/CPMP/BWP/2879/02) published in February 2003 and revised in June 2004 and XXX 2010, which replaced the CPMP Position Statement on "New variant CJD and plasma-derived medicinal products" (CPMP/201/98) issued in February 1998.

Summary

Cumulative epidemiological evidence does not support transmission of sporadic, familial and iatrogenic Creutzfeldt-Jakob disease (CJD) by plasma-derived medicinal products. There is no change to the previous CHMP position that recall of plasma-derived medicinal products is not justified where a donor is later confirmed as having sporadic, familial or iatrogenic CJD.

Variant CJD (vCJD) is an emerging disease and the eventual number of cases of the disease is uncertain. There is a wider distribution and higher level of infectivity/abnormal prion protein in peripheral tissues than is seen with sporadic CJD. Four instances of apparent iatrogenic vCJD infection by blood transfusion in man in the UK provide strong evidence that vCJD is transmissible through blood transfusion. In 2009, the agent was detected in a haemophilia A patient who received intermediate purity FVIII prepared from pooled plasma sourced in the UK before 1998.

Residence in the UK is a recognised risk factor for vCJD and has led to the UK deciding to no longer fractionate from UK plasma. It is consistent with this decision to exclude donors who have spent long periods in the UK during the risk period from donating blood/plasma for fractionation. It is recommended that donors who have spent a cumulative period of 1 year or more in the UK between the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma for fractionation.

There is no recommendation to recall batches if information that would have excluded a donor based on his/her stay in the UK becomes available post-donation, since this is a very conservative precautionary measure.

Available data indicate that the manufacturing processes for plasma-derived medicinal products would reduce vCJD infectivity if it were present in human plasma. Manufacturers are required to estimate the potential of their specific manufacturing processes to reduce infectivity using a step-wise approach. It is recommended that manufacturers consult the relevant competent authorities at each of the milestones in this estimation. CHMP and its Biotechnology Working Party (BWP) will keep progress with these recommendations and the actions to be taken under review.

In support of this recommendation, CHMP and BWP, with the involvement of external experts, have developed guidance on how to investigate manufacturing processes with regard to vCJD risk and CHMP and BWP are available to discuss issues that might arise.

The rationale for this position is that if, in the future, further cases of vCJD occur in countries collecting blood and plasma for the manufacture of plasma-derived medicinal products, a process previously shown to be able to reduce TSE infectivity will provide reassurance on the safety of past products, and could help to justify continuing fractionation.

Low levels of infectious TSE agents have been detected in the urine of scrapie-infected rodents and in the urine of deer with Chronic Wasting Disease. However, there is no epidemiological evidence of CJD or vCJD transmission by urine derived medicinal products. A general review of manufacturing

[2] In May 2004 there was a change in the name of the EMEA's scientific committee for human medicines from CPMP to CHMP.

processes for urine-derived medicinal products indicates that it is feasible to apply donor selection criteria when a product is derived from a relatively small and well-defined donor population. In addition, it indicates that manufacturing processes have at least one step that might be theoretically capable of reducing TSE infectivity if it were present in the starting material. It is noted that urine-derived medicinal products are not sourced from urine collected in the UK.

On the basis of this review and other considerations, the use of exclusion criteria for selection for a urine donor panel is encouraged, as a precautionary measure, where feasible. The same exclusion criteria should be applied with respect to CJD and vCJD as used for blood/plasma donors providing starting material for the manufacture of plasma-derived medicinal products but, unlike blood/plasma donors, these criteria would not be checked at each donation. Manufacturers of urine-derived medicinal products are recommended to evaluate the capacity of the manufacturing process to reduce/eliminate TSE agents by following a similar approach to that for plasma-derived medicinal products.

1. Introduction

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease belonging to the group of human Transmissible Spongiform Encephalopathies (TSEs) or prion diseases. Mortality rate of TSEs ranges approximately from 1.5 to 2 persons per million population per year. TSEs can occur sporadically (sporadic CJD (sCJD) and sporadic fatal insomnia), be associated with mutations of the prion protein gene (genetic TSEs (gTSE)), or result from medical exposure to infectious material (iatrogenic CJD (iCJD)). In 1996, a variant form of CJD (vCJD) was identified.[1] There is strong evidence that vCJD is caused by the agent responsible for bovine spongiform encephalopathy (BSE) in cattle.[2,3,4] The most likely hypothesis is that vCJD has occurred through exposure to BSE contaminated food.

Human TSEs, including in particular vCJD, were addressed in expert meetings/workshops at the EMEA in January 1998, January 1999, December 1999, May 2000, and December 2000. A CPMP Position Statement on variant CJD and plasma-derived medicinal products was issued in February 1998[5f] and the outcome of the subsequent meetings was published on the EMEA website.[5] An EMEA Expert Workshop on Human TSEs and Medicinal Products was held on 19-21 June 2002. This provided the scientific basis for a new CPMP Position Statement issued in 2003.[5b] A further EMEA Expert Workshop was held in January 2004 to review the current state of knowledge of vCJD, in the light of the recent report of a possible human transmission by blood transfusion.[6] In addition, the Workshop discussed the CPMP Discussion document on the investigation of manufacturing processes with respect to vCJD.[5a] In October 2005, a follow-up workshop was held to discuss the number of vCJD cases reported in France and other European countries and the potential effect of additional donor exclusion measures. Urine-derived medicinal products were specifically discussed at an EMEA expert workshop in July 2007[5g] after publication of experiments indicating transmission of prions via urine using a hamster model.

Blood and blood components for transfusion are outside the scope of this Position Statement. Recommendations on the suitability of blood and plasma donors and the screening of donated blood in the European Community were described in Council Recommendation 98/463/EC.[7c] European legislation on human blood and blood components entered into force on 8 February 2003[7a] Under this legislation, a Commission Directive on certain technical requirements for blood and blood components, including eligibility criteria for donors, entered into force in April 2004.[7b] In addition, Council of Europe Recommendation No. R (95) 15 contains a technical appendix on the use, preparation and quality assurance of blood components and details the current requirements for donors.[79]

In December 2003, following the announcement of a possible case of vCJD transmission by blood transfusion, Commissioner Byrne made a statement highlighting EU activities in the area of vCJD and announcing a meeting of the Working Group of the Blood Regulatory Committee to consider the latest information available from the UK.[7d] The meeting took place in January 2004 and a summary statement was produced.[7e]

The Scientific Steering Committee (SSC) and the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) of the European Commission have published a number of opinions relating to TSEs, which are of relevance to blood and blood components for transfusion, as well as to plasma-derived medicinal products.[8] WHO Guidelines on TSEs are also of relevance to both blood components for transfusion and plasma-derived medicinal products.[9] The Council of Europe has made recommendations for blood and blood components for transfusion.[10]

2. Human TSEs current status

2.1. Sporadic, genetic and iatrogenic forms of human TSEs

There is no evidence that sporadic, genetic or iatrogenic forms of human TSEs have been transmitted from person to person through exposure to plasma products or urinary derived medicinal products. Systematic surveillance for CJD of all types has been undertaken in a number of countries, including a collaborative study in the EU since 1993,[11,12] and no case of sporadic, genetic or iatrogenic CJD has been causally linked to prior treatment with plasma products. Cases of sporadic CJD with a history of drug treatment for infertility have not been identified but there is uncertainty about the validity of this observation. (See the report of the 2007 EMA expert meeting for further details.[5g]) Although there is evidence that plasma products have not been implicated in transmission of sporadic, genetic or iatrogenic CJD, the strength of the evidence excluding transmission by urinary derived medicinal products is less secure.

2.2. Variant CJD

The official UK figures for vCJD at the beginning of April 2010 were a total of 172 definite or probable vCJD cases.[13] (One case diagnosed in Hong Kong was classified as a UK case and is included in the UK figures.) Outside of the UK, there have been 25 cases in France[15], 5 in Spain, 4 in the Republic of Ireland, 3 in the Netherlands, 3 in the USA, 2 in Portugal and Italy and single cases in Canada, Saudi Arabia and Japan. 2 of the Irish cases, 2 of the US cases, 1 French case and the Canadian case had spent more than 6 months in the UK during the period 1980-1996 and were probably infected while in the UK. [14] The third US case has been reported as most likely infected when living in Saudi Arabia. The possibility of cases occurring in other countries cannot be excluded.

Two cases of vCJD identified in Spain occurred in the same family. No family links have been reported in any other vCJD cases to date.

All definite and probable cases, which have been genotyped so far, are Met-Met homozygotes at codon 129 of the prion protein (PrP) gene.[16] In 2009 a possible case of variant CJD was reported in the UK with a heterozygous codon 129 genotype. [17]

Analysis of the UK figures for the quarterly incidence of deaths indicates that vCJD incidence in the UK is currently in decline. However, interpretation requires caution as there may be a long tail or more than one peak to the epidemic.[18]

A UK study screening specimens from surgically removed appendices and tonsils for accumulation of prion protein in the lymphoreticular system has been carried out in order to try and obtain some estimation of the number of people that might be incubating vCJD in the UK.[19] Three positive appendix specimens have been found as a result of the screening of 12,674 appendix and tonsil specimens. However, the pattern of lymphoreticular accumulation in two of these samples was dissimilar from that seen in known cases of vCJD, raising the possibility that they may be false positives. With respect to this possibility, the authors comment that although it is uncertain whether immunohistochemical accumulation of prion protein in the lymphoreticular system is specific for vCJD, it has not been described in any other disease, including other forms of human prion disease or a range of inflammatory and infective conditions. Subsequent genetic analysis of residual tissue samples from these 2 cases found that both were valine homozygotes at codon 129 in the prion protein gene[20] This finding might account for the immunohistochemical features in these cases; all patients who have developed vCJD and have undergone a comparable genetic analysis have been methionine homozygotes at codon 129 in the prion protein gene.

Statistical analysis on this finding of 3 positive specimens gives the following estimations of numbers who may be incubating vCJD:

237 infections per million population (95% confidence interval (CI): 49-692 per million)

Assuming that this estimate relates to those aged 10-30 years[3], 3,808 individuals (CI 785-11 128) aged 10-30 years may be incubating vCJD in the UK.

These estimations are higher than predictions from modelling of the clinical data (upper 95% confidence interval of 540 future cases).[21] It is not known whether those incubating vCJD will eventually develop clinical disease. However, estimates of numbers possibly incubating are important with respect to any potential for secondary transmission (e.g. by blood donation, surgical instruments) while individuals are in the incubation phase. It should be noted that plasma-derived medicinal products have not been manufactured from donations collected in the UK since 1998.

A larger study of an archive of tonsil tissue from 63,007 people of all ages removed during routine tonsillectomies has been published.[22] 2,753 samples were from the 1961- 1985 birth cohort in which most cases of vCJD have arisen and 19,808 were from the 1986-1995 birth cohort that may also have been orally exposed to bovine spongiform encephalopathy. None of the samples were unequivocally reactive to two enzyme immunoassays and none of the initial reactives were positive for PrP^{TSE} by immunohistochemistry or immunoblotting. The estimated 95% confidence interval for the prevalence of PrP^{TSE} in the 1961-1995 birth cohort was 0-113 per million and in the 1961-1985 birth cohort 0-289 per million. These estimates are lower than the previous study of appendix tissue, but are still consistent with this study. Archiving of tonsil tissues continues and further studies are planned.

3. Human tissue distribution of infectivity/abnormal prion protein.

Tissue distribution has been investigated by detection of the abnormal prion protein PrP^{TSE} or by infectivity assays. Detection of PrP^{TSE} in tissues has often been associated with infectivity, however it should be noted that, in some circumstances, infectivity can be present without detection of PrP^{TSE} or PrP^{TSE} be present in absence of infectivity.[23] This may be related to limitations of assay methods for PrP^{TSE}, however, in some cases the reason for this finding is not known. It is thus recommended that

[3] The reason the age range of 10-30 years is specified is because 83% of the samples were from individuals in this age range.

any study on tissue or fluid distribution of the abnormal prion protein be confirmed with an infectivity assay.

A wider distribution and higher level of PrP^{TSE} in human peripheral tissues, including the lymphoreticular system, has been found in vCJD compared with sporadic CJD.[24;25,26] Limited data from infectivity assays of vCJD tissues are consistent with the PrP^{TSE} findings.[27] In clinical vCJD cases high titres of infectivity are found in the brain and spinal cord and lower levels in spleen and tonsil[27]. While PrP^{TSE} and infectivity are occasionally found in the spleen of sporadic CJD, the levels of PrP^{TSE} are lower than in vCJD.[8i] It is also suspected that lymphoid tissue involvement in sCJD is associated with a relatively long duration of clinical illness whereas it occurs preclinically in vCJD. PrP^{TSE} accumulations have been observed in muscles of some patients with both sporadic and variant CJD.[28]

It is likely that the distribution of PrP^{TSE} and infectivity in iCJD is more similar to sCJD than vCJD.[29] Data are lacking for gCJD.

4. Infectivity in blood and transmissibility via blood

4.1. Animal blood

Low levels of infectivity have been found in the blood of rodents experimentally infected with animal and human TSE agents.[30,31,32,33] Experiments indicate that approximately half the infectivity is in the cellular components, mainly the buffy coat, and the remainder in the plasma. Experimental studies indicate that the vCJD agent behaves in a similar way (qualitatively and quantitatively) to a genetic TSE agent[4] when adapted to RIII/Fa/Dk mice.[33] Infectivity has also been detected in buffy coat of a prosimian microcebe experimentally infected with a macaque-adapted BSE strain.[34]

The infectivity in rodent blood was transmitted by intravenous inoculation, but 5-7 fold less efficiently than by the intracerebral route.[31] In one study with mouse-adapted vCJD agent, the intravenous and intracerebral routes were found to be equally efficient for the buffy coat fraction but not for the plasma fraction.[33] However, studies in primates show that survival times were similar after intravenous or intracerebral inoculation of infected brain material.[35,36] Unpublished studies presented at scientific meetings[37,38] indicate that blood of primates experimentally infected with human TSE agent is infectious from about half way through the incubation period.

Furthermore, information from intra-species transfusion experiments indicates that experimental BSE in orally infected sheep or natural scrapie infection in sheep can be transmitted to sheep by blood transfusion.[39,40] Transmission efficiency was high for both BSE and natural scrapie, and the majority of transmissions resulted from blood collected more than half way through the incubation period[41]. The level of infectivity in sheep blood cannot be established from these experiments.

The European Union has provided funding for animal transmission projects.

4.2. Human blood

The tracing of recipients of blood transfusion from UK donors who have subsequently developed vCJD (the TMER study) has revealed four instances of secondary transmission.[42] These individuals had received transfusion of non-leucodepleted red cells from donors who were clinically healthy at the time of donation but subsequently (17–40 months later) developed variant CJD. Three of the four patients developed disease after incubation periods ranging from 6.5 to 8.5 years; the fourth died 5 years after

[4] Mouse-adapted GSS strain of human TSE (brain tissue obtained from a case of Gerstmann-Sträussler-Scheinker syndrome).

transfusion of an illness unrelated to prion disease but tested positive for PrP^{TSE} in the spleen and lymph nodes. This asymptomatic prion-infected patient was heterozygous (methionine/valine) at codon 129 of the *PRNP* gene. Taken together, these instances are strong evidence that vCJD is transmissible through blood transfusion.

Recently, another presumed case of prion infection was identified in an elderly haemophilic patient who was heterozygous at codon 129 in the prion protein gene.[43] The patient, who died of unrelated pathology, had received large quantities of UK-sourced fractionated plasma products, including some units derived from plasma pools which contained plasma from a donor who later developed variant CJD. This patient was identified through an intensive search for PrP^{TSE} positivity in all post-mortem tissues, although only 1 of 24 samples taken from the spleen tested positive. Whether someone with this limited distribution of PrP^{TSE} would be infectious is unknown, but from a public health perspective, this patient represents a warning that some plasma-derived products might contain residual prion infectivity.

The surveillance described above emphasises the importance of the TMER study for identifying the risk of blood transfusion in transmitting vCJD. Moreover, national databases of blood donors and the maintenance of traceability from donor to recipient and vice versa are essential to establish whether a vCJD case has been a blood donor (UK experience has shown that questioning of family members is unreliable for establishing whether a patient has been a blood donor). Traceability is a specific requirement in Article 14 of Directive 2002/98/EC.[7a]

Infectivity or PrP^{TSE} were not detected in blood of vCJD cases using methods capable of detecting infectivity/PrP^{TSE} in peripheral tissues such as tonsil or spleen, indicating that if infectivity is present it is at levels below the sensitivity of these methods. [27,24]

There is no epidemiological evidence that blood of sporadic CJD may transmit disease.[44,45] Prospective studies, similar to the TMER study, are in progress in the UK and USA and have not yet revealed any possible case of sporadic CJD linked to blood transfusion. However, current data are scanty to unequivocally exclude the possibility that such an event could occur in a small number of cases with a long (10 or more years) incubation period.[46]

A review of transmission studies to detect infectivity in the blood of humans with CJD (sporadic, iatrogenic and variant) shows that although experimental transmissions to animal models have occasionally been reported[47-50], other studies failed to detect infectivity.[51,27] It remains possible that PrP^{TSE} is present at low levels in the blood of clinically affected cases of sCJD. Data are lacking for gCJD but the assumption is that the tissue distribution of infectivity will be more similar to sCJD than vCJD.

For the purpose of risk assessments, it is recommended that, as a worst case assumption, a relative efficiency of the intravenous and intracerebral routes of 1:1 should be used.[52] This is because the accumulated information now available from animal studies indicates that the intravenous route can be an efficient route of transmission and in certain cases can give a transmission rate and/or an incubation period similar to the intracerebral route (see also 4.1).

5. Detection techniques

Several techniques are under development for the detection of PrP^{TSE} in blood including methods based on epitope protection[53] and PrP^{TSE} specific antibodies[54]. Approaches based on surrogate markers are also under investigation. Development and validation of all methods is on-going but there is no screening test yet. Confirmatory tests that have been proposed include Protein Mis-folding Cyclic Amplification (PMCA) [55] which is extremely sensitive, but has not yet been validated.

Several WHO reference preparations are available and further materials are under development[9b]. These reference preparations will allow calibration of assays versus infectivity bioassays, and can be used for collaborative studies to compare the performance of different assays to see whether they are sufficiently sensitive and specific to justify further evaluation for screening blood.

PrP^{TSE} detection methods for screening human blood for evidence of infection are being considered for inclusion as Annex II List A devices under the IVD Directive. There are very few samples of blood or plasma from clinically affected patients or from individuals known to have been infected at a particular time. This contrasts with other blood borne agents such as viruses. Alternative development and evaluation strategies have been proposed to assess whether a candidate assay is sufficiently promising to be given access to the available samples.[56]

6. Leucoreduction and specific prion affinity filters

Leucoreduction is used in transfusion medicine to reduce the level of white blood cells in blood and blood components. It was implemented in the UK in 1999.

The rationale for considering leucoreduction as a precautionary measure is:

- The lymphoreticular involvement in vCJD
- The detection of low levels of infectivity, in studies with rodents, in the buffy coat (associated with white blood cells).

The SCMPMD opinion on leucoreduction [8a, 8b] for blood and blood components for transfusion states that it might be a precautionary step to remove white cells as completely as possible. For plasma for fractionation the opinion states the following:

'Taken together, there is no compelling scientific evidence to date for the introduction of leucoreduction of plasma for fractionation, or other methods aiming at removal of cells and debris, as a precaution against vCJD transmission. The question should be further explored by suitable experiments.'

Results reported at the 2002 EMEA Workshop, suggested that leucoreduction does not provoke fragmentation of cells and lysis. Results of a comprehensive study involving a number of different filters and procedures indicate that leucodepletion is not detrimental in terms of the generation of microvesicles or the release of prion proteins[57].

Infectivity data from hamster studies indicate that leucoreduction alone is not totally protective against prion transmission, with between 42 to 72 percent reduction in infectivity of whole blood[58,59].

Specific affinity ligands that bind prion proteins are being evaluated for their ability to reduce TSE infectivity present in blood and plasma.

A study in hamsters showed that a leucocyte-reduction filter based on modified polyester fibres exhibited a prion clearance capability between 99.0 to 99.9 percent on the endogenous and exogenous infectivity of red cell concentrates[60].

Initial studies using leucoreduced human red blood cell concentrates spiked with hamster brain-derived scrapie infectivity indicate that some ligands immobilised on a chromatographic resin matrix are capable to removing 3 to 4 log ID_{50} per ml[59]. A further study using scrapie-infected hamster whole blood demonstrated an overall reduction of infectivity of more than 1.22 log ID[61].

The prion binding capacity of an affinity ligand chromatography step has been investigated in the processing of a plasma medicinal product using hamster brain derived spiking material[62]. This preliminary data requires further evaluation before conclusions can be drawn on possible efficacy.

7. Manufacturing processes for plasma-derived medicinal products

Taking account of the available data concerning blood infectivity, it is of utmost importance to investigate the capacities of the manufacturing process (fractionation) to eliminate/inactivate the infectious material potentially present in the plasma pool used as the starting material for preparation of plasma-derived products. Initial results from animal studies, using blood from rodents infected by intracerebral inoculation, indicated that the fractionation process contributes to the removal of endogenous plasma infectivity.[30,31] Information reported at the EMEA Workshops in 2002 and 2004 suggested that endogenous infectivity might persist through the fractionation process to a greater extent than would be expected from spiking studies,

Many investigational studies have now been carried out with different strains of agent and spiking materials of different nature and purity, and using different assays to follow the partition of PrP^{TSE} and/or infectivity. In most cases, the correlation between the capacity to partition PrP^{TSE} and infectivity has been demonstrated for the spiking preparations used until now (mainly brain homogenates of various strains). It is now confirmed that biochemical assays can be useful for spiking experiments to investigate manufacturing processes in a reasonable timeframe and less costly protocols than the *in vivo* bioassay. However it is still necessary to correlate such results with those from infectivity assays in animals. Cell-based assays may also be useful if properly validated for this purpose.

Studies aimed at investigating the contribution of the various manufacturing steps to reduction of infectivity (including precipitation followed by centrifugation or depth filtration, chromatography and nanofiltration) have accumulated convergent data supporting the removal of infectivity by steps that are commonly used in the manufacture of plasma-derived medicinal products.[62-68] For coagulation factors derived from cryoprecipitate, downstream fractionation using various precipitating agents or conditions allow to discard PrP^{TSE} in the precipitates. Reduction level achieved may vary according to the specific manufacturing process and probably depends on the concentration of the precipitating agent and salts, and the pH. Chromatographic steps, classically used in the separation of coagulation factors but also in the purification of other plasma derivatives have been described to remove TSE infectivity or PrP^{TSE}. Again, the reduction factors may be variable according to the fraction eluted. However, caution is still needed in the interpretation of those data since the effectiveness of a given step is dependent on a number of variables including the process conditions and the state/nature of the agent in the spiking preparation sample and in the spiked product intermediate. Consequently, effectiveness of removal may vary from one manufacturer to another. In addition, recent studies have highlighted the fact that removal capacity may be variable according to the state of dispersion of the agent in the spiking preparation particularly for steps based on retention mechanisms.

Overall, there is a need i) to investigate the partitioning or removal capacities of the various fractionation steps used in the preparation of the plasma-derived medicinal products, ii) to investigate the partition and removal of endogenous infectivity and the extent to which this is comparable with data from spiking studies, iii) to gain better knowledge of the form of infectivity present in blood in order to confirm the relevance of the spiking material used in the validation studies.

8. Infectivity in urine

Low levels of infectivity have been detected in urine of scrapie-infected rodents by several research groups and in the urine of deer with Chronic Wasting Disease.[5g, 9c]

Gregory *et al.*[69] demonstrated that the disease could be transmitted by intracerebral inoculation of pooled urine from scrapie-sick hamsters. The infectivity titre of the urine was calculated to be around 3.8 infectious doses/ml. Titration of kidney and urinary bladders from the same animals gave 20,000-fold greater concentrations. Histologic and immunhistochemical examination of these tissues showed no indication of inflammation or other pathologic changes, except for occasional deposits of disease-associated prion protein in kidneys.

Kariv-Inbal *et al.*[70] have observed transmission of the disease after intraperitoneal (i.p.) administration of enriched urine fractions from scrapie sick hamsters. Transmission via the oral route was also investigated. The recipient hamsters remained without symptoms but secondary transmission was observed after inoculation of brain extract from an asymptomatic hamster.

Seeger *et al.*[71] have studied transmission via urine using mouse models of chronic inflammation. They have detected prionuria in scrapie infected mice with coincident chronic lymphocytic nephritis. Transmission has been shown upon intracerebral inoculation of purified proteins from pooled urine collected from scrapie sick or presymptomatic mice. In contrast, prionuria was not observed in scrapie infected mice displaying isolated glomerulonephritis without interstitial lymphofollicular foci or in scrapie infected wild type mice lacking inflammatory conditions.

Prionuria was also detected in chronic wasting disease (CWD) of deer. Experiments by Haley *et al.*[72] provided evidence that concentrated urine from deer at the terminal stage of the disease, that also showed mild to moderate nephritis histopathologically, was infectious when inoculated into transgenic mice expressing the cervid PrP gene. In addition, the urine collected from the CWD sick deer that was used for mouse inoculation, showed positive results when assayed for PrP^{TSE} by serial rounds of protein misfolding cyclic amplification (PMCA) assay. The concentration of abnormal prion protein was very low as indicated by undetectable PrP^{TSE} by traditional assays and prolonged incubation periods and incomplete TSE attack rates in the transgenic mice.

Using the highly sensitive PMCA technology Gonzalez-Romero *et al.*[73] and Murayama *et al.*[74] have detected PrP^{TSE} in urine of scrapie sick hamsters. The results by Gonzalez-Romero *et al.* suggest that the concentration of PrP^{TSE} in urine is in average 10-fold lower than in blood. Animal experiments have demonstrated that *in vitro* generated PrP^{TSE} by PMCA starting from urine produced a disease indistinguishable from the one induced by infected brain material.[73]

Epidemiological evidence in the last 25 years, during which urinary-derived medicinal products and particularly gonadotrophins have been widely used, does not suggest a risk from sporadic CJD. Since epidemiological evidence has identified the few cases of iatrogenic transmission of CJD through the use of pituitary-derived gonadotrophins, it is possible that transmission from urinary-derived gonadotrophins would have been detected if it had occurred.

9. Recommendations and proposals

9.1. Sporadic, genetic and iatrogenic CJD and plasma-derived medicinal products

Cumulative epidemiological evidence does not support transmission of sporadic, genetic and iatrogenic CJD by blood, blood components or plasma-derived medicinal products.[75, 76, 12] Nevertheless, rigorous epidemiological studies for tracing blood-related sCJD cases have not yet reached sufficient statistical power to formally exclude the possibility of blood transmission in a small number of cases. Moreover, the experimental evidence of peripheral tissue infectivity in various subtypes of sCJD is very limited but available data show presence of infectivity in spleen and lymph nodes in human TSEs other than vCJD.

The implementation of appropriate actions in relation to CJD depends on accurate diagnosis in suspected cases. There is a potential for diagnostic confusion between sporadic and variant CJD, particularly in younger age groups.

Donor selection criteria include criteria to exclude donors who might be at higher risk of developing CJD. The following permanent deferral criteria are specified in Commission Directive 2004/33/EC: Persons who have a family history which places them at risk of developing a TSE, or persons who have received a corneal or dura mater graft, or who have been treated in the past with medicines made from human pituitary glands.[7b] Precautionary recalls of batches of plasma-derived medicinal products after post-donation reports of CJD or CJD risk factors in a donor contributed to severe shortages of certain products.[9a]

On the basis of the current epidemiological evidence, the CHMP recommendation that recall of plasma-derived medicinal products is not justified where a donor is later confirmed as having sporadic, genetic or iatrogenic CJD or CJD risk factors is maintained.

9.2. Variant CJD and plasma-derived medicinal products

Uncertainties still exist concerning the number of cases of vCJD that will occur although the number of cases is in decline in the UK and France. Variant CJD has a different distribution of infectivity in tissue outside the central nervous system to sporadic CJD.

There is now strong epidemiological evidence of human to human transmission of vCJD by blood transfusion (see Section 4.2). In addition, one vCJD infection was detected in a patient with haemophilia treated with high doses of intermediate purity factor VIII. Estimates of the relative risks of exposure through diet, surgery, endoscopy, blood transfusion and receipt of UK-sourced plasma products suggest that the most likely route of infection in the patient with haemophilia was receipt of UK plasma products. At least one batch came from a pool containing a donation from a donor who later developed vCJD.[43,77,]

The following measures are aimed at minimising the risk of transmission of the agent by plasma-derived medicinal products.

9.2.1. Exclusion Criteria

a) Consideration of Country-based exclusions

There is currently no screening test to detect donors who may be incubating the disease or in the early clinical stages. Therefore, other approaches are considered in order to try and identify donors who may present a higher risk.

UK plasma

Residence in the UK is a recognised risk factor for vCJD and has led to the UK deciding no longer to fractionate from UK plasma.

Exclusion of donors based on cumulative period of time spent in the UK

Since UK donors are excluded from donating plasma for the manufacture of plasma-derived medicinal products in the UK, it is consistent to exclude donors who have spent long periods in the UK. This is supported by the finding of vCJD cases, which have a risk factor of long periods spent in the UK, in other countries[5].

It is, therefore, recommended that donors who have spent a cumulative period of 1 year or more in the UK between the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma for fractionation. Countries are highly encouraged to choose their national cumulative period limit for plasma-derived medicinal products according to a nationally calculated benefit/risk balance, which will take into account the endogenous risk of BSE exposure (and introduction in the food chain) and the risk of shortages of blood and plasma for the manufacture of medicinal products. The national limit is recommended to be of cumulative periods in the UK below or equal to 1 year.

Countries may still apply a stricter limit than 1 year for exclusion of donors for blood/plasma collected for fractionation within the country (e.g. 6 months) but will accept plasma-derived medicinal products from other countries provided that at least the one-year time limit is applied.

The rationale for this recommendation is to exclude donors who have the highest individual risk from stays in the UK and to be consistent with the UK decision to no longer fractionate from UK plasma. This is further explained in the first version of this Position Statement published in February 2003.[5b]

French plasma and plasma from other BSE-exposed European countries

France published an analysis of the risk of transmission of vCJD by blood and its derivatives sourced from French plasma in December 2000.[78g] This concluded that plasma collected in France could continue to be used for fractionation. The safety margin for plasma-derived medicinal products was considered to be sufficient. However, introduction of additional steps to further increase the safety margin of some products was recommended (e.g. nanofiltration of Factor VIII introduced in January 2001). Leucodepletion for plasma for fractionation, as for plasma for transfusion products, was also recommended in 2001 as a precautionary measure. The subsequent risk-analyses published in 2002, 2003, 2004, 2005, 2007 and 2009 re-confirmed these conclusions and acknowledged that the size of epidemic was revised to a lower estimate by more recent modeling, and the risk to collect blood from vCJD-incubating donors lower than previously estimated. [78]

Based on the limited data on human exposure to BSE-risk materials in other European countries it is still difficult to estimate the epidemiological risk in those countries which have small number of vCJD cases or have not yet reported any vCJD cases.

Donors who have spent a cumulative period of time in France and other BSE-exposed countries

Exclusion of donors who have spent a cumulative period of time in France is not recommended because of the lower risk associated with time spent in France compared with time spent in the UK (the risk in France is estimated to be 1/10 of that in UK). Since the previous version of the Position Statement, endogenous vCJD cases occurred in some other countries (see Section 2. Human TSEs current status) placing them close to or lower than France in terms of incidence and ratio of risk in

[5] Two cases in Ireland, two cases in US, one case in France and the Canadian case associated with long periods spent in the UK.

comparison to UK. Exclusion of donors who have spent time in other European countries having a risk ratio in the same order of magnitude as France is not recommended.

Concluding remarks

Country-based exclusions may appear unjustified in the sense that the vast majority of donors who will be excluded will not develop the disease. There is a lack of spare plasma capacity to make up for shortfalls if countries that are major producers of plasma-derived medicinal products discontinue the use of nationally collected plasma for fractionation.

b) Other possible exclusion criteria

Commission Directive 2004/33/EC indicates that further deferral criteria for vCJD may be recommended as a precautionary measure.[7b]

Other possible exclusion criteria that could be considered include permanent exclusion of recipients of blood transfusion (general exclusion or exclusion of recipients of transfusion in UK[6]), transplant recipients, and donors who have undergone neurosurgery.

Caution is needed because of the risk of loss of donors and consequent supply problems. Since such criteria could apply to both blood and blood components, and plasma-derived medicinal products, it was appropriate to consider this further within the scope of Directive 2002/98/EC.[7a] The technical meeting of blood experts, convened by the European Commission in January 2004, considered exclusion criteria, as well as blood component preparation and processing, recipient tracing and surveillance, and optimal use of blood.[7e]

9.2.2. Leucoreduction and specific prion affinity filters

The benefit of inclusion of leucoreduction to improve the safety of plasma has not been demonstrated.

At present it is not appropriate to recommend the introduction of leucoreduction for the safety of plasma-derived products.

Efficacy of introducing recently developed affinity media / filters is still under investigation.

9.2.3. Manufacturing processes for plasma-derived medicinal products

The available data support the reduction of infectivity by steps in the manufacturing process. Manufacturers are required to estimate the potential of their specific manufacturing processes to reduce infectivity. This should follow a step-wise approach as described below and illustrated in the accompanying flow diagram. It is recommended that manufacturers consult the relevant competent authorities at each of the milestones in this estimation. A decision to undertake an infectivity assay and/or to add a further manufacturing step(s) to increase reduction capacity should only be made after a careful consideration of all benefit-risk factors for a certain product.

Firstly, manufacturers should compare their own processes to those with published data on reduction of infectivity in order to estimate the theoretical potential of their specific manufacturing processes to reduce infectivity. *(Flow diagram, step 1)*

Whereas the general information available on manufacturing processes provides useful background information, the actual effectiveness of a manufacturing process might be dependent on the specific

[6] In April 2004, the UK implemented exclusion of persons who have previously received transfusions of whole blood components since January 1980, as a precautionary approach.

process conditions. Manufacturers should consider the relevance of the published data to their specific manufacturing processes and whether the removal capacity can be expected to be comparable.

If it cannot be concluded that the removal capacity would be expected to be comparable, it is recommended that manufacturers undertake product-specific investigational studies on key steps in their manufacturing processes using biochemical assays. Priority should be given to studies on products with the lowest potential removal capacity. *(Flow diagram, step 2)*

Investigations using biochemical assays may be sufficient if a clear correlation with infectivity data has already been established for similar processes (e.g. ethanol fractionation). If such a correlation is not established (e.g. a novel step) and the step is considered critical for removal of infectivity for the specific product (e.g. it is the only step for removal), the investigations should be confirmed using an infectivity assay for the critical step(s). *(Flow diagram, step 3)*

The above steps will allow manufacturers to estimate the reduction capacity of their manufacturing processes. *(Flow diagram, step 4)*

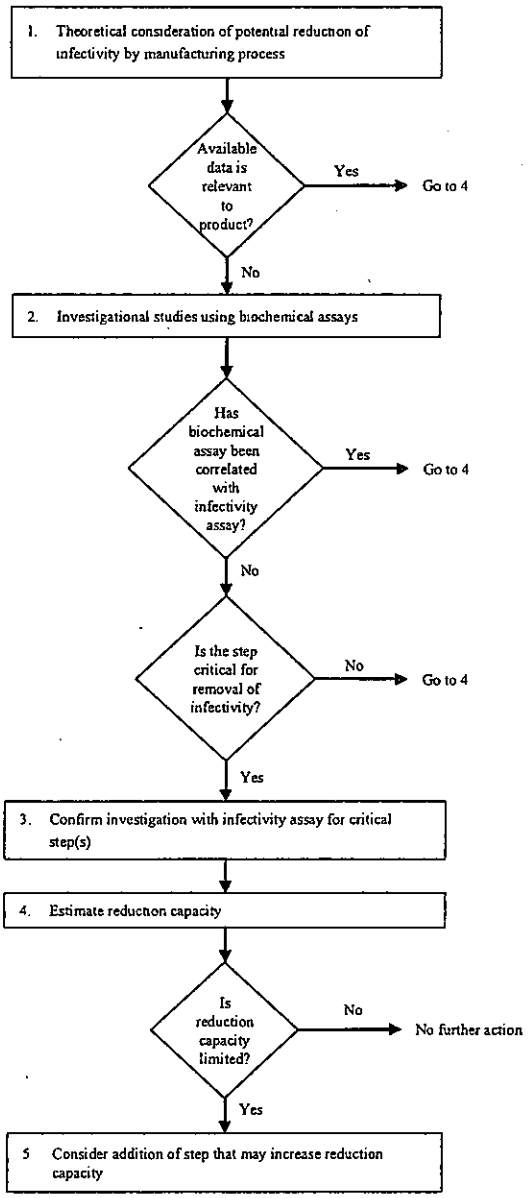
In cases where the overall reduction capacity is limited, manufacturers should consider the addition of steps that may increase the removal capacity where this is feasible without compromising the safety, quality and availability of the existing products. Discussion with the relevant competent authorities is recommended. *(Flow diagram, step 5)*

The outcome of the estimates of the theoretical potential of manufacturing processes to reduce infectivity and the results of product-specific investigational studies should be reported to the relevant competent authorities for the medicinal products concerned, as information becomes available. Applicants submitting new marketing authorisation applications for plasma-derived medicinal products will be expected to include such information in the application dossier. The outcome of the estimation of the theoretical potential to reduce infectivity should always be included in the application.

In support of these recommendations, CHMP's Biotechnology Working Party, with the involvement of external experts, has developed guidance on how to investigate manufacturing processes with regard to vCJD risk.[5a]

Figure 1: Plasma-Derived Medicinal Products: estimation of potential reduction capacity of specific manufacturing processes

Important Note: this flow diagram should be read in conjunction with the preceding text in 9.2.3. It is recommended to consult the relevant competent authorities at the milestones in this estimation. Give priority to studies on products with the lowest potential removal capacity.



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569 **9.2.4. Recall of batches where information becomes available post-**
570 **donation**

571 In view of the lack of adequate information on vCJD, it is prudent to recall batches of plasma-derived
572 medicinal products where a donor to a plasma pool subsequently develops vCJD. Recall should also
573 include medicinal products containing plasma-derived products as excipients. However, in both cases,
574 consequences for essential medicinal products where alternatives are not available will need careful
575 consideration by the competent authorities.

A case-by-case consideration would be appropriate where plasma-derived products have been used in the manufacture of other medicinal products. This consideration would include the nature of the product, the amount used, where it is used in the manufacturing process and the downstream processing.

Look-back to identify the fate of donations should be taken as far as possible. Regulatory authorities, Official Medicines Control Laboratories, surveillance centres and the supply chain should be informed of all batches of product and intermediate implicated whether or not supplies of the batch are exhausted.

There is no recommendation to recall batches if information becomes available post-donation, which would have excluded a donor based on his/her stay in the UK since this donation exclusion criteria is a very conservative precautionary measure (see 9.2.1).

9.2.5. Albumin used as an excipient or in manufacturing processes

The available data on the removal of infectivity during the fractionation process used in the manufacture of albumin indicates that the risk of transmission of infectivity by albumin would be particularly low. Nevertheless, in the case of albumin used as an excipient, recall is still recommended as a precautionary measure where a donor to a plasma pool subsequently develops vCJD. A single batch of albumin may be used to produce a number of batches of a medicinal product because of the small amounts that are typically used as an excipient. As a consequence, a recall could affect complete stocks of a product and create severe shortages. Therefore, to avoid a negative impact on supply, companies should consider the origin of plasma and select countries where the probability of having to recall batches is as limited as possible.

Development of substitutes for plasma-derived albumin used as an excipient or in manufacturing processes is encouraged although it is recognised that this can be difficult (requiring development and validation and usually non-clinical and clinical investigations) and should thus be considered as a long-term approach.

9.2.6. Substitution with alternative products

Use of alternative products to plasma-derived medicinal products could be considered, where these are available. It is felt that this choice should remain with users, taking into account the needs of the individual patient. It should be noted that plasma-derived products such as albumin may be used in the manufacture of recombinant products.

9.2.7. Optimal Use

Optimal use of plasma-derived medicinal products is encouraged, as this will maximise the benefits of the products compared with any potential risk.

9.3. Urine-derived medicinal products

The recommendations for urine-derived medicinal products are based on the following considerations:

There is no epidemiological evidence of CJD and vCJD transmission by urine-derived medicinal products.

TSE infectivity in urine has been reported in some animal models.

The review of manufacturing processes described below.

Investigational studies of infectivity reduction by the manufacturing processes should be done following the same general, stepwise approach as recommended for plasma derived medicinal products (see Section 9.2.3).[5a]

Results from different assay systems are not necessarily directly comparable (Western blot, cell based assays, bioassay). The approach recommended for plasma-derived medicinal products would be applicable (i.e. confirm reduction capacity using infectivity assays for steps critical for reduction of infectivity if a clear correlation between data from biochemical assays and infectivity assays has not been established for similar process steps). For inactivation studies, investigation of different TSE strains should be considered as they may vary in resistance.

Potential accumulation of prions on chromatographic columns or a potential batch to batch contamination due to carry-over of prions should be addressed in the studies.

Bibliographic data could be acceptable as additional supportive data to the investigational studies provided. Similarity of the compared process and materials should be established. Extrapolation of results for plasma-derived medicinal products is not justified particularly for chromatographic steps at the beginning of the manufacturing process because of the high protein content in plasma.

General review of the manufacturing processes indicates that, in each manufacturing process, there is at least one step that might be theoretically capable of reducing infectivity if it were present in the starting material. In cases where the reduction capacity is limited, manufacturers should consider the addition of steps that may increase the overall removal capacity.

For particular products, such as hormones from a relatively small well-defined donor population, some manufacturers have put in place limited exclusion criteria for the selection of a donor for inclusion in a donor panel. For other products manufactured from very large donor pools (e.g. urokinase), such measures are more difficult to apply.

Urine should be collected from countries where there is a surveillance system for both human and animal TSEs. It is noted that urine-derived medicinal products are not sourced from urine collected in the UK.

On the basis of these considerations, the use of exclusion criteria for selection for a donor panel are encouraged, as a precautionary measure, where feasible. The same exclusion criteria should be applied with respect to CJD and vCJD as used for blood/plasma donors providing starting material for the manufacture of plasma-derived medicinal products. Although these criteria would not be checked at each donation unlike blood/plasma donors, manufacturers should follow up the donor criteria at defined intervals. The exclusion of donors with known inflammation of kidney and/or chronic renal inflammatory diseases is encouraged.

Record keeping for traceability is recommended for products where it is possible to trace back to donor level.

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医薬品　研究報告 調査報告書

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研究報告の概要

HIV や C 型肝炎をはじめとする血漿製剤によるウイルス感染のリスクは、供血者の選別および検査の導入、ならびに 1986 年の有効なウイルス不活化工程の採用以降、実質的に排除された。
しかし、vCJD の発生後、英国製血液製剤・血漿製剤の安全性に関する新たな懸念が持ち上がり、感染および二次感染拡大のリスクを最小限に抑えるため、2004 年に、後に vCJD を発症したドナーから採取された血漿を含んでいるかどうかにかかわらず、1980 年から 2001 年までの間に英国でプールされた血液凝固因子製剤を投与された患者全員にそのことが通知された。
通知以降、英国における vCJD の新規臨床症例は減少し、過去に関係する血液または血液製剤の投与を受けたことが確認されている vCJD 患者は見つかっていない。
しかし、一般母集団における無症候性 vCJD 感染の有病率は不明であり、適切で有効な vCJD のスクリーニング試験がいつ頃利用可能になるかは不明である。
血友病患者において最近確認された 1 例目の無症候性の vCJD 感染症例ならびにメチオニン／バリン異型接合患者における vCJD 報告は、遺伝性出血性疾患患者をはじめとする「リスクのある」母集団における継続調査が必要であることを示している。
供血者における vCJD に関連する異常プリオンタンパク質の保有率が不明であること、有効な試験法がないことを考え合わせると、現在実施されている対策を続けることが、出血性疾患患者を含む患者における vCJD 二次感染の拡大を減らす最善の手段であると思われる。

使用上の注意記載状況・その他参考事項等

重要な基本的注意
現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
英国における vCJD 対策に関する報告である。 現時点まで血友病以外で血漿分画製剤から vCJD 伝播が疑われた報告はなく、血漿分画製剤の製造工程でプリオンが除去できるとの情報もある。 なお、当社血漿分画製剤の原料血漿は現在まで英国の血漿を使用していない。	今後とも vCJD に関する安全性情報等に留意していく。

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ORIGINAL ARTICLE *Transfusion transmitted disease*

Risk reduction strategies for variant Creutzfeldt–Jakob disease transmission by UK plasma products and their impact on patients with inherited bleeding disorders

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Summary. The appearance and rapid evolution of BSE in UK cattle in the mid 1980s, with compelling data supporting variant Creutzfeldt–Jakob disease (vCJD) as its human manifestation, pose a potentially severe threat to public health. Three clinical cases and one asymptomatic case of vCJD infection have been reported in UK recipients of non-leucodepleted red cell transfusions from donors subsequently diagnosed with vCJD. Plasma from both these and other donors who later developed vCJD has contributed towards plasma pools used to manufacture clotting factor concentrate. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Surveillance Study has detected asymptomatic vCJD postmortem in a haemophilic patient treated with UK plasma products including two batches of clotting factor linked to a donor who subsequently developed vCJD. Over 4000 bleeding disorder patients treated with UK plasma products are recorded on the UKHCDO National Haemophilia Database. The risk of vCJD transmission by plasma products is not known. However, public health precautions have been implemented since 2004 in all UK inherited bleeding disorder patients who received UK-sourced plasma products between 1980 and 2001 to minimize the possible risk of onward vCJD transmission. We evaluate vCJD surveillance and risk management measures taken for UK inherited bleeding disorder patients, report current data and discuss resultant challenges and future directions.

Keywords: haemophilia, inherited bleeding disorders, UK plasma products, variant Creutzfeldt–Jakob disease

Introduction

The first reports of a prion disease in humans, Creutzfeldt–Jakob disease (CJD), appeared in the 1920s [1,2] with a distinct clinico-pathological variant being described in 1996, variant Creutzfeldt–Jakob disease (vCJD) [3] in which significant involvement of lymphoreticular tissues was demonstrated [4,5]. Compelling epidemiological, clinical, neuropathological and experimental data support vCJD as the human manifestation of bovine spongiform encephalopathy (BSE) [4,6,7], an epidemic of which occurred in UK cattle in the 1980s and early 1990s. The incidence of BSE peaked in 1993, and while the precise origin of the BSE epidemic remains unclear, there is little doubt that the rendering practices employed at that time significantly contributed to its rapid spread throughout the UK. Feeding cattle and sheep ruminant-derived protein was

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banned in 1988 [8], with an ensuing fall in the number of BSE cases. However, such measures were not taken in time to prevent the introduction of BSE-infected cattle carcasses into the human food chain. By January 2010, 167 clinical cases of vCJD attributable to dietary exposure had been reported in the UK by the National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU), a majority of which have been confirmed by neuropathological examination [9]. Much lower but increasing numbers of cases have been reported worldwide, the majority of which are believed to have contracted vCJD in their country of origin [10], probably as a result of the export of UK animals and/or ruminant feed. Although the annual incidence of clinical vCJD in the UK has been steadily declining since 2000 and the extent of the primary vCJD outbreak has been several magnitudes less than previously predicted [11,12], limited information is available to provide accurate estimation of the number of future clinical cases. Where genetic information is available, all confirmed clinical cases of vCJD have thus far been shown to be homozygous for the methionine residue at codon 129 of the prion protein gene (*PRNP*). However, a suspected clinical case of vCJD in an individual heterozygous for methionine/valine has recently been reported [13].

Transfusion transmission of vCJD: early perception of risk, risk reduction measures and plasma product recalls

Distinct from the number of new clinical cases is the unknown prevalence in the UK of presymptomatic, or subclinical, vCJD infection, i.e. where asymptomatic individuals harbour vCJD infection as discussed elsewhere [10,14]. It is from this group of individuals that the risk of secondary vCJD transmission arises, with the characteristic prominent lymphoreticular phase giving rise to the possibility of transmission via surgical instruments, blood and blood products and organ (including bone marrow) transplantation. This differs from classical sporadic CJD, which has been shown to be transmissible by neurosurgical instruments, pituitary derived hormones and corneal transplants but in which transmission by blood or blood products has not been demonstrated [15–21]. The widespread transmission of hepatitis C and human immunodeficiency virus (HIV) infections by plasma products prior to 1986 raised ongoing concerns about the possible emergence of new blood-borne pathogens. These led to the publication of therapeutic guidelines by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) recommending, where possible, that plasma-derived factor VIII (FVIII) and factor IX (FIX) concentrates be replaced with recombinant products in the treatment of patients with haemophilia A and B [22]. The first report of clinical vCJD cases in 1996 [3] raised concerns amongst UK haemophilia clinicians that the infective agent may be transmissible by blood products [23]. Around the same time, a collaborative study, the Transfusion Medicine Epidemiology Review (TMER), was established between the NCJDSU and the four UK blood services (UKBS) with the aim of identifying any association between CJD (including variant) and blood transfusion [24]. At that time, 17 patients were recorded as having donated blood prior to being diagnosed with vCJD and there was concern that there may be many more infected, yet asymptomatic individuals amongst the donor population. It was estimated that even a modest prevalence of vCJD in the general population could result in an infected donation entering the plasma pools from which clotting factor concentrates were prepared. Together with the almost exclusive restriction of vCJD to the UK at that time, these concerns greatly influenced the UKHCDO's decision in 1997 to recommend the use of bovine material-free recombinant products, as well as fractionated products from non-UK plasma donations [23]. Treatment with recombinant factor concentrates was funded in 1998 for haemophilic patients aged <16 years and was extended to include all adult patients by ascending age from 2003/2004 and completed in 2005/2006.

In the absence of a test to detect preclinical vCJD infection, a number of precautionary donor selection and component processing measures have been introduced since 1998 to minimize the possible risk of secondary vCJD transmission by blood and its components (Table 1) [25–29]. The uncertainty of vCJD transmissibility by plasma products led to the recommendation by the Committee for Proprietary Medicinal Products that a product be recalled where a donor subsequently diagnosed with vCJD had contributed to the plasma pool (termed an 'implicated' batch) [30]. In 1997, there were two Bio Products Laboratory (BPL, the plasma fractionator for the UK National Blood Service) recalls of clotting factor concentrates [31], both of which included batches of in-date FVIII concentrate.

The first risk assessment of plasma vCJD infectivity

Theoretically, the degree of exposure of an individual recipient to vCJD infection is dependent on the prevalence of subclinical infection within the donor

Table 1. Measures taken in the UK to minimize risk of variant Creutzfeldt–Jakob disease (vCJD) transmission by blood and plasma product transfusion.

I. Rationalization of clinical use of blood and blood products. Department of Health initiatives: Better Blood Transfusion 1998, 2002, 2007
II. Donor selection
a. Use of non-UK donors for plasma product fractionation (announced 1998, implemented 1999)
b. Use of non-UK plasma donors in under 16 s or adult recipients of large plasma volumes (2002)
c. Exclusion of recipients of blood transfusion since 1980 from donor pool (2004)
d. Exclusion of individuals from donor pool who are unsure whether they have received a blood transfusion since 1980 (2004).
e. Exclusion of donors where recipients have developed vCJD where blood transfusion cannot be excluded as source of vCJD and where no infected donor has been identified (2005)
III. Component processing
a. Leucodepletion of all blood products to white cell concentration $<10^6\ L^{-1}$ (announced 1998, implemented 1999)
b. Use of recombinant factors in selected patients with haemophilia A and B (1998) and all others (2003–2005)
IV. Product recall where donor confirmed as suffering from vCJD found to have contributed to plasma pool

Table 2. Possible determinants of risk of variant Creutzfeldt–Jakob disease (vCJD) transmission by transfusion of blood and plasma products.

I. Levels of infectivity in donor population
a. Prevalence of sub-clinical infection – geographical variation
II. Exposure of recipient to infected donors
a. Infectivity of donation within incubation period
b. Quantity of plasma/leucocytes within component
c. Number of donors contributing towards component/size of plasma pool
d. Number of transfusions received
e. Manufacturing process: e.g. leucodepletion, plasma fractionation, inactivation procedures
III. Susceptibility of recipient
a. Genotype e.g. codon 129 *PRNP*
b. Age
c. Other

population, the manufacturing process of a given blood component and the number of transfusions received (Table 2). The partitioning of prion infectivity during the manufacture of plasma products has been extensively investigated and is reported elsewhere [32–37]. In addition, there is individual variation in susceptibility to infection, with possible influences including age and *PRNP* genotype. An independent assessment of the risk to patients of exposure to vCJD infectivity in blood products was carried out on behalf of the Department of Health (DH) by Det Norske Veritas Consulting (DNV) and reported in 1999 [38]. To estimate the numbers of new infections and possible resultant vCJD cases, the authors attempted to estimate the proportion of UK blood donations that may be infected with vCJD, the possible level and distribution of vCJD infectivity in blood components and plasma products derived from those donations and the likely level of exposure to infectivity of defined sets of patient groups. Substantive data surrounding several of the variables used in these calculations were lacking, necessitating various assumptions and that data be extrapolated from spiked animal models [39,40]. Based on the assumption that blood is equally infective throughout the incubation period of the disease, the likely proportion of infected donations was estimated as between 1/200 and $1/10^6$, depending on the median incubation period of the disease. Over the same range of infected donations, the recipient's risk of infection was predicted to range between unity and $1/10^6$, depending on the patient group. Each infected donation was estimated to result in 2.6 infected recipients (assuming roughly equal contributions from red cell and plasma product transfusions), approximately 80% of whom may live long enough to develop vCJD [38].

The subsequent confirmation of a further clinical case of vCJD in an individual whose blood donations had previously contributed towards plasma pools resulted in a further BPL recall in 2000 [41]. Unlike the 1997 recalls, all batches of clotting factor concentrate had passed their respective expiry dates at the time of this recall. In Scotland, two donations from an individual later diagnosed with vCJD had contributed to the Scottish National Blood Transfusion Service (SNBTS) fractionation pools, and the affected FVIII and FIX products that had been issued to centres in Scotland and Northern Ireland between 1987 and 1989 were described in the SNBTS notification of 2001.

Management of early plasma product recalls

At the time of the 1997 and 2000 BPL and 2001 SNBTS notifications, the haemophilia centres issued with implicated batches of clotting factor were asked to return any remaining stock and recall any remaining unused batches supplied to patients. No public health precautions were advised at the time of these recalls. The 1997 product recall letters from BPL to haemophilia centres cited the following advice that had been provided by the ethics committee local to the NCJDSU: 'the recipients (patients) should not be informed that the product that they

had received has been recalled for this reason [subsequent diagnosis of vCJD in donor] [31]'. In response to queries raised by clinicians and hospital trusts about this directive, the DH confirmed to medical directors that patients who had received implicated blood products should not be informed [42]. This was based on three considerations: first, that it was not known (the word used was 'unlikely') whether vCJD was transmissible by blood products; secondly, that there was no diagnostic test in existence, and finally that no preventative treatment was available. The consensus given by the DH at the time was that patients would 'not benefit from this knowledge, and that uncertainty created by informing patients could cause unjustified worry and create a permanent blight on their lives' [42]. However, many haemophilia physicians either directly informed patients who had received an implicated batch, or provided all their patients with information about vCJD, giving them the option to be informed whether or not they had received an implicated batch(es). In the case of paediatric patients, parents were similarly contacted. The establishment of the CJD Incidents Panel (CJDIP) in 2000 on behalf of the Chief Medical Officer provided an independent expert committee that advised on issues involving possible vCJD transmission in healthcare settings.

vCJD surveillance in UK patients with inherited bleeding disorders

Over 20 000 UK patients with inherited bleeding disorders are currently registered on the National Haemophilia Database (NHD) of whom around one-fifth have been treated with clotting factor concentrate derived from UK-sourced plasma donations. A pilot retrospective histopathological study of the brains of 22 haemophilic patients who died of HIV-related illnesses during part of the period of potential vCJD infection showed no evidence of vCJD [43]. A 5-year surveillance study of patients with haemophilia was commissioned and funded by the DH in 2000 and co-ordinated by the UKHCDO following ethical approval being given by the London Multi-Centre Research Ethics Committee (MREC/01/2/11). The aims of this study were to determine the extent of exposure of individual patients with inherited bleeding disorders to implicated batches of clotting factor concentrate, to analyse tissue biopsies and autopsy material for vCJD and to notify possible and confirmed clinical cases of vCJD in the UK haemophilic population. It was hoped that all haemophilic patients undergoing surgical procedures involving the central nervous system and lymphoid tissue (including tonsil, lymph nodes and spleen) would consent to participate in the study. It was anticipated that in addition to facilitating the appropriate monitoring and long-term follow-up of patients, the findings from this study would inform future assessments of the risk of vCJD transmission posed by plasma products. The control group comprised haemophilic patients who had not received known implicated batches of clotting factor. At the outset of the study, haemophilia centres were provided with details, including issue dates of known implicated BPL or SNBTS batches they had received and requested to provide recipient data identifiable only by the patient's unique NHD number and date of birth. Participation in this study was voluntary. The data to be collected and recorded in a special file on the NHD was the degree of exposure to UK plasma products between 1980 and 2001, including the dates of first and last exposure to an implicated batch and its quantity.

Second risk assessment and CJDIP recommendations

Concern about the possibility of vCJD transmission by blood and blood products was heightened following the demonstration of blood transmission of BSE in a sheep model [44]. Unlike previous experimental models in which prions were inoculated by the intracerebral route, the sheep in this study had been orally infected with BSE and were therefore more representative of the situation in humans. Furthermore, transmission was shown to occur with blood taken during both the preclinical and clinical stages of infection [45].

A second DNV risk assessment undertaken on behalf of DH was reported in 2003 [46]. This was conducted to inform the management of individuals who had received implicated batches of blood and plasma products. The assessment was based on the various published experimental data in animals to model the potential vCJD infectivity in blood and its various components including plasma products [15,45,47]. The assumptions of this risk assessment were accepted by the Spongiform Encephalopathy Advisory Committee, the Committee on the Microbiological Safety of Blood and Tissue, and by the Committee on Safety of Medicines. CJDIP advised that surviving recipients of implicated red cell concentrates be informed and public health precautions implemented to minimize the risk of secondary vCJD transmission. Together with batch-specific manufacturing data, the risk assessment was used by CJDIP to estimate the potential vCJD infectivity in each batch of implicated plasma product. The likely risk

to treated patients was compared with the 'at-risk' threshold developed by CJDIP to guide the management of other 'at-risk' patient groups [48]. If patients had been exposed to a 'threshold' of 1% or greater potential risk of infection over and above the general risk to the UK population believed to have resulted from dietary exposure to the BSE agent, CJDIP advised that they should be notified and requested to take public health precautions. This 1% additional risk equates to an exposure of 0.02 ID_{50}, which is the equivalent level of infection at which public health precautions are implemented for patients exposed to vCJD via surgical instruments [49]. For each of the major assumptions underlying the risk assessment, the most precautionary option was chosen. The implicated plasma products were divided into three groups based on the assessed risk [50]. Amongst those considered to pose a high risk were FVIII, FIX and antithrombin concentrates, of which as little as one vial of treatment led to an exposure in excess of the defined risk threshold. Products in the medium-risk group included those in which exposure to substantial quantities was required to reach the risk threshold such as immunoglobulins, and the low-risk group comprised products with such low levels of potential infectivity as could effectively be ignored as causing any additional vCJD risk. The low-risk group also included some FVIII products that had been manufactured using implicated albumin as an excipient. Details of the majority of batches of implicated plasma products and their distribution directly to centres or through consignees were provided by BPL and SNBTS. To reduce the possibility of onward transmission of vCJD, it was recommended by CJDIP in 2004 that public health precautions be taken in recipients of 'high risk', and 'medium risk' implicated plasma products who had exceeded the 1% additional risk threshold.

Transmission of vCJD by blood transfusion

The CJDIP recommendations to implement public health measures in 'at-risk' recipients of implicated red cell and plasma products were reinforced by the subsequent recognition of the first case of vCJD transmission by blood transfusion [51]. TMER surveillance of the 66 recipients of red cell transfusions derived from the 17 vCJD patients who had previously donated blood has established that of the 24 identified recipients who survived more than 5 years following transfusion, three to date have shown evidence of vCJD infection [52]. In addition to these three clinical secondary cases of vCJD [51,53,54], a further asymptomatic case has been reported, in which the patient died from unrelated pathology with no evidence of neurological disease, but with post-mortem evidence of prion accumulation in lymphoreticular tissue [55]. All affected red cell donations are known to have been made relatively close to the onset of clinical symptoms in the donor, consistent with the increasing level of prion infectivity demonstrated throughout the incubation period in some animal models [56]. The incubation period in these secondary transfusion transmitted cases was around half the length of that estimated for primary oral infections from BSE. All three clinical cases were methionine homozygotes at codon 129 [51,53,54], while the asymptomatic case was methionine/valine heterozygous [55]. As a significant proportion of patients in the TMER recipient cohort did not survive long enough to develop clinical disease should they have been infected by vCJD, it is possible that the observed number of infected recipients underestimates the transmissibility of vCJD by blood transfusion. Likewise, it is possible that other surviving recipients are currently harbouring subclinical infection.

2004 vCJD plasma product patient notification exercise

UKHCDO advice

By the time of the 2004 CJDIP recommendations, the fate of products manufactured from 23 plasma donations derived from nine UK plasma donors who later developed vCJD had been established. These donations had undergone fractionation to produce albumin, immunoglobulin and clotting factor concentrates, including 16 batches of FVIII and eight batches of FIX that were distributed in the UK. TMER surveillance identified that these donations included plasma from at least one donor who, it is likely, had already transmitted vCJD via red cell concentrates [57]. At this time, it was considered likely that further batches of UK-sourced plasma products would become implicated as future vCJD cases arose. Therefore, to prevent secondary spread to other patients a 'population' or 'umbrella' approach was implemented in patients with inherited bleeding disorders who had received UK plasma-sourced products between 1980 and 2001. This policy was advised by UKHCDO and endorsed by CJDIP, DH and the Haemophilia Society, the UK charity representing patients with inherited bleeding disorders. As a result, all patients with bleeding disorders who had been treated with UK-sourced pooled factor concentrates between 1980 and 2001 were considered to be 'at-risk' of vCJD for public

health purposes and precautions were required to minimize the potential risk of secondary transmission. The start date of 1980 was when BSE was believed to have entered the human food chain and the end date of 2001 was the last possible expiry date of any product manufactured by UK fractionators and sourced from UK donors. This approach was based on the assumption that many further vCJD implicated batches of clotting factor concentrate would subsequently be identified and that only small volumes of implicated FVIII or FIX treatment were required for the recipient to be deemed 'at-risk' of vCJD. It was anticipated at that time that extending the 'at-risk' group of patients with inherited bleeding disorders and anti-thrombin deficiency in this way would significantly reduce the risk of secondary vCJD transmission. Such an approach differed from that taken in patients with primary immunodeficiency disorders in whom immunoglobulin forms the mainstay of treatment. As much larger quantities of this product are required to reach the 'at-risk' threshold, individual risk assessments were undertaken in these patients.

National advice: HPA responsibilities

The patient notification exercise was conducted in September 2004 and coordinated on behalf of the DH by the Health Protection Agency (HPA) in England, Wales and Northern Ireland, and the Scottish Centre for Infection and Environmental Health. Several professional and patient organizations, support groups and other stakeholders were involved in the consultation, planning and training for the notification exercise for patients with bleeding disorders, including representatives of UKHCDO, UKBS, the plasma fractionators and the Haemophilia Society. All clinicians responsible for the care of patients with bleeding disorders were provided with information to enable them to notify their patients and advise those for whom public health precautions were required. A date for contacting patients and their general practitioners was specified, which coincided with a national press release. At the same time, the Haemophilia Society informed its members by post about the notification process and provided a fact sheet on vCJD.

Haemophilia clinicians were provided with information sheets and a template letter to patients drafted by HPA/UKHCDO. Haemophilia centres were required to trace all recipients of clotting factors sourced from UK plasma between 1980 and 2001 and document their 'at-risk' status in the patient's medical records including details of exposure to implicated batches. Where a patient's care had been transferred to another centre, clinicians were instructed to forward recipient treatment details to the current centre, which was then responsible for informing the patient. All patients with bleeding disorders were to be notified, provided with written information and given an opportunity to discuss and find out whether they had received UK sourced plasma clotting factors in the specified time period (and were therefore considered 'at-risk'), as well as being given an option to find out whether or not they had received implicated batches. 'At-risk' patients were advised to inform providers of medical, surgical or dental treatment so that appropriate measures could be taken to minimize the risk of secondary vCJD transmission by instruments. They were also advised to inform their families in the event that a future emergency situation should arise and advised not to donate blood, tissues or organs which, in any event, this patient population is precluded from. 'At-risk' patients were advised that their clinical care should not be compromised in any way and invited to discuss the implications of the notification exercise. The original ethical approval was amended to facilitate recording of these relevant data for surveillance purposes on the NHD as previously described. Patients were requested to contact their clinician should they not wish their details to be recorded in this way.

BPL responsibilities

Haemophilia clinicians were contacted directly by BPL or SNBTS with details of any vCJD implicated batches they had been issued. While this accounted for the majority of the implicated batches, the data were incomplete at the time of the 2004 notification exercise, and the eventual tracing of product distribution of FVIII and FIX concentrate issued in 1988 through consignees resulted in a further patient notification in 2006 by which time, this information had become available.

Haemophilia clinician action

All 104 UK haemophilia centres received details of the 2004 exercise electronically 2 weeks prior to the date specified for notifying patients. The notification process comprised the identification of 'at-risk' patients, patient and general practitioner notification, NHD notification, responding to patient reply slips, implementation of patient counselling services and devising hospital policies through which the public health measures could be implemented. As

'at-risk' patients were identified, any who had recently undergone a surgical procedure involving specified tissues where the instruments used had not yet undergone 10 subsequent cycles of use/decontamination would need to be identified so that advice could be sought from CJDIP regarding the quarantine and handling of these instruments. Pertinent to the notification process was the adoption by hospital trusts of a multidisciplinary approach with collaborative links formed between haemophilia clinicians, infection control services, surgeons, gastroenterologists and others. Education of health care professionals in each hospital trust was imperative to enable the effective implementation of public health policies in 'at risk' patients. The number of patients with bleeding disorders registered at a given centre ranges from single figures to over 1500 and there was significant variation between centres in the resources available to implement the guidance within the specified time period. While the use of electronic records in many centres greatly facilitated the tracing of clotting factor concentrate, these frequently did not cover the early part of the 1980–2001 period, a difficulty that was compounded in some centres by incomplete or unavailable manual records. Infection control policies were informed by guidance from the Advisory Committee on Dangerous Pathogens TSE Working Group [58] and hospital trusts were required to devise means to implement the public health measures in 'at-risk' patients.

Variation in implementation of HPA guidance

Based on local knowledge of their patient group, some clinicians opted to contact only 'at-risk' patients to minimize any possible confusion and prevent unnecessary anxiety in the not insignificant proportion of patients registered with bleeding disorders who had never received UK plasma derived clotting factor concentrate. The UKHCDO requested that haemophilia centres pass on information in situations where patients had moved to another centre. The effectiveness of this varied; some patients were notified by more than one centre, and other patients may have remained untraced as they moved between centres. This difficulty in tracing and contacting patients is now being resolved as the UKHCDO moves towards a data-sharing approach between centres carrying out public health notifications. While there has been no formal evaluation of this notification, there have been anecdotal reports of clinicians notifying only patients known to have received implicated batches of their vCJD risk status. Furthermore, as the notification process requested patients to clarify their 'at-risk' status, it is possible that some patients remain unaware that they pose a public health risk unless specific action has been taken by clinicians to inform them.

A lack of understanding of the nature of the notification process has resulted in some 'at-risk' patients feeling stigmatized, and there have also been instances of patients being incorrectly labelled as having, rather than being at risk of, vCJD. Despite such difficulties, the telephone helplines set up for patients during the notification exercise as well as NHS Direct received few calls. Moreover, the findings from a study of other at-risk vCJD individuals are reassuring; no adverse long-term behavioural or emotional sequelae have been reported in individuals who have either undergone surgery involving contaminated instruments or who have donated blood to patients subsequently diagnosed with vCJD [59].

Endoscopy

A significant challenge that has arisen from the public health notification exercises surrounds endoscopic biopsy. The possible contamination of the biopsy forceps and the endoscope channel as a result of vCJD infectivity in the gut mucosa of subclinically infected individuals [60] led to the 2003 recommendation to quarantine endoscopes and retain their use only for the specified patient should invasive procedures such as biopsy or diathermy be required in an 'at-risk' patient [58]. For several years, the cost implications that resulted from the individualization of endoscopes in 'at-risk' patients requiring biopsy were borne by the hospital trust concerned. This resulted in variation between trusts in the threshold at which biopsies have been performed in these patients, thus raising the possibility that patient care may have been compromised in some cases. In 2008, the DH provided central funding for the refurbishment of suitable quarantined endoscopes used on patients at risk of vCJD [61]. Sufficient resources will similarly be required to ensure the continued implementation of appropriate public health measures in an ageing 'at-risk' bleeding disorder patient population while maintaining high standards of clinical care.

UK products distributed to other countries

As well as being supplied throughout the UK, implicated plasma donations contributed towards pooled plasma products that have been distributed to 13 countries: Belgium, Brazil, Brunei, Egypt, France, India, Ireland, Israel, Jordan, Netherlands, Oman,

Turkey and the United Arab Emirates. It is estimated that patients in at least four of these countries have been exposed to a level of infectivity exceeding the 'at-risk' threshold and the relevant Health Ministries have been contacted by the HPA and informed of the UK approach to risk assessment and patient notification. In the United States, a recent Food and Drug Administration risk assessment has concluded that the risk of vCJD infection from FVIII concentrate is very low [62].

Current results of the notification exercise and UKHCDO surveillance study

Patient exposure to UK plasma products including vCJD implicated batches

The collection of data of patients who received implicated batches and its entry on the NHD remains ongoing and has been greatly assisted by online registration. Annual returns historically provided by haemophilia centres to the NHD detail patient's treatment including product type and adverse events. From these data, it has been possible to estimate the number of patients treated with UK plasma products between 1980 and 2001. Furthermore, details of patient exposure entered into the database have been cross-checked against batch information provided to individual centres by BPL to establish the extent to which implicated batches are accounted for. Recently, similar total data for implicated batches supplied by SNBTS has been provided. This audit indicates that not all of the recipients for some of the batches have been notified to the NHD.

Using the NHD annual data, the estimated number of patients who received UK plasma products between 1980 and 2001 is 4581, of whom 792 are notified as having been treated with one or more than one implicated batch. The units of treatment received by the latter group of patients account for only 12.7 of the 23.7 million units of implicated batches released and 792 is therefore an underestimate of the number of patients treated with an implicated batch. The quantities of each released implicated batch supplied to UK haemophilia centres together with the units accounted for in the notification exercise is presented in Table 3. The percentage of each batch that is accounted for is also shown. For some of these batches, the accounting of use by the patient notification exercise is disappointingly low. The reasons for the low notification of

Table 3. Implicated batches of clotting factor concentrate by batch number, product name, release and expiry dates, and units released and used.

Batch number	Product name*	Factor type	Release date	Expiry date	Units released	Sum of units used	% Units accounted for
FHB4116	8Y	VIII	June 1992	April 1995	775 000	280 710	36
FHB4189	8Y	VIII	April 1993	March 1996	1 233 500	735 725	59
FHB4419	8Y	VIII	July 1995	June 1998	1 022 000	656 600	64
FHB4547	8Y	VIII	September 1996	September 1997	902 000	873 821	94
FHB4596	8Y	VIII	May 1997	March 2000	1 398 500	1 054 410	75
FHC0059	8Y	VIII	September 1988	July 1989	528 720	58 560	11
FHC0289	8Y	VIII	May 1990	March 1993	633 500	266 960	42
FHC0369	8Y	VIII	December 1990	October 1993	604 500	199 060	32
FHC4237	8Y	VIII	March 1994	October 1996	1 268 500	982 977	77.4
FJA0020	9A	IX	October 1988	August 1989	533 500	88 025	16
FJA0092	9A	IX	May 1990	April 1991	511 800	92 990	18
FJA4239	9A	IX	July 1993	December 1996	251 000	141 435	56
FJA4308	9A	IX	June 1994	April 1997	573 000	379 540	66
FHM399	High Purity F8	VIII	November 1991	April 1994	812 000	169 055	20
FHM405	High Purity F8	VIII	May 1992	October 1994	905 500	304 500	33
3502–70210	HT DEFIX	IX	Not known	Not known	230 184	216 220	93.9
FHE4437	REPLENATE	VIII	September 1995	July 1997	1 547 000	818 095	52
FHE4536	REPLENATE	VIII	September 1996	July 1998	2 069 000	1 224 270	59
FHE4548	REPLENATE	VIII	October 1996	September 1998	1 690 000	965 400	57
FHF4625	REPLENATE	VIII	July 1997	June 1999	2 290 000	1 035 900	45
FJM4327	REPLENINE	IX	October 1994	February 1996	1 607 500	1 139 915	70
FJM4437	REPLENINE	IX	November 1995	March 1997	832 500	379 380	45
FJM4596	REPLENINE	IX	April 1997	September 1998	838 500	592 380	70
FJM4625	REPLENINE	IX	July 1997	November 1998	875 000	22 145	2.5
0304–70510	Z8	VIII	Not known	Not known	123 690	16 150	13
0301–70320	Z8	VIII	Not known	Not known	125 440	Not known	0

*For further details [see ref. 22].

some implicated batches are not known, although patient refusal for the inclusion of their data may be a contributory factor. The last year an implicated batch was identified was 1999 and no further blood donors who donated plasma prior to developing vCJD have been identified since the 2004 notification.

Tissue-based vCJD surveillance

Following the 2004 notification exercise, the vCJD surveillance study was extended and remains ongoing, although the number referred for postmortem remains low. There were 669 deaths in bleeding disorder patients between 2004 and 2008 including 269 treated with UK plasma products and 37 recipients of implicated batches. However, only a small number of study postmortems have been performed [63]. The report of the first asymptomatic case of probable transmission of vCJD by clotting factor concentrates [63] emphasizes the need for higher recruitment to this study if we are to improve our understanding of the risk of vCJD transmission via infected plasma products. Active vCJD surveillance of prospective tissue samples and autopsy material continues. The Office of National Statistics has provided information about deaths of haemophilic patients including whether the death certificate indicates that a postmortem was or may have been done. This is currently under investigation in the hope of providing further postmortem material for study.

Information to patients (February 2009)

The postmortem arm of the surveillance study has detected PrP^{res} in the spleen of a patient with haemophilia who had had no evidence of any neurological disorder while alive [63]. This patient was known to have been treated with at least one implicated batch of BPL FVIII 8Y. A decision was made to inform bleeding disorder patients of this finding even though the investigation of this case was continuing. A toolkit of letters and information sheets prepared by HPA/UKHCDO was electronically mailed to all Haemophilia Centres with instructions for patients to be informed as soon as possible by post. Many centres decided to post letters to only the patients in the at-risk group.

Further investigation of this patient's complete clinical records showed that he had received treatment with UK-sourced FVIII concentrates including two implicated batches of 8Y, each of which contained a plasma donation from the same donor who subsequently went on to develop vCJD. The patient had also been transfused with 14 units of red cells between 1998 and 2007 and had had invasive endoscopies. Further information about this is contained in a separate paper [63]. Of these potential risk factors, the only link to contact with a patient with vCJD was the two implicated 8Y batches. A further risk assessment by the Department of Health interprets the most likely source of vCJD in this patient as being treatment with UK plasma products [64].

Whilst to date no haemophilia or bleeding disorder patient has been diagnosed with, or died from, clinical vCJD, this information has increased anxiety among some at-risk patients as this is the first information linking treatment with an implicated batch and the detection of PrP^{res} in lymphoid tissue in a patient with haemophilia. However, it is too early to estimate the full implications of these findings on this group and other people treated with blood and plasma products produced in the UK from UK-sourced plasma.

Conclusions

The risk of transmission of viruses by plasma products including HIV and hepatitis C has been virtually eliminated since the introduction of improved donor selection and testing and the employment of effective viral inactivation processes in 1986. However, new concerns regarding the safety of UK blood and plasma products have arisen following the emergence of vCJD. An early precautionary approach was adopted in UK bleeding disorder patients with the aim of minimizing the possible risk of vCJD transmission and its secondary spread. These include their exclusion as blood and tissue donors; an approach that has subsequently been extended to include all recipients of cellular blood products in the UK. Public health measures were implemented in 2004 in all patients who had received UK pooled plasma clotting factor concentrates between 1980 and 2001, irrespective of whether these had contained plasma from a donor known to have later developed vCJD. Challenges have resulted from this approach and these have been discussed in this paper. Our understanding of the risk of vCJD transmission by plasma products has increased over time and informed risk reduction measures. Since the 2004 public health notification exercise, the numbers of new clinical vCJD cases in the UK have declined and no further vCJD patients have been identified as having previously donated implicated blood or blood products. However, the prevalence of subclinical vCJD infection in the general population, including the extent of infection among methionine/valine heterozygotes and valine/valine homozygotes, remains unknown. It is also not known how soon a suitable validated screening test for vCJD

will become available. Although the current risk assessment indicates that only small volumes of implicated clotting factor concentrates are sufficient to cross the additional 1% risk threshold at which public health measures are required, vCJD infectivity amongst implicated batches varies. The recent identification of the first case of asymptomatic vCJD in a haemophilic patient [63] as well as the report of vCJD in a methionine/valine heterozygous individual [13] highlight the need for the continued surveillance of individuals in the 'at-risk' population, including patients with inherited bleeding disorders. Attempts to improve the numbers of postmortem examinations by patients consenting in life or by consent of bereaved relatives needs urgent consideration. Patients who have received implicated batches are currently undernotified to the NHD. Taken together with the unknown prevalence of the abnormal prion protein associated with vCJD among blood donors and the absence of a validated test, continued employment of the population approach appears to be the best means of reducing secondary spread of vCJD between patients, including those with bleeding disorders. Further follow-up may lead to improved understanding of the risk of vCJD to this patient population and the re-evaluation of the current considered 'at-risk' groups for public health purposes.

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販売名(企業名)	－					

研究報告の概要

現在までに、後に変異型クロイツフェルト・ヤコブ病(vCJD)を発症した患者からの輸血によるvCJD感染例は4例報告されている。
vCJDを発症した患者からの供血血液を追跡し受血者を特定すると共に、vCJD登録患者の受血歴と照合したところ、共通の供血者からの輸血が行われていた可能性が示唆された2例について検証した。
患者Aは2006年に18歳でvCJDにより死亡しており、1989年に新生児特別治療室で4回の輸血を受けていたことが確認されたが、輸血された赤血球(RBC)成分の詳細や供血者を特定できる記録はなかった。
患者Bは1998年にvCJDを発症し41歳で死亡しており、1993年6月と10月に2度の輸血を受けており合計103名の供血者の血液に曝露していた。この103名は全て特定され、うち18名が患者Aへ輸血された時期にも供血しており、その内1名の供血者の血液が患者Aへの輸血が行われた病院に送られていた。
この供血者は、1989年初頭～2005年1月まで26回の供血を行っており、輸血用に29の血液成分(患者Bに輸血された成分および患者Aの入院先へ配給されたRBC成分を含む)と、11の血漿成分を提供した。血漿成分は1998年にイギリス国内血漿の使用が中止になる前に、分画のためバイオプロダクトラボラトリーに供給された。
この2名の患者以外に残りの27の血液成分が輸血された患者は特定できなかったが、vCJD登録患者の中にこの献血者と結びつける受血歴のある患者はいなかった。
一人の供血者からの2例のvCJD感染の発生を示しているか、または偶然の一致であるかどうかを評価するため、調査を行ったが、2名の受血者の関連性の説明として偶然の一致を除外することはできないが、状況からvCJDを発症しなかった共通の供血者によって結びついたvCJDの血液感染例が新たに2例発生したことが示唆された。

使用上の注意記載状況・その他参考事項等

重要な基本的注意
現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的なvCJD等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
vCJD登録患者のうち共通の供血者からの輸血を受けていた可能性のある2名に関する報告である。 現時点まで血友病以外で血漿分画製剤からvCJD伝播が疑われた報告はなく、血漿分画製剤の製造工程でプリオンが除去できるとの情報もある。 なお、当社血漿分画製剤の原料血漿は現在まで英国の血漿を使用していない。	今後ともvCJDに関する安全性情報等に留意していく。

Variant Creutzfeldt-Jakob disease in a transfusion recipient: coincidence or cause?

Gurjit Chohan, Charlotte Llewelyn, Jan Mackenzie, Simon Cousens, Angus Kennedy, Robert Will, and Patricia Hewitt

BACKGROUND: To date there have been four instances of infection transmitted through blood transfusions derived from individuals who later developed variant Creutzfeldt-Jakob disease (vCJD). The identification of further transmission of vCJD through this route would have important implications for risk assessment and public health.

STUDY DESIGN AND METHODS: Through the UK Transfusion Medicine Epidemiology Review (TMER) the fate of blood donations from individuals who develop vCJD is traced and recipients of labile components are identified. The details of recipients are cross-checked with the register of vCJD cases held at the National CJD Surveillance Unit (NCJDSU) to identify any linkage between donors and recipients. In the reverse study, when individuals with vCJD are found to have a history of blood transfusion the donors of the transfused blood components are traced and their details cross-checked with the vCJD register to identify any missed or unrecognized linkage between donors and recipients.

CASE REPORT: A case of vCJD has been identified with a history of blood transfusion in infancy. The donors who provided the components transfused cannot be identified, but a blood donor known to have donated blood to another individual who subsequently developed vCJD could have been a donor to the index case.

RESULTS: The at-risk donor is alive 20 years after the relevant donation and continued to donate for some years, until identified as at risk, with 27 other blood components issued for use in patients, none of whom are known to have developed vCJD.

CONCLUSION: Circumstantial evidence has raised the possibility that the case in this report represents a further instance of transfusion transmission of vCJD. However, detailed investigation indicates that the pattern of events may have occurred by chance and disease in this individual may have been caused by transmission of bovine spongiform encephalopathy infection, as is the presumed cause in other primary cases of vCJD.

The Transfusion Medicine Epidemiology Review (TMER) is a collaborative study between the UK National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU) and the UK Blood Transfusion Services (UKBS), which was set up in 1997 to identify whether variant Creutzfeldt-Jakob disease (vCJD) was transmissible through blood transfusion. Results from the TMER up to January 3, 2006, have been published.[1] In this article we report on the subsequent identification of a possible link between two vCJD cases who could have received transfusions from a common donor, although this cannot be confirmed.

To date, four instances of probable transmission of vCJD by blood transfusion have been identified by the TMER, including three clinical cases of vCJD and a sub- or preclinical infection.[1,2] Current surviving recipients (n = 21) of blood transfusions derived from individuals

ABBREVIATIONS: TMER = Transfusion Medicine Epidemiology Review; UKBS = UK Blood Transfusion Services; vCJD = variant Creutzfeldt-Jakob disease.

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who later went on to develop vCJD have been informed that they are at greater risk of developing vCJD and, although the level of this risk is uncertain, the four infections through blood transfusion identified to date have developed in a cohort of only 32 individuals who have survived at least 5 years since transfusion.

The identification of further instances of transfusion transmission of vCJD would have important implications for the assessment of risk and for public health. This case report describes the development of vCJD in an individual with a history of blood transfusion derived from donors who cannot be identified but it is possible, based on detailed investigation, that one of the four donors may have been a donor to another vCJD case.

MATERIALS AND METHODS

The TMER study involves the NCJDSU notifying the UKBS of all incident definite or probable cases of vCJD.[1] A search is made via blood donor centers to identify cases that had previously donated blood components and details of the recipients of these components are sought. Identifiers of the recipients are forwarded to the NCJDSU to determine whether any of these individuals appear on the register of vCJD cases. The reverse study involves the NCJDSU notifying the UKBS of all cases of vCJD reported to have received a blood transfusion and the donors are then identified through blood centers and the identifiers checked against the vCJD case register. The study was granted ethical approval by the local research ethics committee.

RESULTS

Case report

Individual A was reported as a case of possible vCJD in 2006 and died of pathologically confirmed vCJD 6 months later, aged 18 years. The age-specific incidence of vCJD in the 15- to 19-year age group is 0.39 per million. The clinical and pathologic features were characteristic of vCJD, which are similar in primary and secondary cases of vCJD. This case was born in 1989 at 29 weeks' gestation and was cared for in a special care baby unit (Hospital X) for approximately 2 months before discharge. The parents reported a history of blood transfusion during the hospital admission, as would be expected in a neonate of this gestation. Staff at the NCJDSU later obtained copies of microfiched medical records, from which it was possible to establish that there were four blood transfusion episodes in early 1989, during the admission to Hospital X. The evidence for these transfusions comprised entries in the clinical notes and records of hemoglobin measurements. However, the medical records contained no details of the red blood cell (RBC) components transfused and no copies of laboratory reports or transfusion records that would allow tracing to specific donors. The hospital blood transfusion laboratory does not have records dating back to 1989.

It has been established that the transfusions were given before the introduction of dedicated RBC units for neonatal use (which allow 1 unit of RBCs to be divided into smaller aliquots and used at different times for the same neonate, thus reducing donor exposure). It is likely therefore that the transfusion episodes represent four different donor exposures. For each of the four transfusions, a small volume of RBCs would have been withdrawn from one adult blood pack.

A second individual (B) developed definite vCJD in 1998 and died at the age of 41 years. The age-specific incidence of vCJD in the 40- to 44-year age group is 0.08 per million. He was identified as having received a total of 103 donor exposures during the course of two separate transfusion episodes between June and October 1993, in a different hospital (Y). Because Hospital X (and thus Individual A) was supplied by the same blood center as Hospital Y and Individual B, the question arose as to whether the two cases might have shared a common donor.

The 103 donors to Individual B have all been identified and assessed as being "at risk of vCJD for public health purposes." Ninety-nine of these donors are alive more than 20 years after the transfusions to Individual A and four have died of causes of death unrelated to CJD or any other neurologic disorder according to their death certificates.

From a review of records of the 103 at-risk donors from 2003, it was established that 18 of the cohort had donated in early 1989, at the relevant time for transfusion to Individual A. The records of these 18 donors were examined to determine whether the RBC components donated in early 1989 were issued to Hospital X, in which Individual A had received the blood transfusions. One such donor has been identified, who donated a unit of RBCs in early 1989, which was issued to Hospital X 6 days later. This unit would have been 13 days old at the time of the first transfusion episode recorded in the medical notes of Individual A or 29 days old at the time of the next transfusion episode.

The pediatrician at Hospital X, who cared for Baby A, has confirmed that in 1989 there were no specific guidelines for top-up transfusions of premature babies. There was no system for allocating a particular unit for sequential top-up transfusions on the same baby, and provision of specific neonatal RBC units only came into place in the mid-1990s. It is probable that, in 1989, standard RBC units would have been provided of blood group O or A, depending on the blood group of the baby. The donor in question is group O. The hospital used "fresher" units by preference, and it is highly unlikely that they would have used 29-day-old RBCs, but the pediatrician could not exclude the pos-

sibility that 13-day-old RBCs would have been used for a top-up transfusion. There is therefore a possible common donor to Individuals A and B.

It should be noted that the potential common donor made 26 donations in all, and the early 1989 donation was the first of these. The donor continued donating until January 2005. The 26 donations were processed and provided 29 blood components that were issued for direct clinical use (including the component transfused to Individual B, and the RBC unit issued to Hospital X in February 1989) and 11 plasma components, which were issued to the Bio-Products Laboratory for fractionation, before the use of UK plasma was discontinued in 1998.

To assess whether the potential link observed might be a coincidence rather than reflecting the occurrence of two vCJD transmissions from a single donor, further examination of records was performed to try to establish the likelihood that a randomly selected donor who attended in the relevant time period in 1993 (i.e., the time of the transfusion episodes to Individual B) would, by chance, also have attended in the time period of the transfusions given to Baby A in 1989. Unfortunately, due to a change in record systems at the end of 1992, it was not possible to interrogate individual donor records over these two time periods.

Donor records over similar time periods in later years were therefore examined. For example, we identified donors during the relevant period in 1997 and looked back to determine how many of those donors had donated in the relevant months 4 years earlier (the transfusion to Individual A was in 1989 and Individual B in 1993). This exercise was performed for three combinations of years: 1997/1993, 1998/1994, and 1999/1995.

The results were fairly consistent over the three periods examined, with 10% to 14% of donors donating in both the relevant time periods. Hospital X receives approximately 10% of the blood supply from the blood center in question, so it would be expected that about 10% of the (approx.) 10% who had donated at the right time in 1993 would also have donated at the right time in 1989 with the donation being issued to Hospital X. Thus, the finding that one of the 103 (i.e., roughly 1%) identified donors who donated to Recipient B in 1993 had also donated in the period during which Baby A was transfused in 1989, and whose blood was issued to Hospital X, is just what might be expected by "coincidence," suggesting that coincidence cannot be ruled out as an explanation for the link between the two recipients who developed vCJD.

DISCUSSION

The case of vCJD described in this report (Individual A) received blood transfusions in infancy in 1989, but the donors who provided these components cannot be identified because medical records are incomplete for the period in question. Nevertheless, a blood donor who has been judged to be at risk of developing vCJD, because of a donation transfused to another vCJD case, is known to have donated blood that could have been transfused to Individual A. The question is whether the development of vCJD in Individuals A and B was caused by transmission of infection through blood transfusion from a common, infected donor. While we cannot rule out this possibility, further investigation suggests the observed pattern of events would not be unexpected in the absence of any causal link between the two cases.

Investigation of other donors at the same center indicates that there is a 10% probability that an individual donor would continue to provide blood over a 4-year period and a similar chance that this blood was used in Hospital X where the transfusions to Individual A took place. The fact that one of 103 at-risk donors provided blood on two occasions separated by 4 years and that this blood was used in a particular hospital is therefore not surprising. It is also of note that 48% of blood donors in this region are blood group O, as is the "common" donor and both recipients.

This exercise has highlighted the difficulties in trying to retrospectively link hospital and UK blood service records after an interval of 18 years. The implementation of the Blood Safety and Quality Regulations (2005) enacting a series of EU Directives on quality and safety standards for UK blood establishments and hospitals now means that there is a statutory requirement to ensure that systems are put in place to ensure future full traceability of blood components issued and for these records to be maintained for 30 years. Had this been in place 20 years ago, we would have been able to establish with certainty whether or not Individuals A and B shared a common donor.

The at-risk donor is still alive more than 20 years after the donation potentially transfused to Individual A and this would represent protracted survival in an individual infected with vCJD.[3] In the three clinical cases of established transfusion transmission the two donors developed symptoms of vCJD 17, 21, and 40 months after providing the three implicated donations. However, both these individuals and all three of their infected recipients were methionine homozygous at Codon 129 of the human prion protein gene (*PRNP*), as were Individuals A and B. It is possible that individuals with an alternative genotype at this locus could be infected and survive for many years, and possibly beyond the normal life span, without developing clinical disease.[4] The Codon 129 genotype of the at-risk donor is unknown.

The at-risk donor provided 25 donations between 1989 and 2005, subsequent to the one potentially transfused to Individual A. A total of 28 individual blood components from these 25 donations were issued to hospitals for clinical use, including the transfusion to Individual B. While the fate of the remaining 27 blood components has

not been traced to named recipients, no other cases of vCJD that appear on the NCJDSU database have a history of blood transfusion, which could link them to this donor. Because of the sophisticated CJD surveillance systems that exist in the UK, it is very unlikely that any of the recipients could have developed vCJD but not been reported.

Two of the previous transfusion-transmitted cases received blood from a common donor, with donations separated by 4 months, indicating that it is possible that infectivity in blood in vCJD is sustained through part or all of the incubation period, consistent with some,[5,6] but not all,[7] animal studies. Symptoms of vCJD developed in these transfusion-transmitted cases between 6 and 8 years post-transfusion. Individual A was transfused 17 years before onset of vCJD and the incubation period, if this was transfusion transmission, was therefore more than double that observed previously. However, the transfusions in Case A took place in infancy and there is evidence of reduced susceptibility and extension of incubation periods in neonatal mice experimentally exposed to scrapie as a result of inefficient infection of the immature spleen.[8] If Individual A was infected by blood transfusion, it is surprising that no other recipient from the common donor has developed vCJD, even allowing for some deaths from the underlying condition before symptoms of vCJD might have appeared. Although the Codon 129 genotype of the at-risk donor and the other 27 recipients is not known, approximately 40% of the Caucasian population are methionine homozygous at Codon 129 of *PRNP*.[9]

In conclusion, circumstances raised the possibility that an additional two cases of transfusion-transmitted vCJD have arisen, which are linked by a common donor who has not developed vCJD. The records at the time of the first transfusion are incomplete and an assessment of the likelihood of transfusion transmission depends on a range of considerations, including the chances of blood being provided by a single donor to two recipients in different hospitals, the protracted survival in the donor and Recipient A, and the absence of disease in a cohort of other individuals who received blood transfusions derived from the same donor. Although transfusion transmission cannot be excluded in the case of Individual A, it is also possible that disease in this individual was caused by transmission of bovine spongiform encephalopathy infection through the food chain, the presumed cause of vCJD in other primary cases.[10] The likelihood of food-borne exposure in Case A cannot be estimated directly from the dietary history, but there is evidence of increased susceptibility to primary vCJD in younger age groups.[11]

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CONFLICT OF INTEREST

The authors declare no competing financial interest.

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Ｂ　個別症例報告概要

○　総括一覧表
○　報告リスト

個別症例報告のまとめ方について

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

感染症定期報告の報告状況(2010/9/1～2010/11/30)

血対課ID	ID	受理日	番号	報告者名	一般名	生物由来成分名	原材料名	原産国	含有区分	文献	症例	適正使用措置
100203	2	2010/9/22	100523	バクスター	乾燥濃縮人血液凝固第Ⅷ因子	乾燥人血液凝固第Ⅷ因子	人血漿	米国	有効成分	有	有	無
100204	3	2010/9/22	100524	バクスター	乾燥濃縮人血液凝固第Ⅷ因子	人血清アルブミン	人血漿	米国	添加物	有	有	無
100215	14	2010/9/29	100548	CSLベーリング	人血清アルブミン 人血液凝固第ＸⅢ因子 フィブリノゲン加第ＸⅢ因子	人血清アルブミン	ヒト血液	米国、ドイツ、オーストリア	有効成分添加物	有	有	無
100221	20	2010/10/14	100582	化学及血清療法研究所	乾燥濃縮人アンチトロンビンⅢ	アンチトロンビンⅢ	ヒト血液	日本	有効成分	有	有	無
100238	37	2010/10/27	100667	CSLベーリング	フィブリノゲン加第ＸⅢ因子 人血液凝固第ＸⅢ因子	人血液凝固第ＸⅢ因子	ヒト血液	米国、ドイツ、オーストリア	有効成分	有	有	無
100253	52	2010/10/28	100685	化学及血清療法研究所	フィブリノゲン加第ＸⅢ因子 乾燥濃縮人活性化プロテインC 乾燥濃縮人血液凝固第Ⅸ因子 乾燥スルホ化人免疫グロブリン 人血清アルブミン 乾燥濃縮人血液凝固第Ⅷ因子	人血清アルブミン	ヒト血液	日本	有効成分添加物	有	有	無

別紙様式第4

感染症発生症例一覧

	番号		感染症の種類		発現国	性別	年齢(歳)	発現時期(年/月/日)	転帰	出典	区分	備考			
			器官別大分類	基本語								識別番号	報告日	MedDRA(Ver.)	
第15回	13-	2	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	1999	不明	症例報告	外国製品	09000005	2010/5/27	13.1	第15回症例番号13-2は第13回症例報告番号13-2において報告した
第15回	15-	1	臨床検査	HIV検査陽性	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	03000030	2010/3/30	13.1	
第15回	15-	2	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	10000010	2010/6/23	13.1	
第15回	15-	2	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	10000010	2010/6/23	13.1	
第14回	13-	1	感染症および寄生虫症	HIV感染	フランス	男性	49	1983	不明	症例報告	外国製品	08000041	2010/1/19	12.1	第14回症例番号13-1は前回報告における第13回症例番号13-1において報告したものの追加報告
第14回	13-	1	感染症および寄生虫症	A型肝炎	フランス	男性	49	1996/5/7	不明	症例報告	外国製品	08000041	2010/1/19	12.1	第14回症例番号13-1は前回報告における第13回症例番号13-1において報告したものの追加報告
第14回	13-	1	感染症および寄生虫症	B型肝炎	フランス	男性	49	2003/2/24	不明	症例報告	外国製品	08000041	2010/1/19	12.1	第14回症例番号13-1は前回報告における第13回症例番号13-1において報告したものの追加報告
第14回	13-	1	感染症および寄生虫症	C型肝炎	フランス	男性	49	2003/2/24	不明	症例報告	外国製品	08000041	2010/1/19	12.1	第14回症例番号13-1は前回報告における第13回症例番号13-1において報告したものの追加報告
第13回	13-	1	感染症および寄生虫症	HIV感染	フランス	男性	49	不明	不明	症例報告	外国製品	08000041	2009/3/18	12.1	
第13回	13-	1	感染症および寄生虫症	C型肝炎	フランス	男性	49	1996	不明	症例報告	外国製品	08000041	2009/3/18	12.1	
第13回	13-	2	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	1999	不明	症例報告	外国製品	09000005	2009/5/18	12.1	
第12回	12-	1	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	死亡	症例報告	外国製品	08000023	2008/10/27	11.0	
第12回	12-	2	感染症および寄生虫症	急性HIV感染	アメリカ	男性	不明	不明	死亡	症例報告	外国製品	08000023	2008/10/27	11.0	
第11回	5-	231	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000274	2008/4/21	11.0	第11回症例番号5-231は第5回症例番号5-231において報告したものの追加報告
第11回	5-	231	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000274	2008/4/21	11.0	第11回症例番号5-231は第5回症例番号5-231において報告したものの追加報告
第10回	10-	1	臨床検査	C型肝炎ウイルス	ブラジル	男性	小児	2004/5/25	不明	症例報告	外国製品	07000015	2007/10/29	10.1	
第10回	10-	1	臨床検査	C型肝炎ウイルス	ブラジル	男性	小児	2004/5/25	不明	症例報告	外国製品	07000015	2007/12/28	10.1	追加報告
第10回	10-	2	感染症および寄生虫症	急性HIV感染	アメリカ	男性	34	不明	不明	症例報告	外国製品	07000017	2007/12/6	10.1	
第10回	10-	2	臨床検査	C型肝炎ウイルス	アメリカ	男性	34	不明	不明	症例報告	外国製品	07000017	2007/12/6	10.1	
第10回	10-	3	感染症および寄生虫症	C型肝炎	ベルギー	男性	不明	1991	未回復	症例報告	外国製品	07000028	2008/2/25	10.1	
第9回			0*	0	0	0	0	0	0	0	0	0	0	0	* 当該調査期間に対象となる感染症報告はなかった
第8回	7-	012	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	11	2006/5/2	不明	症例報告	外国製品	06000019	2006/9/1	9.0	第8回症例番号7-012は第7回症例番号7-012において報告したものの追加報告
第8回	7-	012	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	11	2006/5/2	不明	症例報告	外国製品	06000019	2006/9/25	9.0	第8回症例番号7-012は第7回症例番号7-012において報告したものの追加報告
第8回	7-	012	臨床検査	ウイルス負荷増加	アルゼンチン	男性	11	2006/5/2	不明	症例報告	外国製品	06000019	2006/9/25	9.0	第8回症例番号7-012は第7回症例番号7-012において報告したものの追加報告
第7回	7-	022	感染症および寄生虫症	A型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000648	2006/3/3	8.1	
第7回	7-	007	感染症および寄生虫症	A型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000013	2006/5/15	9.0	
第7回	7-	023	臨床検査	A型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000649	2006/3/3	8.1	

別紙様式第4

感染症発生症例一覧

	番号		感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考			
			器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)	
第7回	7-	021	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000647	2006/3/3	8.1	
第7回	7-	001	感染症および寄生虫症	B型肝炎	イギリス	男性	24	不明	不明	症例報告	外国製品	06000007	2006/5/1	9.0	
第7回	7-	002	感染症および寄生虫症	B型肝炎	イギリス	男性	9	不明	不明	症例報告	外国製品	06000009	2006/5/10	9.0	
第7回	7-	008	感染症および寄生虫症	B型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000011	2006/5/10	9.0	
第7回	7-	007	感染症および寄生虫症	B型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000013	2006/5/15	9.0	
第7回	7-	006	感染症および寄生虫症	B型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000018	2006/5/22	9.0	
第7回	7-	023	臨床検査	B型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000649	2006/3/3	8.1	
第7回	7-	024	臨床検査	B型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000650	2006/3/3	8.1	
第7回	7-	011	感染症および寄生虫症	C型肝炎	台湾	男性	不明	不明	不明	症例報告	外国製品	05000635	2006/3/2	8.1	
第7回	7-	009	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000637	2006/3/3	8.1	
第7回	7-	013	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000638	2006/3/3	8.1	
第7回	7-	014	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000639	2006/3/3	8.1	
第7回	7-	015	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000640	2006/3/3	8.1	
第7回	7-	016	感染症および寄生虫症	C型肝炎	アルゼンチン	女性	不明	不明	不明	症例報告	外国製品	05000641	2006/3/3	8.1	
第7回	7-	017	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000642	2006/3/3	8.1	
第7回	7-	018	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000643	2006/3/3	8.1	
第7回	7-	019	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000644	2006/3/3	8.1	
第7回	7-	020	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000645	2006/3/3	8.1	
第7回	7-	004	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000646	2006/3/3	8.1	
第7回	7-	022	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000648	2006/3/3	8.1	
第7回	7-	059	感染症および寄生虫症	C型肝炎	イギリス	男性	55	不明	不明	症例報告	外国製品	06000006	2006/5/1	9.0	
第7回	7-	001	感染症および寄生虫症	C型肝炎	イギリス	男性	24	不明	不明	症例報告	外国製品	06000007	2006/5/1	9.0	
第7回	7-	060	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	06000008	2006/5/1	9.0	
第7回	7-	002	感染症および寄生虫症	C型肝炎	イギリス	男性	9	不明	不明	症例報告	外国製品	06000009	2006/5/10	9.0	
第7回	7-	003	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000010	2006/5/10	9.0	
第7回	7-	008	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000011	2006/5/10	9.0	
第7回	7-	007	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000013	2006/5/15	9.0	
第7回	7-	061	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000014	2006/5/15	9.0	
第7回	7-	010	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	死亡	症例報告	外国製品	06000015	2006/5/15	9.0	
第7回	7-	005	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000016	2006/5/15	9.0	
第7回	7-	062	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000017	2006/5/15	9.0	
第7回	7-	006	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	06000018	2006/5/22	9.0	
第7回	7-	012	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	11	2006/5/2	不明	症例報告	外国製品	06000019	2006/6/16	9.0	
第7回	5-	130	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000065	2006/3/30	9.0	第7回症例番号5-130は第5回症例番号5-130と重複症例のため報告破棄
第7回	5-	139	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000104	2006/3/2	8.1	第7回症例番号5-139は第5回症例番号5-139において報告したものの追加報告
第7回	7-	023	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000649	2006/3/3	8.1	
第7回	7-	024	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000650	2006/3/3	8.1	
第7回	7-	025	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000651	2006/3/3	8.1	
第7回	7-	026	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000652	2006/3/3	8.1	
第7回	7-	027	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000653	2006/3/3	8.1	
第7回	7-	028	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000654	2006/3/3	8.1	
第7回	7-	029	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000655	2006/3/3	8.1	
第7回	7-	030	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000656	2006/3/3	8.1	
第7回	7-	031	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000657	2006/3/3	8.1	
第7回	7-	032	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000658	2006/3/3	8.1	
第7回	7-	033	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000659	2006/3/3	8.1	

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢(歳)	発現時期(年/月/日)	転帰	出典	区分	備考			
		器官別大分類	基本語								識別番号	報告日	MedDRA(Ver.)	
第7回	7-034	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000660	2006/3/3	8.1	
第7回	7-035	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000661	2006/3/13	8.1	
第7回	7-036	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000662	2006/3/13	8.1	
第7回	7-037	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000663	2006/3/13	8.1	
第7回	7-038	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000664	2006/3/13	8.1	
第7回	7-039	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000665	2006/3/13	8.1	
第7回	7-040	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000666	2006/3/13	8.1	
第7回	7-041	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000667	2006/3/13	8.1	
第7回	7-042	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000668	2006/3/13	8.1	
第7回	7-043	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000669	2006/3/13	8.1	
第7回	7-044	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000670	2006/3/13	8.1	
第7回	7-045	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000671	2006/3/13	8.1	
第7回	7-046	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000672	2006/3/13	8.1	
第7回	7-047	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000673	2006/3/13	8.1	
第7回	7-048	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000674	2006/3/13	8.1	
第7回	7-049	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000675	2006/3/13	8.1	
第7回	7-050	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000676	2006/3/13	8.1	
第7回	7-051	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000677	2006/3/13	8.1	
第7回	7-052	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000678	2006/3/13	8.1	
第7回	7-053	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000679	2006/3/13	8.1	
第7回	7-054	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000680	2006/3/13	8.1	
第7回	7-055	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000681	2006/3/13	8.1	
第7回	7-056	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000682	2006/3/13	8.1	
第7回	7-057	臨床検査	C型肝炎ウイルス	チリ	男性	不明	不明	不明	症例報告	外国製品	05000683	2006/3/13	8.1	
第7回	7-058	臨床検査	C型肝炎ウイルス	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000684	2006/3/13	8.1	
第7回	5-139	感染症および寄生虫症	HIV感染	香港	男性	不明	1985	死亡	症例報告	外国製品	05000104	2006/3/2	8.1	第7回症例番号5-139は第5回症例番号5-139において報告したものの追加報告
第7回	7-001	感染症および寄生虫症	HIV感染	イギリス	男性	24	1985	不明	症例報告	外国製品	06000007	2006/5/1	9.0	
第7回	7-002	感染症および寄生虫症	HIV感染	イギリス	男性	9	1985	不明	症例報告	外国製品	06000009	2006/5/10	9.0	
第7回	7-003	感染症および寄生虫症	HIV感染	イギリス	男性	不明	1985/10/4	不明	症例報告	外国製品	06000010	2006/5/10	9.0	
第7回	7-004	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1986	不明	症例報告	外国製品	05000646	2006/3/3	8.1	
第7回	7-005	感染症および寄生虫症	HIV感染	イギリス	男性	不明	1986	不明	症例報告	外国製品	06000016	2006/5/15	9.0	
第7回	7-006	感染症および寄生虫症	HIV感染	イギリス	男性	不明	1986	不明	症例報告	外国製品	06000018	2006/5/22	9.0	
第7回	7-007	感染症および寄生虫症	HIV感染	イギリス	男性	不明	1986/3	不明	症例報告	外国製品	06000013	2006/5/15	9.0	
第7回	7-008	感染症および寄生虫症	HIV感染	イギリス	男性	不明	1986/4/9	不明	症例報告	外国製品	06000011	2006/5/10	9.0	
第7回	7-009	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1988	不明	症例報告	外国製品	05000637	2006/3/3	8.1	
第7回	7-010	感染症および寄生虫症	HIV感染	イギリス	男性	不明	1988/5	死亡	症例報告	外国製品	06000015	2006/5/15	9.0	
第7回	7-011	感染症および寄生虫症	HIV感染	台湾	男性	不明	1997/4/17	不明	症例報告	外国製品	05000635	2006/3/2	8.1	
第7回	5-130	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000065	2006/3/30	9.0	第7回症例番号5-130は第5回症例番号5-130と重複症例のため報告破棄
第7回	7-013	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000638	2006/3/3	8.1	
第7回	7-020	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000645	2006/3/3	8.1	
第7回	7-021	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000647	2006/3/3	8.1	
第7回	7-044	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000670	2006/3/13	8.1	
第7回	7-045	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000671	2006/3/13	8.1	
第7回	7-046	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000672	2006/3/13	8.1	
第7回	7-047	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000673	2006/3/13	8.1	
第7回	7-048	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000674	2006/3/13	8.1	

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢(歳)	発現時期(年/月/日)	転帰	出典	区分	備考			
		器官別大分類	基本語								識別番号	報告日	MedDRA(Ver.)	
第7回	7-049	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000675	2006/3/13	8.1	
第7回	7-057	感染症および寄生虫症	HIV感染	チリ	男性	不明	不明	死亡	症例報告	外国製品	05000683	2006/3/13	8.1	
第7回	7-058	感染症および寄生虫症	HIV感染	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000684	2006/3/13	8.1	
第6回	6-126	感染症および寄生虫症	A型肝炎	アルゼンチン	男性	不明	不明	回復	症例報告	外国製品	05000534	2006/2/8	8.1	
第6回	6-148	感染症および寄生虫症	A型肝炎	アルゼンチン	男性	不明	不明	回復	症例報告	外国製品	05000559	2006/2/13	8.1	
第6回	6-153	感染症および寄生虫症	A型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000565	2006/2/13	8.1	
第6回	6-159	感染症および寄生虫症	A型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000587	2006/2/16	8.1	
第6回	6-161	感染症および寄生虫症	A型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000589	2006/2/16	8.1	
第6回	6-032	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	14	1994	不明	症例報告	外国製品	05000458	2005/10/28	8.1	
第6回	4-06	感染症および寄生虫症	B型肝炎	イギリス	男性	11	不明	不明	症例報告	外国製品	04000081	2005/9/16	8.1	第6回症例番号4-06は前回報告における第4回症例番号4-06において報告したものの追加報告
第6回	5-136	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000100	2005/10/27	8.0	第6回症例番号5-136は前回報告における第5回症例番号5-136において報告したものの追加報告
第6回	5-101	感染症および寄生虫症	B型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000404	2005/10/21	8.1	第6回症例番号5-101は前回報告における第5回症例番号5-101において報告したものの追加報告
第6回	6-059	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000453	2005/10/25	8.1	
第6回	6-087	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000490	2005/12/20	8.1	
第6回	6-146	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000558	2006/2/13	8.1	
第6回	6-013	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000567	2006/2/13	8.1	
第6回	6-002	感染症および寄生虫症	B型肝炎	アルゼンチン	不明	不明	不明	不明	症例報告	外国製品	05000569	2006/2/13	8.1	
第6回	6-003	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000585	2006/2/16	8.1	
第6回	6-163	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000591	2006/2/16	8.1	
第6回	6-166	感染症および寄生虫症	B型肝炎	ペルー	男性	不明	不明	不明	症例報告	外国製品	05000598	2006/2/16	8.1	
第6回	6-176	感染症および寄生虫症	B型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000613	2006/2/22	8.1	
第6回	6-007	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	1985	不明	症例報告	外国製品	05000571	2006/2/13	8.1	
第6回	6-015	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	1986	不明	症例報告	外国製品	05000619	2006/2/22	8.1	
第6回	6-025	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	1990	不明	症例報告	外国製品	05000536	2006/2/8	8.1	
第6回	6-026	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	1990	不明	症例報告	外国製品	05000537	2006/2/8	8.1	
第6回	6-032	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	14	1994	不明	症例報告	外国製品	05000458	2005/10/28	8.1	
第6回	6-035	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	32	1995/5/24	不明	症例報告	外国製品	05000607	2006/2/22	8.1	
第6回	6-037	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	2001	不明	症例報告	外国製品	05000562	2006/2/13	8.1	
第6回	6-038	感染症および寄生虫症	C型肝炎	アルゼンチン	女性	不明	2003	不明	症例報告	外国製品	05000628	2006/2/24	8.1	
第6回	4-06	感染症および寄生虫症	C型肝炎	イギリス	男性	11	不明	不明	症例報告	外国製品	04000081	2005/9/16	8.1	第6回症例番号4-06は前回報告における第4回症例番号4-06において報告したものの追加報告
第6回	5-101	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000404	2005/10/21	8.1	第6回症例番号5-101は前回報告における第5回症例番号5-101において報告したものの追加報告
第6回	6-045	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000439	2005/9/9	8.0	
第6回	6-049	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000443	2005/9/14	8.0	
第6回	6-050	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	41	不明	不明	症例報告	外国製品	05000444	2005/9/14	8.0	
第6回	6-051	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000445	2005/9/14	8.0	
第6回	6-052	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000446	2005/9/14	8.0	
第6回	6-054	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000448	2005/9/16	8.0	
第6回	6-055	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	当該製品	05000449	2005/9/22	8.1	
第6回	6-056	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000450	2005/10/4	8.1	
第6回	6-057	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000451	2005/10/19	8.1	
第6回	6-058	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000452	2005/10/25	8.1	

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢(歳)	発現時期(年/月/日)	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA(Ver.)
第6回	6-059	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000453	2005/10/25	8.1
第6回	6-060	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000454	2005/10/25	8.1
第6回	6-061	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	05000455	2005/10/27	8.1
第6回	6-062	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	24	不明	不明	症例報告	外国製品	05000457	2005/10/27	8.1
第6回	6-063	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000459	2005/10/28	8.1
第6回	6-064	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000460	2005/10/28	8.1
第6回	6-066	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000464	2005/11/2	8.1
第6回	6-069	感染症および寄生虫症	C型肝炎	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000467	2005/11/2	8.1
第6回	6-070	感染症および寄生虫症	C型肝炎	ドミニカ共和国	男性	不明	不明	不明	症例報告	外国製品	05000468	2005/11/2	8.1
第6回	6-071	感染症および寄生虫症	C型肝炎	ペルー	不明	不明	不明	不明	症例報告	外国製品	05000469	2005/11/2	8.1
第6回	6-072	感染症および寄生虫症	C型肝炎	ペルー	男性	不明	不明	不明	症例報告	外国製品	05000470	2005/11/2	8.1
第6回	6-075	感染症および寄生虫症	C型肝炎	チリ	男性	不明	不明	不明	症例報告	外国製品	05000478	2005/12/2	8.1
第6回	6-076	感染症および寄生虫症	C型肝炎	チリ	男性	不明	不明	不明	症例報告	外国製品	05000479	2005/12/2	8.1
第6回	6-077	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	死亡	症例報告	外国製品	05000480	2005/12/2	8.1
第6回	6-079	感染症および寄生虫症	C型肝炎	チリ	男性	不明	不明	不明	症例報告	外国製品	05000482	2005/12/2	8.1
第6回	6-080	感染症および寄生虫症	C型肝炎	チリ	男性	不明	不明	死亡	症例報告	外国製品	05000483	2005/12/2	8.1
第6回	6-086	感染症および寄生虫症	C型肝炎	チリ	男性	不明	不明	死亡	症例報告	外国製品	05000489	2005/12/2	8.1
第6回	6-087	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000490	2005/12/20	8.1
第6回	6-088	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000496	2006/2/6	8.1
第6回	6-125	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000533	2006/2/8	8.1
第6回	6-126	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	未回復	症例報告	外国製品	05000534	2006/2/8	8.1
第6回	6-128	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000538	2006/2/8	8.1
第6回	6-129	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000539	2006/2/8	8.1
第6回	6-131	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000543	2006/2/10	8.1
第6回	6-132	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000544	2006/2/10	8.1
第6回	6-133	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000545	2006/2/10	8.1
第6回	6-134	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000546	2006/2/10	8.1
第6回	6-135	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000547	2006/2/10	8.1
第6回	6-136	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000548	2006/2/10	8.1
第6回	6-144	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000556	2006/2/13	8.1
第6回	6-145	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000557	2006/2/13	8.1
第6回	6-146	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000558	2006/2/13	8.1
第6回	6-147	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000573	2006/2/14	8.1
第6回	6-148	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	未回復	症例報告	外国製品	05000559	2006/2/13	8.1
第6回	6-149	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000560	2006/2/13	8.1
第6回	6-150	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000561	2006/2/13	8.1
第6回	6-152	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000564	2006/2/13	8.1
第6回	6-153	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000565	2006/2/13	8.1
第6回	6-154	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000566	2006/2/13	8.1
第6回	6-013	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000567	2006/2/13	8.1
第6回	6-155	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000568	2006/2/13	8.1
第6回	6-157	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000579	2006/2/16	8.1
第6回	6-158	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000580	2006/2/16	8.1
第6回	6-001	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000582	2006/2/16	8.1
第6回	6-159	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000587	2006/2/16	8.1
第6回	6-160	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000588	2006/2/16	8.1
第6回	6-161	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000589	2006/2/16	8.1
第6回	6-162	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000590	2006/2/16	8.1

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考			
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)	
第6回	6-163	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000591	2006/2/16	8.1	
第6回	6-014	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000592	2006/2/16	8.1	
第6回	6-018	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000593	2006/2/16	8.1	
第6回	6-019	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000594	2006/2/16	8.1	
第6回	6-004	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000595	2006/2/16	8.1	
第6回	6-164	感染症および寄生虫症	C型肝炎	パラグアイ	男性	不明	不明	不明	症例報告	外国製品	05000596	2006/2/16	8.1	
第6回	6-165	感染症および寄生虫症	C型肝炎	パラグアイ	男性	不明	不明	不明	症例報告	外国製品	05000597	2006/2/16	8.1	
第6回	6-166	感染症および寄生虫症	C型肝炎	ペルー	男性	不明	不明	不明	症例報告	外国製品	05000598	2006/2/16	8.1	
第6回	6-169	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000601	2006/2/21	8.1	
第6回	6-173	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000605	2006/2/21	8.1	
第6回	6-174	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000606	2006/2/21	8.1	
第6回	6-022	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000609	2006/2/22	8.1	
第6回	6-175	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000612	2006/2/22	8.1	
第6回	6-024	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000624	2006/2/24	8.1	
第6回	6-183	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000625	2006/2/24	8.1	
第6回	6-184	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000626	2006/2/24	8.1	
第6回	6-185	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000627	2006/2/24	8.1	
第6回	6-012	感染症および寄生虫症	C型肝炎	台湾	男性	不明	不明	不明	症例報告	外国製品	05000629	2006/2/24	8.1	
第6回	6-010	感染症および寄生虫症	C型肝炎	台湾	男性	不明	不明	不明	症例報告	外国製品	05000630	2006/2/24	8.1	
第6回	6-011	感染症および寄生虫症	C型肝炎	台湾	男性	不明	不明	不明	症例報告	外国製品	05000633	2006/2/24	8.1	
第6回	6-001	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1983	不明	症例報告	外国製品	05000582	2006/2/16	8.1	
第6回	6-002	感染症および寄生虫症	HIV感染	アルゼンチン	不明	不明	1984	不明	症例報告	外国製品	05000569	2006/2/13	8.1	
第6回	6-003	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1984	不明	症例報告	外国製品	05000585	2006/2/16	8.1	
第6回	6-004	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1984	不明	症例報告	外国製品	05000595	2006/2/16	8.1	
第6回	6-005	感染症および寄生虫症	HIV感染	台湾	男性	不明	1984/10/18	不明	症例報告	外国製品	05000620	2006/2/22	8.1	
第6回	6-006	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1985	不明	症例報告	外国製品	05000570	2006/2/13	8.1	
第6回	6-008	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1985	不明	症例報告	外国製品	05000608	2006/2/22	8.1	
第6回	6-009	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1985	不明	症例報告	外国製品	05000610	2006/2/22	8.1	
第6回	6-010	感染症および寄生虫症	HIV感染	台湾	男性	不明	1985/1/3	不明	症例報告	外国製品	05000630	2006/2/24	8.1	
第6回	6-011	感染症および寄生虫症	HIV感染	台湾	男性	不明	1985/11/13	不明	症例報告	外国製品	05000633	2006/2/24	8.1	
第6回	6-012	感染症および寄生虫症	HIV感染	台湾	男性	不明	1985/5/1	不明	症例報告	外国製品	05000629	2006/2/24	8.1	
第6回	6-013	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1986	不明	症例報告	外国製品	05000567	2006/2/13	8.1	
第6回	6-014	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1986	不明	症例報告	外国製品	05000592	2006/2/16	8.1	
第6回	6-015	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	1986	不明	症例報告	外国製品	05000619	2006/2/22	8.1	
第6回	5-136	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1986	不明	症例報告	外国製品	05000100	2005/10/27	8.0	第6回症例番号5-136は前回報告における第5回症例番号5-136において報告したものの追加報告
第6回	5-101	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	1986/7/16	不明	症例報告	外国製品	05000404	2005/10/21	8.1	第6回症例番号5-101は前回報告における第5回症例番号5-101において報告したものの追加報告
第6回	6-016	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1987	不明	症例報告	外国製品	05000541	2006/2/9	8.1	
第6回	6-017	感染症および寄生虫症	HIV感染	アルゼンチン	女性	不明	1987	不明	症例報告	外国製品	05000581	2006/2/16	8.1	
第6回	6-018	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1987	不明	症例報告	外国製品	05000593	2006/2/16	8.1	
第6回	6-019	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1987	不明	症例報告	外国製品	05000594	2006/2/16	8.1	
第6回	6-036	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	2000	不明	症例報告	外国製品	05000542	2006/2/9	8.1	
第6回	6-020	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	1988	不明	症例報告	外国製品	05000576	2006/2/16	8.1	
第6回	6-021	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1988	不明	症例報告	外国製品	05000584	2006/2/16	8.1	
第6回	6-022	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1989	不明	症例報告	外国製品	05000609	2006/2/22	8.1	
第6回	6-023	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1989	不明	症例報告	外国製品	05000611	2006/2/22	8.1	
第6回	6-024	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1989	不明	症例報告	外国製品	05000624	2006/2/24	8.1	

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考			
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)	
第6回	6-028	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1990	不明	症例報告	外国製品	05000623	2006/2/24	8.1	
第6回	6-029	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	1990/1/3	不明	症例報告	外国製品	05000578	2006/2/16	8.1	
第6回	6-030	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1992	不明	症例報告	外国製品	05000583	2006/2/16	8.1	
第6回	6-034	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1994	不明	症例報告	外国製品	05000586	2006/2/16	8.1	
第6回	5-271	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000403	2005/10/27	8.0	第6回症例番号5-271は第6回症例番号5-101と重複症例のため報告破棄
第6回	6-040	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000434	2005/9/1	8.0	
第6回	6-045	感染症および寄生虫症	HIV感染	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000439	2005/9/9	8.0	
第6回	6-046	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000440	2005/9/9	8.0	
第6回	6-048	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000442	2005/9/9	8.0	
第6回	6-053	感染症および寄生虫症	HIV感染	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000447	2005/9/16	8.0	
第6回	6-065	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000463	2005/11/2	8.1	
第6回	6-066	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000464	2005/11/2	8.1	
第6回	6-067	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000465	2005/11/2	8.1	
第6回	6-068	感染症および寄生虫症	HIV感染	ペルー	男性	不明	不明	不明	症例報告	外国製品	05000466	2005/11/2	8.1	
第6回	6-071	感染症および寄生虫症	HIV感染	ペルー	不明	不明	不明	不明	症例報告	外国製品	05000469	2005/11/2	8.1	
第6回	6-072	感染症および寄生虫症	HIV感染	ペルー	男性	不明	不明	不明	症例報告	外国製品	05000470	2005/11/2	8.1	
第6回	6-076	感染症および寄生虫症	HIV感染	チリ	男性	不明	不明	不明	症例報告	外国製品	05000479	2005/12/2	8.1	
第6回	6-077	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	死亡	症例報告	外国製品	05000480	2005/12/2	8.1	
第6回	6-078	感染症および寄生虫症	HIV感染	パナマ	男性	不明	不明	死亡	症例報告	外国製品	05000481	2005/12/2	8.1	
第6回	6-080	感染症および寄生虫症	HIV感染	チリ	男性	不明	不明	死亡	症例報告	外国製品	05000483	2005/12/2	8.1	
第6回	6-081	感染症および寄生虫症	HIV感染	チリ	男性	不明	不明	死亡	症例報告	外国製品	05000484	2005/12/2	8.1	
第6回	6-082	感染症および寄生虫症	HIV感染	パナマ	男性	不明	不明	死亡	症例報告	外国製品	05000485	2005/12/2	8.1	
第6回	6-083	感染症および寄生虫症	HIV感染	パナマ	男性	不明	不明	死亡	症例報告	外国製品	05000486	2005/12/2	8.1	
第6回	6-084	感染症および寄生虫症	HIV感染	パナマ	男性	不明	不明	死亡	症例報告	外国製品	05000487	2005/12/2	8.1	
第6回	6-085	感染症および寄生虫症	HIV感染	パナマ	男性	不明	不明	死亡	症例報告	外国製品	05000488	2005/12/2	8.1	
第6回	6-086	感染症および寄生虫症	HIV感染	チリ	男性	不明	不明	死亡	症例報告	外国製品	05000489	2005/12/2	8.1	
第6回	6-090	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000498	2006/2/6	8.1	
第6回	6-101	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000509	2006/2/8	8.1	
第6回	6-105	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000513	2006/2/8	8.1	
第6回	6-107	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000515	2006/2/8	8.1	
第6回	6-108	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000516	2006/2/8	8.1	
第6回	6-111	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000519	2006/2/8	8.1	
第6回	6-112	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000520	2006/2/8	8.1	
第6回	6-117	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000525	2006/2/8	8.1	
第6回	6-118	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000526	2006/2/8	8.1	
第6回	6-144	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000556	2006/2/13	8.1	
第6回	6-162	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000590	2006/2/16	8.1	
第6回	6-176	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000613	2006/2/22	8.1	
第6回	4-06	臨床検査	HIV検査陽性	イギリス	男性	11	1981/11/23	不明	症例報告	外国製品	04000081	2005/9/16	8.1	第6回症例番号4-06は前回報告における第4回症例番号4-06において報告したものの追加報告
第6回	6-020	肝胆道系障害	肝炎	ブラジル	男性	不明	1988	不明	症例報告	外国製品	05000576	2006/2/16	8.1	
第6回	6-027	肝胆道系障害	肝炎	ブラジル	男性	不明	1990	不明	症例報告	外国製品	05000575	2006/2/16	8.1	
第6回	6-031	肝胆道系障害	肝炎	ブラジル	男性	不明	1993	不明	症例報告	外国製品	05000618	2006/2/22	8.1	
第6回	5-286	肝胆道系障害	肝炎	ブラジル	男性	13	1994	不明	症例報告	外国製品	05000273	2006/2/15	8.0	第6回症例番号5-286は第6回症例番号6-033と重複症例のため報告破棄
第6回	6-033	肝胆道系障害	肝炎	ブラジル	男性	13	1994	不明	症例報告	外国製品	05000572	2006/2/13	8.1	

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考			
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)	
第6回	6-036	肝胆道系障害	肝炎	ブラジル	男性	不明	2000	不明	症例報告	外国製品	05000542	2006/2/9	8.1	
第6回	6-151	肝胆道系障害	肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000563	2006/2/13	8.1	
第6回	6-156	肝胆道系障害	肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000577	2006/2/16	8.1	
第6回	6-089	社会環境	伝染病暴露	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000497	2006/2/6	8.1	
第6回	6-093	社会環境	伝染病暴露	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000501	2006/2/6	8.1	
第6回	6-096	社会環境	伝染病暴露	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000503	2006/2/6	8.1	
第6回	6-097	社会環境	伝染病暴露	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000504	2006/2/6	8.1	
第6回	6-091	臨床検査	A型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000499	2006/2/6	8.1	
第6回	6-137	臨床検査	A型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000549	2006/2/10	8.1	
第6回	6-091	臨床検査	B型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000499	2006/2/6	8.1	
第6回	6-137	臨床検査	B型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000549	2006/2/10	8.1	
第6回	6-142	臨床検査	B型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000554	2006/2/10	8.1	
第6回	6-187	臨床検査	B型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000632	2006/2/24	8.1	
第6回	5-136	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000100	2005/10/27	8.0	第6回症例番号5-136は前回報告における第5回症例番号5-136において報告したものの追加報告
第6回	5-271	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000403	2005/10/27	8.0	第6回症例番号5-271は第6回症例番号5-101と重複症例のため報告破棄
第6回	6-039	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000433	2005/9/1	8.0	
第6回	6-040	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000434	2005/9/1	8.0	
第6回	6-041	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000435	2005/9/1	8.0	
第6回	6-042	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000436	2005/9/1	8.0	
第6回	6-043	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000437	2005/9/1	8.0	
第6回	6-044	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000438	2005/9/9	8.0	
第6回	6-046	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000440	2005/9/9	8.0	
第6回	6-047	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000441	2005/9/9	8.0	
第6回	6-065	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000463	2005/11/2	8.1	
第6回	6-067	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000465	2005/11/2	8.1	
第6回	6-068	臨床検査	C型肝炎ウイルス	ペルー	男性	不明	不明	不明	症例報告	外国製品	05000466	2005/11/2	8.1	
第6回	6-073	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000473	2005/11/21	8.1	
第6回	6-074	臨床検査	C型肝炎ウイルス	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000476	2005/11/30	8.1	
第6回	6-090	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000498	2006/2/6	8.1	
第6回	6-091	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000499	2006/2/6	8.1	
第6回	6-092	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000500	2006/2/6	8.1	
第6回	6-094	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000502	2006/2/6	8.1	
第6回	6-095	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000506	2006/2/6	8.1	
第6回	6-098	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000505	2006/2/6	8.1	
第6回	6-099	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000507	2006/2/8	8.1	
第6回	6-100	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000508	2006/2/8	8.1	
第6回	6-101	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000509	2006/2/8	8.1	
第6回	6-102	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000510	2006/2/8	8.1	
第6回	6-103	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000511	2006/2/8	8.1	
第6回	6-104	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000512	2006/2/8	8.1	
第6回	6-105	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000513	2006/2/8	8.1	
第6回	6-106	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000514	2006/2/8	8.1	
第6回	6-109	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000517	2006/2/8	8.1	
第6回	6-110	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000518	2006/2/8	8.1	
第6回	6-113	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000521	2006/2/8	8.1	
第6回	6-114	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000522	2006/2/8	8.1	

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第6回	6-115	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000523	2006/2/8	8.1
第6回	6-116	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000524	2006/2/8	8.1
第6回	6-118	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000526	2006/2/8	8.1
第6回	6-119	臨床検査	C型肝炎ウイルス	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000527	2006/2/8	8.1
第6回	6-120	臨床検査	C型肝炎ウイルス	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000528	2006/2/8	8.1
第6回	6-121	臨床検査	C型肝炎ウイルス	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000529	2006/2/8	8.1
第6回	6-122	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000530	2006/2/8	8.1
第6回	6-123	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000531	2006/2/8	8.1
第6回	6-124	臨床検査	C型肝炎ウイルス	アメリカ	女性	不明	不明	不明	症例報告	外国製品	05000532	2006/2/8	8.1
第6回	6-127	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000535	2006/2/8	8.1
第6回	6-130	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000540	2006/2/9	8.1
第6回	6-137	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000549	2006/2/10	8.1
第6回	6-138	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000550	2006/2/10	8.1
第6回	6-139	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000551	2006/2/10	8.1
第6回	6-140	臨床検査	C型肝炎ウイルス	アメリカ	女性	不明	不明	不明	症例報告	外国製品	05000552	2006/2/10	8.1
第6回	6-141	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000553	2006/2/10	8.1
第6回	6-142	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000554	2006/2/10	8.1
第6回	6-143	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000555	2006/2/10	8.1
第6回	6-029	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000578	2006/2/16	8.1
第6回	6-167	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000599	2006/2/16	8.1
第6回	6-168	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000600	2006/2/21	8.1
第6回	6-170	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000602	2006/2/21	8.1
第6回	6-171	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000603	2006/2/21	8.1
第6回	6-172	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000604	2006/2/21	8.1
第6回	6-177	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000614	2006/2/22	8.1
第6回	6-178	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000615	2006/2/22	8.1
第6回	6-179	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000616	2006/2/22	8.1
第6回	6-180	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000617	2006/2/22	8.1
第6回	6-181	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000621	2006/2/22	8.1
第6回	6-182	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000622	2006/2/22	8.1
第6回	6-186	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000631	2006/2/24	8.1
第6回	6-187	臨床検査	C型肝炎ウイルス	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000632	2006/2/24	8.1
第5回	5-001	感染症および寄生虫症	A型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000118	2005/3/18	8.0
第5回	5-002	感染症および寄生虫症	A型肝炎	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000244	2005/7/15	8.0
第5回	5-003	感染症および寄生虫症	A型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000245	2005/7/15	8.0
第5回	5-004	感染症および寄生虫症	B型肝炎	ベネズエラ	男性	不明	1994	不明	症例報告	外国製品	05000225	2005/7/11	8.0
第5回	5-001	感染症および寄生虫症	B型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000118	2005/3/18	8.0
第5回	5-002	感染症および寄生虫症	B型肝炎	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000244	2005/7/15	8.0
第5回	5-003	感染症および寄生虫症	B型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000245	2005/7/15	8.0
第5回	5-005	感染症および寄生虫症	B型肝炎	アメリカ	男性	53	不明	不明	症例報告	当該製品	04000114	2005/3/15	7.1
第5回	5-006	感染症および寄生虫症	B型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000119	2005/3/18	8.0
第5回	5-007	感染症および寄生虫症	B型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	05000118	2005/6/9	8.0
第5回	5-008	感染症および寄生虫症	B型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000147	2005/6/20	8.0
第5回	5-004	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	1994	不明	症例報告	外国製品	05000225	2005/7/11	8.0
第5回	5-009	感染症および寄生虫症	C型肝炎	イタリア	男性	不明	1992	不明	症例報告	外国製品	04000127	2005/3/31	8.0
第5回	5-001	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000118	2005/3/18	8.0
第5回	5-002	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000244	2005/7/15	8.0
第5回	5-003	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000245	2005/7/15	8.0
第5回	5-005	感染症および寄生虫症	C型肝炎	アメリカ	男性	53	不明	不明	症例報告	当該製品	04000114	2005/3/15	7.1
第5回	5-006	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000119	2005/3/18	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考			
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)	
第5回	5-007	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	05000118	2005/6/9	8.0	
第5回	5-008	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000147	2005/6/20	8.0	
第5回	5-010	感染症および寄生虫症	C型肝炎	アメリカ	男性	52	不明	不明	症例報告	外国製品	04000103	2005/3/3	7.1	
第5回	5-011	感染症および寄生虫症	C型肝炎	アメリカ	男性	21	不明	不明	症例報告	外国製品	04000106	2005/3/3	7.1	
第5回	5-012	感染症および寄生虫症	C型肝炎	アメリカ	男性	49	不明	不明	症例報告	外国製品	04000111	2005/3/10	7.1	
第5回	5-013	感染症および寄生虫症	C型肝炎	アメリカ	男性	24	不明	不明	症例報告	当該製品	04000112	2005/3/15	7.1	
第5回	5-014	感染症および寄生虫症	C型肝炎	アメリカ	男性	35	不明	不明	症例報告	当該製品	04000113	2005/3/15	7.1	
第5回	5-015	感染症および寄生虫症	C型肝炎	アメリカ	男性	26	不明	不明	症例報告	当該製品	04000115	2005/3/15	7.1	
第5回	5-016	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000117	2005/3/17	8.0	
第5回	5-017	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000005	2005/4/25	8.0	
第5回	5-018	感染症および寄生虫症	C型肝炎	スペイン	男性	不明	不明	不明	症例報告	外国製品	05000007	2005/4/25	8.0	
第5回	5-019	感染症および寄生虫症	C型肝炎	スペイン	男性	48	不明	不明	症例報告	外国製品	05000091	2005/6/1	8.0	
第5回	5-020	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000069	2005/6/1	8.0	
第5回	5-020	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000069	2005/6/15	8.0	
第5回	5-021	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000070	2005/6/1	8.0	
第5回	5-021	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000070	2005/6/15	8.0	
第5回	5-022	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000071	2005/6/1	8.0	
第5回	5-022	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000071	2005/6/15	8.0	
第5回	5-023	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000072	2005/6/1	8.0	
第5回	5-023	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000072	2005/6/15	8.0	
第5回	5-024	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000073	2005/6/1	8.0	
第5回	5-024	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000073	2005/6/15	8.0	
第5回	5-025	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000074	2005/6/1	8.0	
第5回	5-025	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000074	2005/6/15	8.0	
第5回	5-026	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000075	2005/6/1	8.0	
第5回	5-027	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000076	2005/6/1	8.0	
第5回	5-028	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000092	2005/6/1	8.0	
第5回	5-029	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000093	2005/6/1	8.0	
第5回	5-030	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000094	2005/6/1	8.0	
第5回	5-031	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000095	2005/6/1	8.0	
第5回	5-032	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000096	2005/6/1	8.0	
第5回	5-033	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000097	2005/6/1	8.0	
第5回	5-034	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000077	2005/6/1	8.0	
第5回	5-035	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000078	2005/6/1	8.0	
第5回	5-035	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000078	2005/6/15	8.0	
第5回	5-036	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000079	2005/6/1	8.0	
第5回	5-037	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000080	2005/6/1	8.0	
第5回	5-038	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000081	2005/6/1	8.0	
第5回	5-039	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000082	2005/6/1	8.0	
第5回	5-040	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000083	2005/6/1	8.0	
第5回	5-041	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000084	2005/6/1	8.0	
第5回	5-042	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000088	2005/6/1	8.0	
第5回	5-043	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000089	2005/6/1	8.0	
第5回	5-043	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000089	2005/6/15	8.0	
第5回	5-044	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000090	2005/6/1	8.0	
第5回	5-044	感染症および寄生虫症	C型肝炎	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000090	2005/6/15	8.0	
第5回	5-045	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	05000109	2005/6/9	8.0	
第5回	5-046	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000114	2005/6/9	8.0	
第5回	5-047	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000135	2005/6/20	8.0	
第5回	5-048	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000136	2005/6/20	8.0	

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第5回	5-049	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000137	2005/6/20	8.0
第5回	5-050	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000144	2005/6/20	8.0
第5回	5-051	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000145	2005/6/20	8.0
第5回	5-052	感染症および寄生虫症	C型肝炎	コロンビア	男性	不明	不明	不明	症例報告	外国製品	05000150	2005/6/27	8.0
第5回	5-053	感染症および寄生虫症	C型肝炎	ドミニカ共和国	男性	不明	不明	不明	症例報告	外国製品	05000155	2005/6/27	8.0
第5回	5-054	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000183	2005/7/4	8.0
第5回	5-055	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000195	2005/7/8	8.0
第5回	5-056	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000196	2005/7/8	8.0
第5回	5-057	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000215	2005/7/11	8.0
第5回	5-058	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000218	2005/7/11	8.0
第5回	5-059	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000221	2005/7/11	8.0
第5回	5-060	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000223	2005/7/11	8.0
第5回	5-061	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000226	2005/7/11	8.0
第5回	5-062	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000227	2005/7/11	8.0
第5回	5-063	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000228	2005/7/11	8.0
第5回	5-064	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	不明	不明	症例報告	外国製品	05000231	2005/7/12	8.0
第5回	5-065	感染症および寄生虫症	C型肝炎	ドミニカ共和国	男性	不明	不明	不明	症例報告	外国製品	05000234	2005/7/12	8.0
第5回	5-066	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000238	2005/7/15	8.0
第5回	5-067	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000239	2005/7/15	8.0
第5回	5-068	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000243	2005/7/15	8.0
第5回	5-069	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000246	2005/7/15	8.0
第5回	5-070	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000253	2005/7/19	8.0
第5回	5-070	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000253	2005/8/2	8.0
第5回	5-071	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000262	2005/7/22	8.0
第5回	5-072	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000263	2005/7/22	8.0
第5回	5-073	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000281	2005/7/26	8.0
第5回	5-074	感染症および寄生虫症	C型肝炎	アルゼンチン	女性	不明	不明	不明	症例報告	外国製品	05000310	2005/7/27	8.0
第5回	5-075	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000311	2005/7/27	8.0
第5回	5-076	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000312	2005/7/27	8.0
第5回	5-077	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000324	2005/7/27	8.0
第5回	5-078	感染症および寄生虫症	C型肝炎	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000325	2005/7/27	8.0
第5回	5-079	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000327	2005/7/29	8.0
第5回	5-080	感染症および寄生虫症	C型肝炎	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000328	2005/7/29	8.0
第5回	5-081	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000347	2005/8/2	8.0
第5回	5-082	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000348	2005/8/2	8.0
第5回	5-083	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000349	2005/8/2	8.0
第5回	5-084	感染症および寄生虫症	C型肝炎	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000352	2005/8/2	8.0
第5回	5-085	感染症および寄生虫症	C型肝炎	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000361	2005/8/2	8.0
第5回	5-086	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000363	2005/8/2	8.0
第5回	5-087	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000364	2005/8/2	8.0
第5回	5-088	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000365	2005/8/2	8.0
第5回	5-089	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000366	2005/8/2	8.0
第5回	5-090	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000367	2005/8/3	8.0
第5回	5-091	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000369	2005/8/3	8.0
第5回	5-092	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000371	2005/8/3	8.0
第5回	5-093	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000372	2005/8/3	8.0
第5回	5-094	感染症および寄生虫症	C型肝炎	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000375	2005/8/3	8.0
第5回	5-095	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000376	2005/8/3	8.0
第5回	5-096	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000379	2005/8/3	8.0
第5回	5-097	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000380	2005/8/3	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢(歳)	発現時期(年/月/日)	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA(Ver.)
第5回	5-098	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000386	2005/8/3	8.0
第5回	5-099	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000392	2005/8/8	8.0
第5回	5-100	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000393	2005/8/8	8.0
第5回	5-101	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000404	2005/8/15	8.0
第5回	5-102	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	05000416	2005/8/26	8.0
第5回	5-103	感染症および寄生虫症	C型肝炎	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000419	2005/8/26	8.0
第5回	5-009	感染症および寄生虫症	HIV感染	イタリア	男性	不明	1985/3	不明	症例報告	外国製品	04000127	2005/3/31	8.0
第5回	5-072	感染症および寄生虫症	HIV感染	ベネズエラ	男性	不明	1986	不明	症例報告	外国製品	05000263	2005/7/22	8.0
第5回	5-080	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	1990	不明	症例報告	外国製品	05000328	2005/7/29	8.0
第5回	5-002	感染症および寄生虫症	HIV感染	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000244	2005/7/15	8.0
第5回	5-003	感染症および寄生虫症	HIV感染	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000245	2005/7/15	8.0
第5回	5-017	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000005	2005/4/25	8.0
第5回	5-018	感染症および寄生虫症	HIV感染	スペイン	男性	不明	不明	不明	症例報告	外国製品	05000007	2005/4/25	8.0
第5回	5-020	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000069	2005/6/1	8.0
第5回	5-020	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000069	2005/6/15	8.0
第5回	5-021	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000070	2005/6/1	8.0
第5回	5-021	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000070	2005/6/15	8.0
第5回	5-022	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000071	2005/6/1	8.0
第5回	5-022	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000071	2005/6/15	8.0
第5回	5-023	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000072	2005/6/1	8.0
第5回	5-023	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000072	2005/6/15	8.0
第5回	5-024	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000073	2005/6/1	8.0
第5回	5-024	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000073	2005/6/15	8.0
第5回	5-025	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000074	2005/6/15	8.0
第5回	5-025	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000074	2005/6/1	8.0
第5回	5-026	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000075	2005/6/1	8.0
第5回	5-027	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000076	2005/6/1	8.0
第5回	5-028	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000092	2005/6/1	8.0
第5回	5-029	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000093	2005/6/1	8.0
第5回	5-030	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000094	2005/6/1	8.0
第5回	5-031	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000095	2005/6/1	8.0
第5回	5-032	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000096	2005/6/1	8.0
第5回	5-033	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000097	2005/6/1	8.0
第5回	5-034	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000077	2005/6/1	8.0
第5回	5-035	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000078	2005/6/1	8.0
第5回	5-035	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000078	2005/6/15	8.0
第5回	5-036	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000079	2005/6/1	8.0
第5回	5-037	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000080	2005/6/1	8.0
第5回	5-038	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000081	2005/6/1	8.0
第5回	5-039	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000082	2005/6/1	8.0
第5回	5-040	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000083	2005/6/1	8.0
第5回	5-041	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000084	2005/6/1	8.0
第5回	5-042	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000088	2005/6/1	8.0
第5回	5-053	感染症および寄生虫症	HIV感染	ドミニカ共和国	男性	不明	不明	不明	症例報告	外国製品	05000155	2005/6/27	8.0
第5回	5-055	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000195	2005/7/8	8.0
第5回	5-056	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000196	2005/7/8	8.0
第5回	5-067	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000239	2005/7/15	8.0
第5回	5-068	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000243	2005/7/15	8.0
第5回	5-069	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000246	2005/7/15	8.0
第5回	5-071	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000262	2005/7/22	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢(歳)	発現時期(年/月/日)	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA(Ver.)
第5回	5-073	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000281	2005/7/26	8.0
第5回	5-079	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000327	2005/7/29	8.0
第5回	5-082	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000348	2005/8/2	8.0
第5回	5-083	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000349	2005/8/2	8.0
第5回	5-085	感染症および寄生虫症	HIV感染	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000361	2005/8/2	8.0
第5回	5-089	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000366	2005/8/2	8.0
第5回	5-096	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000379	2005/8/3	8.0
第5回	5-097	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000380	2005/8/3	8.0
第5回	5-100	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000393	2005/8/8	8.0
第5回	5-101	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000404	2005/8/15	8.0
第5回	5-103	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000419	2005/8/26	8.0
第5回	5-104	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000004	2005/4/25	8.0
第5回	5-105	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000006	2005/4/25	8.0
第5回	5-106	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	死亡	症例報告	外国製品	05000008	2005/4/28	8.0
第5回	5-107	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000012	2005/5/12	8.0
第5回	5-108	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	死亡	症例報告	外国製品	05000013	2005/5/12	8.0
第5回	5-109	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000015	2005/5/23	8.0
第5回	5-110	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000016	2005/5/23	8.0
第5回	5-111	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000017	2005/5/23	8.0
第5回	5-112	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000018	2005/5/23	8.0
第5回	5-113	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000019	2005/5/23	8.0
第5回	5-114	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000020	2005/5/23	8.0
第5回	5-115	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000021	2005/5/23	8.0
第5回	5-116	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000022	2005/5/23	8.0
第5回	5-117	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000023	2005/5/23	8.0
第5回	5-118	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000025	2005/5/26	8.0
第5回	5-119	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000026	2005/5/26	8.0
第5回	5-120	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	死亡	症例報告	外国製品	05000027	2005/5/26	8.0
第5回	5-121	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000053	2005/5/30	8.0
第5回	5-122	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000054	2005/5/30	8.0
第5回	5-123	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000056	2005/5/30	8.0
第5回	5-124	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000057	2005/5/30	8.0
第5回	5-125	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000058	2005/5/30	8.0
第5回	5-126	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000061	2005/5/30	8.0
第5回	5-127	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000062	2005/5/30	8.0
第5回	5-128	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000063	2005/5/30	8.0
第5回	5-129	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000064	2005/5/30	8.0
第5回	5-130	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000065	2005/5/30	8.0
第5回	5-131	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000066	2005/5/30	8.0
第5回	5-132	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000067	2005/5/30	8.0
第5回	5-133	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000068	2005/5/30	8.0
第5回	5-134	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000098	2005/6/1	8.0
第5回	5-135	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	死亡	症例報告	外国製品	05000099	2005/6/1	8.0
第5回	5-136	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000100	2005/6/1	8.0
第5回	5-137	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	死亡	症例報告	外国製品	05000102	2005/6/1	8.0
第5回	5-138	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000103	2005/6/2	8.0
第5回	5-139	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000104	2005/6/2	8.0
第5回	5-140	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	死亡	症例報告	外国製品	05000105	2005/6/2	8.0
第5回	5-141	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000085	2005/6/1	8.0
第5回	5-142	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000086	2005/6/1	8.0

別紙様式第4

感染症発生症例一覧

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		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)	
第5回	5-142	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000086	2005/6/15	8.0	
第5回	5-143	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000087	2005/6/1	8.0	
第5回	5-143	感染症および寄生虫症	HIV感染	南アフリカ	男性	不明	不明	不明	症例報告	外国製品	05000087	2005/6/15	8.0	
第5回	5-144	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000030	2005/5/30	8.0	
第5回	5-144	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000030	2005/6/15	8.0	
第5回	5-145	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000031	2005/5/30	8.0	
第5回	5-145	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000031	2005/6/15	8.0	
第5回	5-146	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000032	2005/5/30	8.0	
第5回	5-146	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000032	2005/6/15	8.0	
第5回	5-147	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000033	2005/5/30	8.0	
第5回	5-148	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000034	2005/5/30	8.0	
第5回	5-149	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000035	2005/5/30	8.0	
第5回	5-150	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000036	2005/5/30	8.0	
第5回	5-151	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000111	2005/6/9	8.0	
第5回	5-152	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000112	2005/6/9	8.0	
第5回	5-153	感染症および寄生虫症	HIV感染	香港	男性	4	不明	不明	症例報告	外国製品	05000113	2005/6/9	8.0	
第5回	5-154	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000037	2005/5/30	8.0	
第5回	5-155	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000038	2005/5/30	8.0	
第5回	5-156	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000039	2005/5/30	8.0	
第5回	5-157	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000040	2005/5/30	8.0	
第5回	5-158	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000116	2005/6/9	8.0	
第5回	5-159	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000041	2005/5/30	8.0	
第5回	5-160	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000042	2005/5/30	8.0	
第5回	5-161	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000043	2005/5/30	8.0	
第5回	5-162	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000044	2005/5/30	8.0	
第5回	5-162	感染症および寄生虫症	HIV感染	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000044	2005/6/27	8.0	
第5回	5-163	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000045	2005/5/30	8.0	
第5回	5-163	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000045	2005/6/15	8.0	
第5回	5-164	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000046	2005/5/30	8.0	
第5回	5-165	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	不明	症例報告	外国製品	05000047	2005/5/30	8.0	
第5回	5-166	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000048	2005/5/30	8.0	
第5回	5-167	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000049	2005/5/30	8.0	
第5回	5-167	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000049	2005/6/15	8.0	
第5回	5-168	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000050	2005/5/30	8.0	
第5回	5-168	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000050	2005/6/15	8.0	
第5回	5-169	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000051	2005/5/30	8.0	
第5回	5-169	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000051	2005/6/15	8.0	
第5回	5-170	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000052	2005/5/30	8.0	
第5回	5-170	感染症および寄生虫症	HIV感染	香港	男性	不明	不明	死亡	症例報告	外国製品	05000052	2005/6/15	8.0	
第5回	5-171	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000119	2005/6/13	8.0	
第5回	5-172	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000120	2005/6/13	8.0	
第5回	5-173	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000121	2005/6/13	8.0	
第5回	5-174	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000122	2005/6/13	8.0	
第5回	5-175	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000124	2005/6/13	8.0	
第5回	5-176	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000126	2005/6/15	8.0	
第5回	5-177	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000129	2005/6/15	8.0	
第5回	5-178	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000133	2005/6/20	8.0	
第5回	5-179	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000134	2005/6/20	8.0	
第5回	5-180	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000148	2005/6/20	8.0	
第5回	5-181	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000156	2005/6/27	8.0	

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢(歳)	発現時期(年/月/日)	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第5回	5-182	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000159	2005/6/27	8.0
第5回	5-183	感染症および寄生虫症	HIV感染	チリ	男性	不明	不明	不明	症例報告	外国製品	05000161	2005/6/27	8.0
第5回	5-184	感染症および寄生虫症	HIV感染	チリ	男性	不明	不明	不明	症例報告	外国製品	05000162	2005/6/27	8.0
第5回	5-185	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000164	2005/6/27	8.0
第5回	5-186	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000165	2005/6/27	8.0
第5回	5-187	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000167	2005/6/27	8.0
第5回	5-188	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000171	2005/6/30	8.0
第5回	5-189	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000173	2005/6/30	8.0
第5回	5-190	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000175	2005/6/30	8.0
第5回	5-191	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000176	2005/6/30	8.0
第5回	5-192	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000181	2005/6/30	8.0
第5回	5-193	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000182	2005/6/30	8.0
第5回	5-193	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000182	2005/8/8	8.0
第5回	5-194	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000185	2005/7/4	8.0
第5回	5-195	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000186	2005/7/4	8.0
第5回	5-196	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000187	2005/7/4	8.0
第5回	5-197	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000189	2005/7/4	8.0
第5回	5-198	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000190	2005/7/4	8.0
第5回	5-199	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000191	2005/7/4	8.0
第5回	5-200	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000194	2005/7/4	8.0
第5回	5-201	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000202	2005/7/8	8.0
第5回	5-202	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000203	2005/7/8	8.0
第5回	5-203	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000204	2005/7/8	8.0
第5回	5-204	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000206	2005/7/8	8.0
第5回	5-205	感染症および寄生虫症	HIV感染	コロンビア	男性	不明	不明	不明	症例報告	外国製品	05000209	2005/7/8	8.0
第5回	5-206	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000212	2005/7/8	8.0
第5回	5-207	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000213	2005/7/11	8.0
第5回	5-208	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000214	2005/7/11	8.0
第5回	5-209	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000219	2005/7/11	8.0
第5回	5-210	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000230	2005/7/11	8.0
第5回	5-211	感染症および寄生虫症	HIV感染	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000232	2005/7/12	8.0
第5回	5-212	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000233	2005/7/12	8.0
第5回	5-213	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000235	2005/7/12	8.0
第5回	5-214	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000237	2005/7/12	8.0
第5回	5-215	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000240	2005/7/15	8.0
第5回	5-216	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000241	2005/7/15	8.0
第5回	5-217	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000242	2005/7/15	8.0
第5回	5-218	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000248	2005/7/15	8.0
第5回	5-219	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000249	2005/7/15	8.0
第5回	5-220	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000250	2005/7/15	8.0
第5回	5-221	感染症および寄生虫症	HIV感染	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000251	2005/7/15	8.0
第5回	5-222	感染症および寄生虫症	HIV感染	アルゼンチン	女性	不明	不明	死亡	症例報告	外国製品	05000252	2005/7/19	8.0
第5回	5-223	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000254	2005/7/19	8.0
第5回	5-224	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000256	2005/7/19	8.0
第5回	5-225	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000257	2005/7/22	8.0
第5回	5-226	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000258	2005/7/22	8.0
第5回	5-227	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000259	2005/7/22	8.0
第5回	5-228	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000261	2005/7/22	8.0
第5回	5-229	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000264	2005/7/22	8.0
第5回	5-230	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000267	2005/7/22	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第5回	5-231	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000274	2005/7/26	8.0
第5回	5-232	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000276	2005/7/26	8.0
第5回	5-233	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000279	2005/7/26	8.0
第5回	5-234	感染症および寄生虫症	HIV感染	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000297	2005/7/26	8.0
第5回	5-235	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000299	2005/7/26	8.0
第5回	5-236	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000302	2005/7/26	8.0
第5回	5-237	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000282	2005/7/26	8.0
第5回	5-238	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	死亡	症例報告	外国製品	05000283	2005/7/26	8.0
第5回	5-239	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000284	2005/7/26	8.0
第5回	5-240	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000285	2005/7/26	8.0
第5回	5-241	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000286	2005/7/26	8.0
第5回	5-242	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000287	2005/7/26	8.0
第5回	5-243	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000288	2005/7/26	8.0
第5回	5-244	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000292	2005/7/26	8.0
第5回	5-245	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000293	2005/7/26	8.0
第5回	5-246	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000295	2005/7/26	8.0
第5回	5-247	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000296	2005/7/26	8.0
第5回	5-248	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	死亡	症例報告	外国製品	05000305	2005/7/26	8.0
第5回	5-249	感染症および寄生虫症	HIV感染	アルゼンチン	女性	不明	不明	不明	症例報告	外国製品	05000308	2005/7/26	8.0
第5回	5-250	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000314	2005/7/27	8.0
第5回	5-251	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000315	2005/7/27	8.0
第5回	5-252	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000316	2005/7/27	8.0
第5回	5-253	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000317	2005/7/27	8.0
第5回	5-254	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000320	2005/7/27	8.0
第5回	5-255	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000321	2005/7/27	8.0
第5回	5-256	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000334	2005/7/29	8.0
第5回	5-257	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000335	2005/7/29	8.0
第5回	5-258	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000342	2005/8/2	8.0
第5回	5-259	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000350	2005/8/2	8.0
第5回	5-260	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000353	2005/8/2	8.0
第5回	5-261	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000356	2005/8/2	8.0
第5回	5-262	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000358	2005/8/2	8.0
第5回	5-263	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000360	2005/8/2	8.0
第5回	5-264	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000368	2005/8/3	8.0
第5回	5-265	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000383	2005/8/3	8.0
第5回	5-266	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000387	2005/8/3	8.0
第5回	5-267	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000390	2005/8/8	8.0
第5回	5-268	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000396	2005/8/10	8.0
第5回	5-269	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000397	2005/8/10	8.0
第5回	5-270	感染症および寄生虫症	HIV感染	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000401	2005/8/10	8.0
第5回	5-271	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000403	2005/8/11	8.0
第5回	5-272	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000407	2005/8/23	8.0
第5回	5-273	感染症および寄生虫症	HIV感染	ニュージーランド	男性	不明	不明	不明	症例報告	外国製品	05000408	2005/8/23	8.0
第5回	5-274	感染症および寄生虫症	HIV感染	ニュージーランド	男性	不明	不明	不明	症例報告	外国製品	05000410	2005/8/24	8.0
第5回	5-275	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000415	2005/8/24	8.0
第5回	5-276	感染症および寄生虫症	HIV感染	パナマ	男性	不明	不明	死亡	症例報告	外国製品	05000422	2005/8/30	8.0
第5回	5-277	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000423	2005/8/30	8.0
第5回	5-278	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000424	2005/8/30	8.0
第5回	5-279	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000425	2005/8/30	8.0
第5回	5-280	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000427	2005/8/30	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第5回	5-281	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000428	2005/8/30	8.0
第5回	5-282	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000429	2005/8/30	8.0
第5回	5-283	感染症および寄生虫症	HIV感染	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000430	2005/8/30	8.0
第5回	5-284	感染症および寄生虫症	HIV感染	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000431	2005/8/30	8.0
第5回	5-285	感染症および寄生虫症	後天性免疫不全症候群	イギリス	男性	不明	2002	不明	症例報告	外国製品	04000128	2005/3/31	8.0
第5回	5-115	感染症および寄生虫症	後天性免疫不全症候群	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000021	2005/5/23	8.0
第5回	5-153	感染症および寄生虫症	後天性免疫不全症候群	香港	男性	4	不明	不明	症例報告	外国製品	05000113	2005/6/9	8.0
第5回	5-286	肝胆道系障害	肝炎	ブラジル	男性	13	不明	不明	症例報告	外国製品	05000273	2005/7/22	8.0
第5回	5-287	臨床検査	B型肝炎ウイルス	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000107	2005/3/3	7.1
第5回	5-288	臨床検査	B型肝炎ウイルス	イギリス	男性	25	不明	不明	症例報告	外国製品	05000003	2005/4/18	8.0
第5回	5-285	臨床検査	C型肝炎ウイルス	イギリス	男性	不明	1990	不明	症例報告	外国製品	04000128	2005/3/31	8.0
第5回	5-107	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000012	2005/7/29	8.0
第5回	5-108	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000013	2005/5/12	8.0
第5回	5-109	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000015	2005/5/23	8.0
第5回	5-110	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000016	2005/5/23	8.0
第5回	5-111	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000017	2005/5/23	8.0
第5回	5-112	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000018	2005/5/23	8.0
第5回	5-113	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000019	2005/5/23	8.0
第5回	5-114	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000020	2005/5/23	8.0
第5回	5-115	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000021	2005/5/23	8.0
第5回	5-116	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000022	2005/5/23	8.0
第5回	5-117	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000023	2005/5/23	8.0
第5回	5-118	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000025	2005/5/26	8.0
第5回	5-119	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000026	2005/5/26	8.0
第5回	5-120	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000027	2005/5/26	8.0
第5回	5-121	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000053	2005/5/30	8.0
第5回	5-122	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000054	2005/5/30	8.0
第5回	5-123	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000056	2005/5/30	8.0
第5回	5-124	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000057	2005/5/30	8.0
第5回	5-125	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000058	2005/5/30	8.0
第5回	5-126	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000061	2005/5/30	8.0
第5回	5-127	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000062	2005/5/30	8.0
第5回	5-128	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000063	2005/5/30	8.0
第5回	5-129	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000064	2005/5/30	8.0
第5回	5-130	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000065	2005/5/30	8.0
第5回	5-131	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000066	2005/5/30	8.0
第5回	5-132	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000067	2005/5/30	8.0
第5回	5-133	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000068	2005/5/30	8.0
第5回	5-134	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000098	2005/6/1	8.0
第5回	5-135	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000099	2005/6/1	8.0
第5回	5-136	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000100	2005/6/1	8.0
第5回	5-138	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000103	2005/6/2	8.0
第5回	5-139	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000104	2005/6/2	8.0
第5回	5-140	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000105	2005/6/2	8.0
第5回	5-144	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000030	2005/5/30	8.0
第5回	5-144	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000030	2005/6/15	8.0
第5回	5-145	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000031	2005/5/30	8.0
第5回	5-145	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000031	2005/6/15	8.0
第5回	5-146	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000032	2005/5/30	8.0
第5回	5-146	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000032	2005/6/15	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第5回	5-147	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000033	2005/5/30	8.0
第5回	5-148	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000034	2005/5/30	8.0
第5回	5-149	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000035	2005/5/30	8.0
第5回	5-151	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000111	2005/6/9	8.0
第5回	5-152	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000112	2005/6/9	8.0
第5回	5-153	臨床検査	C型肝炎ウイルス	香港	男性	4	不明	不明	症例報告	外国製品	05000113	2005/6/9	8.0
第5回	5-154	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000037	2005/5/30	8.0
第5回	5-156	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000039	2005/5/30	8.0
第5回	5-157	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000040	2005/5/30	8.0
第5回	5-158	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000116	2005/6/9	8.0
第5回	5-159	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000041	2005/5/30	8.0
第5回	5-161	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000043	2005/5/30	8.0
第5回	5-162	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000044	2005/5/30	8.0
第5回	5-162	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000044	2005/6/27	8.0
第5回	5-163	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000045	2005/5/30	8.0
第5回	5-163	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000045	2005/6/15	8.0
第5回	5-164	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000046	2005/5/30	8.0
第5回	5-165	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	不明	症例報告	外国製品	05000047	2005/5/30	8.0
第5回	5-166	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000048	2005/5/30	8.0
第5回	5-167	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000049	2005/5/30	8.0
第5回	5-167	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000049	2005/6/15	8.0
第5回	5-168	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000050	2005/5/30	8.0
第5回	5-168	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000050	2005/6/15	8.0
第5回	5-169	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000051	2005/5/30	8.0
第5回	5-169	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000051	2005/6/15	8.0
第5回	5-170	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000052	2005/5/30	8.0
第5回	5-170	臨床検査	C型肝炎ウイルス	香港	男性	不明	不明	死亡	症例報告	外国製品	05000052	2005/6/15	8.0
第5回	5-173	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000121	2005/6/13	8.0
第5回	5-174	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000122	2005/6/13	8.0
第5回	5-177	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000129	2005/6/15	8.0
第5回	5-180	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000148	2005/6/20	8.0
第5回	5-181	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000156	2005/6/27	8.0
第5回	5-182	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000159	2005/6/27	8.0
第5回	5-185	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000164	2005/6/27	8.0
第5回	5-186	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000165	2005/6/27	8.0
第5回	5-187	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000167	2005/6/27	8.0
第5回	5-187	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000167	2005/8/18	8.0
第5回	5-188	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000171	2005/6/30	8.0
第5回	5-189	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000173	2005/6/30	8.0
第5回	5-190	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000175	2005/6/30	8.0
第5回	5-191	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000176	2005/6/30	8.0
第5回	5-192	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000181	2005/6/30	8.0
第5回	5-194	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000185	2005/7/4	8.0
第5回	5-195	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000186	2005/7/4	8.0
第5回	5-196	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000187	2005/7/4	8.0
第5回	5-197	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000189	2005/7/4	8.0
第5回	5-198	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000190	2005/7/4	8.0
第5回	5-200	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000194	2005/7/4	8.0
第5回	5-201	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000202	2005/7/8	8.0
第5回	5-202	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000203	2005/7/8	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第5回	5-203	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000204	2005/7/8	8.0
第5回	5-204	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000206	2005/7/8	8.0
第5回	5-205	臨床検査	C型肝炎ウイルス	コロンビア	男性	不明	不明	不明	症例報告	外国製品	05000209	2005/7/8	8.0
第5回	5-207	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000213	2005/7/11	8.0
第5回	5-208	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000214	2005/7/11	8.0
第5回	5-209	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000219	2005/7/11	8.0
第5回	5-210	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000230	2005/7/11	8.0
第5回	5-211	臨床検査	C型肝炎ウイルス	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000232	2005/7/12	8.0
第5回	5-213	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000235	2005/7/12	8.0
第5回	5-215	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000240	2005/7/15	8.0
第5回	5-216	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000241	2005/7/15	8.0
第5回	5-217	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000242	2005/7/15	8.0
第5回	5-218	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000248	2005/7/15	8.0
第5回	5-219	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000249	2005/7/15	8.0
第5回	5-220	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000250	2005/7/15	8.0
第5回	5-221	臨床検査	C型肝炎ウイルス	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000251	2005/7/15	8.0
第5回	5-223	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000254	2005/7/19	8.0
第5回	5-224	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000256	2005/7/19	8.0
第5回	5-225	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000257	2005/7/22	8.0
第5回	5-226	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000258	2005/7/22	8.0
第5回	5-227	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000259	2005/7/22	8.0
第5回	5-228	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000261	2005/7/22	8.0
第5回	5-229	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000264	2005/7/22	8.0
第5回	5-230	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000267	2005/7/22	8.0
第5回	5-231	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000274	2005/7/26	8.0
第5回	5-232	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000276	2005/7/26	8.0
第5回	5-233	臨床検査	C型肝炎ウイルス	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000279	2005/7/26	8.0
第5回	5-234	臨床検査	C型肝炎ウイルス	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000297	2005/7/26	8.0
第5回	5-235	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000299	2005/7/26	8.0
第5回	5-236	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000302	2005/7/26	8.0
第5回	5-237	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000282	2005/7/26	8.0
第5回	5-239	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000284	2005/7/26	8.0
第5回	5-241	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000286	2005/7/26	8.0
第5回	5-242	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000287	2005/7/26	8.0
第5回	5-243	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000288	2005/7/26	8.0
第5回	5-245	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000293	2005/7/26	8.0
第5回	5-249	臨床検査	C型肝炎ウイルス	アルゼンチン	女性	不明	不明	不明	症例報告	外国製品	05000308	2005/7/26	8.0
第5回	5-250	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000314	2005/7/27	8.0
第5回	5-251	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000315	2005/7/27	8.0
第5回	5-252	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000316	2005/7/27	8.0
第5回	5-253	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000317	2005/7/27	8.0
第5回	5-254	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000320	2005/7/27	8.0
第5回	5-255	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000321	2005/7/27	8.0
第5回	5-256	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000334	2005/7/29	8.0
第5回	5-258	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000342	2005/8/2	8.0
第5回	5-260	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000353	2005/8/2	8.0
第5回	5-262	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000358	2005/8/2	8.0
第5回	5-265	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000383	2005/8/3	8.0
第5回	5-266	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000387	2005/8/3	8.0
第5回	5-268	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000396	2005/8/10	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考			
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)	
第5回	5-269	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000397	2005/8/10	8.0	
第5回	5-270	臨床検査	C型肝炎ウイルス	ベネズエラ	男性	不明	不明	死亡	症例報告	外国製品	05000401	2005/8/10	8.0	
第5回	5-271	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000403	2005/8/11	8.0	
第5回	5-272	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000407	2005/8/23	8.0	
第5回	5-273	臨床検査	C型肝炎ウイルス	ニュージーランド	男性	不明	不明	不明	症例報告	外国製品	05000408	2005/8/23	8.0	
第5回	5-274	臨床検査	C型肝炎ウイルス	ニュージーランド	男性	不明	不明	不明	症例報告	外国製品	05000410	2005/8/24	8.0	
第5回	5-275	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000415	2005/8/24	8.0	
第5回	5-277	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000423	2005/8/30	8.0	
第5回	5-278	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000424	2005/8/30	8.0	
第5回	5-279	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000425	2005/8/30	8.0	
第5回	5-280	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000427	2005/8/30	8.0	
第5回	5-282	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000429	2005/8/30	8.0	
第5回	5-283	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000430	2005/8/30	8.0	
第5回	5-284	臨床検査	C型肝炎ウイルス	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000431	2005/8/30	8.0	
第5回	5-287	臨床検査	C型肝炎ウイルス	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000107	2005/3/3	7.1	
第5回	5-288	臨床検査	C型肝炎ウイルス	イギリス	男性	25	不明	不明	症例報告	外国製品	05000003	2005/4/18	8.0	
第5回	5-289	臨床検査	C型肝炎ウイルス	イギリス	男性	57	不明	不明	症例報告	外国製品	04000102	2005/3/3	7.1	
第5回	5-290	臨床検査	C型肝炎ウイルス	イギリス	男性	58	不明	不明	症例報告	外国製品	04000104	2005/3/3	7.1	
第5回	5-291	臨床検査	C型肝炎ウイルス	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000120	2005/3/18	8.0	
第5回	5-292	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000024	2005/5/26	8.0	
第5回	5-293	臨床検査	C型肝炎ウイルス	アルゼンチン	男性	不明	不明	不明	症例報告	外国製品	05000055	2005/5/30	8.0	
第5回	5-294	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000059	2005/5/30	8.0	
第5回	5-295	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000060	2005/5/30	8.0	
第5回	5-296	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000101	2005/6/1	8.0	
第5回	5-297	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000108	2005/6/7	8.0	
第5回	5-298	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000110	2005/6/9	8.0	
第5回	5-299	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000115	2005/6/9	8.0	
第5回	5-300	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000117	2005/6/9	8.0	
第5回	5-301	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000123	2005/6/13	8.0	
第5回	5-302	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000127	2005/6/15	8.0	
第5回	5-303	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000128	2005/6/15	8.0	
第5回	5-304	臨床検査	C型肝炎ウイルス	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000130	2005/6/15	8.0	
第5回	5-305	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000131	2005/6/15	8.0	
第5回	5-306	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000132	2005/6/15	8.0	
第5回	5-307	臨床検査	C型肝炎ウイルス	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000138	2005/6/20	8.0	
第5回	5-308	臨床検査	C型肝炎ウイルス	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000139	2005/6/20	8.0	
第5回	5-309	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000140	2005/6/20	8.0	
第5回	5-310	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000141	2005/6/20	8.0	
第5回	5-311	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000142	2005/6/20	8.0	
第5回	5-312	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000143	2005/6/20	8.0	
第5回	5-313	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000146	2005/6/20	8.0	
第5回	5-314	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000149	2005/6/27	8.0	
第5回	5-315	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000151	2005/6/27	8.0	
第5回	5-316	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000152	2005/6/27	8.0	
第5回	5-317	臨床検査	C型肝炎ウイルス	パナマ		不明	不明	不明	症例報告	外国製品	05000153	2005/6/27	8.0	
第5回	5-318	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000154	2005/6/27	8.0	
第5回	5-319	臨床検査	C型肝炎ウイルス	カナダ	男性	不明	不明	不明	症例報告	外国製品	05000157	2005/6/27	8.0	
第5回	5-320	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000158	2005/6/27	8.0	
第5回	5-321	臨床検査	C型肝炎ウイルス	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000160	2005/6/27	8.0	
第5回	5-322	臨床検査	C型肝炎ウイルス	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000163	2005/6/27	8.0	

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第5回	5-323	臨床検査	C型肝炎ウイルス	ドミニカ共和国	男性	不明	不明	不明	症例報告	外国製品	05000166	2005/6/27	8.0
第5回	5-324	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000170	2005/6/30	8.0
第5回	5-325	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000172	2005/6/30	8.0
第5回	5-326	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000174	2005/6/30	8.0
第5回	5-327	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000177	2005/6/30	8.0
第5回	5-328	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000178	2005/6/30	8.0
第5回	5-329	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000179	2005/6/30	8.0
第5回	5-330	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000180	2005/6/30	8.0
第5回	5-331	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000184	2005/7/4	8.0
第5回	5-332	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000188	2005/7/4	8.0
第5回	5-333	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000192	2005/7/4	8.0
第5回	5-334	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000193	2005/7/4	8.0
第5回	5-335	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000197	2005/7/8	8.0
第5回	5-336	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000198	2005/7/8	8.0
第5回	5-337	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000199	2005/7/8	8.0
第5回	5-338	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000200	2005/7/8	8.0
第5回	5-339	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000201	2005/7/8	8.0
第5回	5-340	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000205	2005/7/8	8.0
第5回	5-341	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000207	2005/7/8	8.0
第5回	5-342	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000208	2005/7/8	8.0
第5回	5-343	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000210	2005/7/8	8.0
第5回	5-344	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000211	2005/7/8	8.0
第5回	5-345	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000216	2005/7/11	8.0
第5回	5-346	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000217	2005/7/11	8.0
第5回	5-347	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000220	2005/7/11	8.0
第5回	5-348	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000222	2005/7/11	8.0
第5回	5-349	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000224	2005/7/11	8.0
第5回	5-350	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000229	2005/7/11	8.0
第5回	5-351	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000236	2005/7/12	8.0
第5回	5-352	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000247	2005/7/15	8.0
第5回	5-353	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000255	2005/7/19	8.0
第5回	5-354	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000260	2005/7/22	8.0
第5回	5-355	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000265	2005/7/22	8.0
第5回	5-356	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000266	2005/7/22	8.0
第5回	5-357	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000268	2005/7/22	8.0
第5回	5-358	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000269	2005/7/22	8.0
第5回	5-359	臨床検査	C型肝炎ウイルス	ベネズエラ	男性	不明	不明	不明	症例報告	外国製品	05000270	2005/7/22	8.0
第5回	5-360	臨床検査	C型肝炎ウイルス	コスタリカ	男性	不明	不明	不明	症例報告	外国製品	05000271	2005/7/22	8.0
第5回	5-361	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000275	2005/7/26	8.0
第5回	5-362	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000277	2005/7/26	8.0
第5回	5-363	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000278	2005/7/26	8.0
第5回	5-364	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000298	2005/7/26	8.0
第5回	5-365	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000300	2005/7/26	8.0
第5回	5-366	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000301	2005/7/26	8.0
第5回	5-367	臨床検査	C型肝炎ウイルス	ブラジル	女性	不明	不明	不明	症例報告	外国製品	05000303	2005/7/26	8.0
第5回	5-368	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000304	2005/7/26	8.0
第5回	5-369	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000280	2005/7/26	8.0
第5回	5-370	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000289	2005/7/26	8.0
第5回	5-371	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000290	2005/7/26	8.0
第5回	5-372	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000291	2005/7/26	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第5回	5-373	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000294	2005/7/26	8.0
第5回	5-374	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000306	2005/7/26	8.0
第5回	5-375	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000307	2005/7/26	8.0
第5回	5-376	臨床検査	C型肝炎ウイルス	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000309	2005/7/27	8.0
第5回	5-377	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000313	2005/7/27	8.0
第5回	5-378	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000318	2005/7/27	8.0
第5回	5-379	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000322	2005/7/27	8.0
第5回	5-380	臨床検査	C型肝炎ウイルス	アルゼンチン	女性	不明	不明	不明	症例報告	外国製品	05000323	2005/7/27	8.0
第5回	5-381	臨床検査	C型肝炎ウイルス	アメリカ	男性	41	不明	不明	症例報告	外国製品	05000326	2005/7/27	8.0
第5回	5-382	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000329	2005/7/29	8.0
第5回	5-383	臨床検査	C型肝炎ウイルス	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000330	2005/7/29	8.0
第5回	5-384	臨床検査	C型肝炎ウイルス	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000331	2005/7/29	8.0
第5回	5-385	臨床検査	C型肝炎ウイルス	アルゼンチン	女性	不明	不明	不明	症例報告	外国製品	05000332	2005/7/29	8.0
第5回	5-386	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000333	2005/7/29	8.0
第5回	5-387	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000336	2005/7/29	8.0
第5回	5-388	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000337	2005/7/29	8.0
第5回	5-389	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000338	2005/7/29	8.0
第5回	5-390	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000339	2005/7/29	8.0
第5回	5-391	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000343	2005/8/2	8.0
第5回	5-392	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000344	2005/8/2	8.0
第5回	5-393	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	死亡	症例報告	外国製品	05000345	2005/8/2	8.0
第5回	5-394	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000346	2005/8/2	8.0
第5回	5-395	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000351	2005/8/2	8.0
第5回	5-396	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000354	2005/8/2	8.0
第5回	5-397	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000355	2005/8/2	8.0
第5回	5-398	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000357	2005/8/2	8.0
第5回	5-399	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000359	2005/8/2	8.0
第5回	5-400	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000362	2005/8/2	8.0
第5回	5-401	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000370	2005/8/3	8.0
第5回	5-402	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000373	2005/8/3	8.0
第5回	5-403	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000374	2005/8/3	8.0
第5回	5-404	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000377	2005/8/3	8.0
第5回	5-405	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000378	2005/8/3	8.0
第5回	5-406	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000381	2005/8/3	8.0
第5回	5-407	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000382	2005/8/3	8.0
第5回	5-408	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000384	2005/8/3	8.0
第5回	5-409	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000385	2005/8/3	8.0
第5回	5-410	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000388	2005/8/8	8.0
第5回	5-411	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000389	2005/8/8	8.0
第5回	5-412	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000391	2005/8/8	8.0
第5回	5-413	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000395	2005/8/10	8.0
第5回	5-414	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000398	2005/8/10	8.0
第5回	5-415	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000399	2005/8/10	8.0
第5回	5-416	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000400	2005/8/10	8.0
第5回	5-417	臨床検査	C型肝炎ウイルス	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000405	2005/8/18	8.0
第5回	5-418	臨床検査	C型肝炎ウイルス	ニュージーランド	男性	不明	不明	不明	症例報告	外国製品	05000409	2005/8/24	8.0
第5回	5-419	臨床検査	C型肝炎ウイルス	オーストラリア	男性	不明	不明	不明	症例報告	外国製品	05000411	2005/8/24	8.0
第5回	5-420	臨床検査	C型肝炎ウイルス	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000412	2005/8/24	8.0
第5回	5-421	臨床検査	C型肝炎ウイルス	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000413	2005/8/24	8.0
第5回	5-422	臨床検査	C型肝炎ウイルス	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000414	2005/8/24	8.0

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	備考		
		器官別大分類	基本語								識別番号	報告日	MedDRA (Ver.)
第5回	5-423	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000418	2005/8/26	8.0
第5回	5-424	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000420	2005/8/26	8.0
第5回	5-425	臨床検査	C型肝炎ウイルス	ニュージーランド	男性	不明	不明	不明	症例報告	外国製品	05000421	2005/8/30	8.0
第5回	5-426	臨床検査	C型肝炎ウイルス	パナマ	男性	不明	不明	不明	症例報告	外国製品	05000426	2005/8/30	8.0
第5回	5-427	臨床検査	C型肝炎ウイルス	ブラジル	男性	不明	不明	不明	症例報告	外国製品	05000432	2005/8/30	8.0
第5回	5-001	臨床検査	HIV検査陽性	イギリス	男性	不明	1986/3	不明	症例報告	外国製品	04000118	2005/3/18	8.0
第5回	5-288	臨床検査	HIV検査陽性	イギリス	男性	25	1985/10/25	不明	症例報告	外国製品	05000003	2005/4/18	8.0
第5回	5-006	臨床検査	HIV検査陽性	イギリス	男性	不明	1985	不明	症例報告	外国製品	04000119	2005/3/18	8.0
第5回	5-287	臨床検査	HIV検査陽性	イギリス	男性	不明	1984/2/16	不明	症例報告	外国製品	04000107	2005/3/3	7.1
第5回	5-285	臨床検査	HIV検査陽性	イギリス	男性	不明	1983/12	不明	症例報告	外国製品	04000128	2005/3/31	8.0
第4回	4-01	感染症および寄生虫症	A型肝炎	イギリス	男性	29	不明	不明	症例報告	外国製品	04000077	2004/10/8	7.1
第4回	4-01	感染症および寄生虫症	B型肝炎	イギリス	男性	29	不明	不明	症例報告	外国製品	04000077	2004/10/8	7.1
第4回	4-02	感染症および寄生虫症	B型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000078	2004/10/8	7.1
第4回	4-03	感染症および寄生虫症	B型肝炎	イギリス	男性	11	不明	不明	症例報告	外国製品	04000081	2004/10/8	7.1
第4回	4-04	感染症および寄生虫症	C型肝炎	イギリス	男性	15	1990/7	不明	症例報告	外国製品	04000076	2004/10/8	7.1
第4回	4-01	感染症および寄生虫症	C型肝炎	イギリス	男性	29	不明	不明	症例報告	外国製品	04000077	2004/10/8	7.1
第4回	4-02	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000078	2004/10/8	7.1
第4回	4-03	感染症および寄生虫症	C型肝炎	イギリス	男性	11	不明	不明	症例報告	外国製品	04000081	2004/10/8	7.1
第4回	4-05	感染症および寄生虫症	C型肝炎	イギリス	男性	31	不明	不明	症例報告	外国製品	04000080	2004/10/8	7.1
第4回	4-06	感染症および寄生虫症	C型肝炎	イギリス	男性	34	不明	不明	症例報告	外国製品	04000079	2004/10/8	7.1
第4回	4-07	感染症および寄生虫症	C型肝炎	アメリカ	男性	25	不明	不明	症例報告	当該製品	04000100	2005/2/24	7.1
第4回	4-08	感染症および寄生虫症	C型肝炎	アメリカ	男性	41	不明	不明	症例報告	当該製品	04000099	2005/2/24	7.1
第4回	4-09	感染症および寄生虫症	C型肝炎	アメリカ	男性	27	不明	不明	症例報告	外国製品	04000098	2005/2/24	7.1
第4回	4-10	感染症および寄生虫症	C型肝炎	アメリカ	女性	22	不明	不明	症例報告	外国製品	04000095	2005/2/21	7.1
第4回	4-11	感染症および寄生虫症	C型肝炎	アメリカ	男性	17	不明	不明	症例報告	外国製品	04000094	2005/2/21	7.1
第4回	4-12	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	不明	不明	症例報告	外国製品	04000075	2004/10/8	7.1
第4回	4-13	感染症および寄生虫症	HIV感染	イギリス	男性	32	1988/8	不明	症例報告	外国製品	04000074	2004/10/8	7.1
第4回	4-06	感染症および寄生虫症	HIV感染	イギリス	男性	34	1985/1/9	不明	症例報告	外国製品	04000079	2004/10/8	7.1
第4回	4-01	感染症および寄生虫症	HIV感染	イギリス	男性	29	1985	不明	症例報告	外国製品	04000077	2004/10/8	7.1
第4回	4-04	感染症および寄生虫症	HIV感染	イギリス	男性	15	1984/12/14	不明	症例報告	外国製品	04000076	2004/10/8	7.1
第4回	4-05	臨床検査	HIV検査陽性	イギリス	男性	31	1987	不明	症例報告	外国製品	04000080	2004/10/8	7.1
第4回	4-03	臨床検査	HIV検査陽性	イギリス	男性	11	1981/11/23	不明	症例報告	外国製品	04000081	2004/10/8	7.1
第3回	3-1	感染症および寄生虫症	C型肝炎	トルコ	男性	44	2001/11/22	不明	症例報告	当該製品	04000001	2004/4/1	7.0

100203	2	2010/9/22	100523	バクスター	乾燥濃縮人血液凝固第Ⅷ因子	乾燥人血液凝固第Ⅷ因子	人血漿	米国	有効成分
100204	3	2010/9/22	100524	バクスター	乾燥濃縮人血液凝固第Ⅷ因子	人血清アルブミン	人血漿	米国	添加物

感染症発生症例一覧

	番号	感染症の種類		発生国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第15回	1	感染症および寄生虫症	C型肝炎	ドイツ	男	28	2010年4月	不明	症例報告	外国製品	識別番号3-10000006 報告日:2010年5月20日
	1	臨床検査	A型肝炎抗体陽性	ドイツ	男	28	2010年4月	不明	症例報告	外国製品	識別番号3-10000006 報告日:2010年5月20日
	2	感染症および寄生虫症	A型肝炎	ドイツ	女	71	2009/12/14	不明	症例報告	外国製品	識別番号3-09000024 報告日:2010年7月8日
	2	感染症および寄生虫症	B型肝炎	ドイツ	女	71	2009/12/14	不明	症例報告	外国製品	識別番号3-09000024 報告日:2010年7月8日
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	71	2009/12/14	不明	症例報告	外国製品	識別番号3-09000024 報告日:2010年7月8日
第14回	1	感染症および寄生虫症	A型肝炎	ドイツ	女	66	不明	不明	症例報告	外国製品	識別番号3-09000010 報告日:2010年6月10日*
	1	臨床検査	A型肝炎抗体陽性	ドイツ	女	66	2009年6月	不明	症例報告	外国製品	識別番号3-09000010 報告日:2010年6月10日*
第13回	1	感染症および寄生虫症	C型肝炎	ドイツ	男	66	2009/5/1	不明	症例報告	外国製品	識別番号3-09000009 報告日:2009年7月22日
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	77	2009/1/5	不明	症例報告	外国製品	識別番号3-08000040 報告日:2009年2月17日
第12回		報告なし									
第11回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	24	2008/1/10	不明	症例報告	外国製品	識別番号3-07000031 報告日:2008年3月25日
	2	臨床検査	C型肝炎抗体陽性	日本	女	37	2007/9/11	不明	症例報告	当該製品	識別番号1-07000251 報告日:2008年4月30日
第10回	1	感染症および寄生虫症	B型肝炎	日本	女	33	2007/8/7	回復	症例報告	当該製品	識別番号1-07000093 報告日:2007年10月11日
第9回	1	感染症および寄生虫症	C型肝炎	ドイツ	男	50	2007/6/18	不明	症例報告	外国製品	識別番号3-07000010 報告日:2007年8月6日
	1	臨床検査	C型肝炎抗体陽性	ドイツ	男	50	2007/6/18	不明	症例報告	外国製品	識別番号3-07000010 報告日:2007年8月6日
	1	臨床検査	C型肝炎RNA陽性	ドイツ	男	50	2007/6/18	不明	症例報告	外国製品	識別番号3-07000010 報告日:2007年8月6日
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	61	2007年1月	不明	症例報告	外国製品	識別番号3-06000032 報告日:2007年3月30日
	2	臨床検査	C型肝炎陽性	ドイツ	女	61	2007年1月	不明	症例報告	外国製品	識別番号3-06000032 報告日:2007年3月30日
第8回		報告なし									
第7回		報告なし									
第6回	1	感染症および寄生虫症	B型肝炎	ドイツ	女	77	2005/9/28	未回復	症例報告	外国製品	識別番号:3-05000493 報告日:2005年12月27日
第5回	1	感染症および寄生虫症	C型肝炎	日本	男	68	2004/7/6	未回復	症例報告	当該製品	識別番号:1-04000325 報告日:2005年3月18日

	番号	感染症の種類		発生国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第4回	1	臨床検査	C型肝炎陽性	フランス	男	68	2004/08	不明	症例報告	外国製品	識別番号:3-04000088 報告日:2004年11月22日
第3回	1	臨床検査	C型肝炎陽性	カナダ	男	81	1996	不明	症例報告	外国製品	識別番号:3-04000048 報告日:2004年07月30日
第2回	1	感染症および寄生虫症	C型肝炎	日本	男	78	2003/10/20	未回復	症例報告	当該製品	識別番号:1-03000030 報告日:2003/12/26
	2	肝胆道系障害	肝機能異常NOS	日本	男	62	2003/04/07	軽快	症例報告	当該製品	識別番号:A03-22 報告日:2003/08/14
第1回	報告なし										

*:第14回報告のA型肝炎の1例(識別番号3-09000010)について、「A型肝炎抗体陽性」が追加となり、今回調査期間中に追加報告を行った。

MedDRA /J Ver.13.1

100215	14	2010/9/29	100548	CSLベーリング	人血清アルブミン 人血液凝固第XIII因子 フィブリノゲン加第XIII因子	人血清アルブミン	ヒト血液	米国、ドイツ、オーストリア	有効成分添加物

別紙様式第 4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第 15 回	15-3	感染症および寄生虫症	C 型肝炎	ドイツ	男	28	2010/4	不明	自発報告	外国製品	10000003、1 回(完了) 平成 22 年 5 月 13 日 MedDRA ver.13.0
	15-3	感染症および寄生虫症	A 型肝炎	ドイツ	男	28	2010/4	不明	自発報告	外国製品	10000003、1 回(完了) 平成 22 年 5 月 13 日 MedDRA ver.13.0
	15-3	感染症および寄生虫症	医薬品を介する感染因子の伝播	ドイツ	男	28	2010/4	不明	自発報告	外国製品	10000003、1 回(完了) 平成 22 年 5 月 13 日 MedDRA ver.13.0
	15-2	感染症および寄生虫症	C 型肝炎	ドイツ	男	53	2009/11/05	不明	自発報告	外国製品	09000028、2 回(完了) 平成 22 年 3 月 26 日 MedDRA ver.12.1
	15-2	感染症および寄生虫症	医薬品を介する感染因子の伝播	ドイツ	男	53	2009/11/05	不明	自発報告	外国製品	09000028、2 回(完了) 平成 22 年 3 月 26 日 MedDRA ver.12.1
	15-1	感染症および寄生虫症	A 型肝炎	ドイツ	女	66	2009/06	不明	自発報告	外国製品	10000012、1 回(完了) 平成 22 年 7 月 29 日 MedDRA ver.13.0
	15-1	感染症および寄生虫症	医薬品を介する感染因子の伝播	ドイツ	女	66	2009/06	不明	自発報告	外国製品	10000012、1 回(完了) 平成 22 年 7 月 29 日 MedDRA ver.13.0
第 12 回	12-2	感染症および寄生虫症	C 型肝炎	ドイツ	女	78	2009/01/05	不明	自発報告	外国製品	08000037、2 回(完了;同一症例をアルブミンの番号 12-1 で報告) 平成 21 年 4 月 14 日 MedDRA ver.12.0
	12-1	感染症および寄生虫症	B 型肝炎	ドイツ	男	35	不明	不明	自発報告	外国製品	08000027、3 回(完了) 平成 21 年 2 月 12 日 MedDRA ver.11.1

	番号	感染症の種類		発現国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第 12 回	12-1	感染症および寄生虫症	HIV感染	ドイツ	男	35	不明	不明	自発報告	外国製品	08000027、3 回(完了) 平成 21 年 2 月 12 日 MedDRA ver.11.1
	12-1	感染症および寄生虫症	医薬品を介する感染因子の伝播	ドイツ	男	35	不明	不明	自発報告	外国製品	08000027、3 回(完了) 平成 21 年 2 月 12 日 MedDRA ver.11.1
第 11 回	11-1	感染症および寄生虫症	C 型肝炎	ドイツ	女	60	2007/04/13	不明	自発報告	外国製品	08000001、3 回(完了) 平成 20 年 7 月 25 日 MedDRA ver.11.0
	11-1	感染症および寄生虫症	医薬品を介する感染因子の伝播	ドイツ	女	60	不明	不明	自発報告	外国製品	08000001、3 回(完了) 平成 20 年 7 月 25 日 MedDRA ver.11.0
第 10 回	10-1	感染症および寄生虫症	B 型肝炎	ドイツ	男	24	2008/01/10	不明	自発報告	外国製品	07000022、3 回(完了;同一症例をアルブミンの番号 10-1 で報告) 平成 20 年 3 月 31 日 MedDRA ver.10.1
第 8 回	8-1	感染症および寄生虫症	C 型肝炎	ドイツ	女	41	2006/11/21	不明	自発報告	外国製品	06000026、2 回(完了) 平成 18 年 12 月 27 日 MedDRA ver.9.1
第 6 回	6-2	感染症および寄生虫症	C 型肝炎	ドイツ	女	63	2005/11/10	不明	自発報告	外国製品	06000003、2 回(追加) 平成 18 年 5 月 15 日 MedDRA ver.9.0
	6-1	感染症および寄生虫症	B 型肝炎	ドイツ	男	74	2005/10/21	未回復	自発報告	外国製品	05000491、1 回(完了) 平成 17 年 12 月 22 日 MedDRA ver.8.1

100221	20	2010/10/14	100582	化学及血清療法研究所	乾燥濃縮人アンチトロンビンIII	アンチトロンビンIII	ヒト血液	日本	有効成分

感染症発生症例一覧

	番号	感染症の種類		発生国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第15回	1	感染症および寄生虫症	C型肝炎	ドイツ	男	28	2010/04	不明	症例報告	外国製品	識別番号3-10000006 報告日:2010年5月20日
	1	臨床検査	A型肝炎抗体陽性	ドイツ	男	28	2010/04	不明	症例報告	外国製品	識別番号3-10000006 報告日:2010年5月20日
第14回	1	感染症および寄生虫症	A型肝炎	ドイツ	女	71	2009/12/14	不明	症例報告	外国製品	識別番号3-09000024 報告日:2010年8月20日*
	1	感染症および寄生虫症	B型肝炎	ドイツ	女	71	2009/12/14	不明	症例報告	外国製品	識別番号3-09000024 報告日:2010年8月20日*
	1	感染症および寄生虫症	C型肝炎	ドイツ	女	71	2009/12/14	不明	症例報告	外国製品	識別番号3-09000024 報告日:2010年8月20日*
第13回	1	感染症および寄生虫症	A型肝炎	ドイツ	女	68	不明	不明	症例報告	外国製品	識別番号3-09000010 報告日:2010年8月6日*
第12回	報告なし										
第11回	1	臨床検査	C型肝炎抗体陽性	日本	女	37	2007/9/11	不明	症例報告	当該製品	識別番号1-07000251 報告日:2008年4月30日
第10回	1	感染症および寄生虫症	B型肝炎	日本	女	33	2007/8/7	回復	症例報告	当該製品	識別番号1-07000093 報告日:2007年10月11日
第9回	1	感染症および寄生虫症	C型肝炎	ドイツ	男	50	2007/6/18	不明	症例報告	外国製品	識別番号3-07000010 報告日:2007年8月6日
	1	臨床検査	C型肝炎抗体陽性	ドイツ	男	50	2007/6/18	不明	症例報告	外国製品	識別番号3-07000010 報告日:2007年8月6日
	1	臨床検査	C型肝炎RNA陽性	ドイツ	男	50	2007/6/18	不明	症例報告	外国製品	識別番号3-07000010 報告日:2007年8月6日
第8回	報告なし										
第7回	報告なし										
第6回	1	感染症および寄生虫症	B型肝炎	ドイツ	女	77	2005/9/28	未回復	症例報告	外国製品	識別番号3-05000493 報告日:2005年12月27日
第5回	報告なし										
第4回	1	臨床検査	C型肝炎陽性	フランス	男	68	2004/08	不明	症例報告	外国製品	識別番号3-04000088 報告日:2004年11月22日
第3回	報告なし										
第2回	報告なし										
第1回	1	感染症および寄生虫症	C型肝炎	フランス	男	57	2003/6/16	不明	症例報告	外国製品	識別番号D03-38 報告日:2003年9月4日 取り下げ報告:2003年11月7日

*:今回調査期間に追加報告を行った。

MedDRA /J Ver.13.1

100238	37	2010/10/27	100667	CSLベーリング	フィブリノゲン 加第XIII因子 人血液凝固 第XIII因子	人血液凝固 第XIII因子	ヒト血液	米国、ドイツ、オーストリア	有効成分

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第15回	15-1	感染症および寄生虫症	A型肝炎	ドイツ	女	66	2009/06	不明	自発報告	外国製品	10000012、1回(完了) 平成22年7月29日 MedDRA ver.13.0
	15-1	感染症および寄生虫症	医薬品を介する感染因子の伝播	ドイツ	女	66	2009/06	不明	自発報告	外国製品	10000012、1回(完了) 平成22年7月29日 MedDRA ver.13.0
	15-1	臨床検査	肝酵素上昇	ドイツ	女	66	2009/06	不明	自発報告	外国製品	10000012、1回(完了) 平成22年7月29日 MedDRA ver.13.0
	15-1	臨床検査	A型肝炎抗体陽性	ドイツ	女	66	2009/06	不明	自発報告	外国製品	10000012、1回(完了) 平成22年7月29日 MedDRA ver.13.0
第12回	12-1	感染症および寄生虫症	C型肝炎	ドイツ	女	78	2009/01/05	不明	自発報告	外国製品	08000037、2回(完了;同一症例をアンチトロンビンIIIで報告) 平成21年4月14日 MedDRA ver.12.0
第11回	11-1	肝胆道系障害	肝機能異常	日本	男	63	2004/02/13	不明	自発報告	当該製品	08000292、2回(完了) 平成20年7月1日 MedDRA ver.11.0
第10回	10-1	感染症および寄生虫症	B型肝炎	ドイツ	男	24	2008/01/10	不明	自発報告	外国製品	07000022、3回(完了;同一症例をアンスロビンP番号10-1で報告) 平成20年3月31日 MedDRA ver.10.1
第7回	7-2	感染症および寄生虫症	B型肝炎	日本	男	70	不明	死亡	自発報告	当該製品	06000076、2回(完了;因果関係が否定されたため、報告対象外として完了報告) 平成18年10月20日 (第7回の番号7-2の症例と同一である) MedDRA ver.9.0

	番号	感染症の種類		発現国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第7回	7-1	感染症および寄生虫症	B型肝炎	日本	男	34	2005/12/21	回復	自発報告	当該製品	06000004、2回(完了) 平成18年5月15日 MedDRA ver.8.1
第5回	5-1	臨床検査	C型肝炎抗体陽性	日本	女	87	2005/8/4	不明	自発報告	当該製品	05000116、2回(取下) 平成17年9月5日 MedDRA ver.8.0

100253	52	2010/10/28	100685	化学及血清療法研究所	フィブリノゲン加第XIII因子 乾燥濃縮人活性化プロテインC 乾燥濃縮人血液凝固第IX因子 乾燥スルホ化人免疫グロブリン 人血清アルブミン 乾燥濃縮人血液凝固第VIII因子	人血清アルブミン	ヒト血液	日本	有効成分添加物