

医薬品 研究報告 調査報告書

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一般的名称	2009年10月26日	2009年10月26日	該当なし	
販売名(企業名)	研究報告の公表状況	Report to the Board of Directors: Current Status of TSEs and Transfusion Safety :AABB Weekly Report 2009年10月22日号Vol.15 No.39	公表国 米国	
問題点(プリオン遺伝子のコドン129遺伝子がMM型と同一でない特定の人達の中から見つかった) TTD (Transfusion Transmitted Diseases) Committee が伝達性海綿状脳症(TSE)の状況および輸血の安全性に関する報告書を AABB Board の次回会合で提出予定である。報告の概要は以下のとおりである。数人の感染者(症状発現なし)が、プリオン遺伝子のコドン129遺伝子がMM型と同一でない特定の人達の中から見つかり、疾患の第二波の可能性や潜在的なキャリアのグループが拡大することに対して懸念されている。供血後に vCJD を発症した供血者3人から採取された血液の輸血により vCJD プリオンが合計4人に伝播している。受血者の3例は vCJD を発症したが、1例は vCJD の症状がなく、他の原因で死亡した。その患者の脾臓とリンパ節で異常プリオン蛋白が発見されたが、興味あることにその患者のプリオン遺伝子のコドン129がMV型であることが判明した。非MM遺伝子型での感染の潜在的な重要性についての検討を以下に簡潔に示す。最近、供血後に vCJD を発症した供血者の血漿が含まれていたことが判明した血液凝固第VIII因子製剤を投与された一人の血友病患者において病原性 vCJD プリオンが発見された。その患者は vCJD の症状が現れなかった。モデリング研究では感染はおそらく血漿分画製剤による示唆された。アメリカ赤十字社は、Transfusion に掲載された論文で、供血後に古典的 CJD を発症した供血者から伝播するエビデンスが不足していると報告している。その研究では、供血後に CJD を発症した36人の供血者の血液を投与された436人の受血者のルックバック調査をしたが、CJD の症例はなかった。暴露経験のある受血者を英国の vCJD に暴露した患者のコホートスタディーと比較すると CJD を発症するリスクが有意に低かった (p=0.012)。この研究は、輸血による古典的 CJD の感染性に関するエビデンスが不足していることをサポートしている。血友病患者及び非MM型の特定の人達から vCJD プリオンが発見された結果、米国 FDA は米国由来の血漿分画製剤の受血者に関する vCJD 伝播のリスクモデルを改訂した。新しいモデルは2009年6月に開催された伝達性海綿状脳症諮問委員会によって発表された。一人当たりの年間の最低の推定リスクは5倍から18倍に上昇したが、まだ1200万人に1人の低さであり、最大の推定リスクは12000人に1人のまま変わらず、FDAは、米国患者へのリスクは「極めて低い」と見なしている。ヒトプリオン遺伝子のコドン129には数種のバリエーションがあり、3つの主要な遺伝子型、MM型、MV型とVV型がある。現在まで評価された全ての症候性の vCJD 患者のコドン129の遺伝子型がMM型であった。英国人の約40%がこの遺伝子型である。しかし病原性プリオンがMVまたはVV遺伝子型である無症候性の人達で発見されている。これにより2つの疑問が生じてくる。最初の疑問は、非MM遺伝子型の人達での vCJD の「第二波」が起こるかどうかということである。これはたぶん潜伏期間がより長期化したためである。二番目は非MM遺伝子型を持つ人達が vCJD プリオンの感染キャリアになり得るかということである。2つとも解決が待たれる。	研究報告の概要 I11	使用上の注意記載状況・その他参考事項等		
報告企業の意見	今後の対応			
当社製品を製造する原料血漿は、ドイツ、米国、オーストリア由来であり、また英国等の滞在期間、通算滞在歴に基づき供血停止基準を設けて収集している。本剤の添付文書に、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、本剤の投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与することを記載し、注意喚起している。	今後とも新しい感染症に関する情報収集に努める所存である。			

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Report to the Board of Directors: Current Status of TSEs and Transfusion Safety  
Executive Summary:

There continues to be concern about transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood transfusion, with a total of 4 reported cases, plus a potential case of transmission of the prion via a UK-derived plasma derivative, known to have contained potentially infectious donations. Some infections (but no disease) have been found among individuals who are not homozygous for MM at the 129 codon of the PrP gene, raising concern about a possible second wave of disease and an expanded group of potential carriers. There has been no published progress in blood donor testing technologies. One method for prion removal from red cell concentrates has been evaluated by authorities in the UK and Ireland.

Information about transfusion transmitted infectivity:

There have now been a total of four cases of transmission of the vCJD prion by transfusion of blood collected from three donors who subsequently developed vCJD. Three of the cases resulted in the development of vCJD in the recipient, while one was detected in the spleen and one lymph node of a transfused patient who died of other causes. This individual had no symptoms of vCJD (1, 2). Interestingly, he was found to be (MV) heterozygous at codon 129 of the PrP gene. The potential significance of infection among non-MM genotypes is discussed briefly below. More recently, evidence of pathologic vCJD prions was found in a hemophilic recipient of F VIII concentrates known to have included plasma from a donor who subsequently developed vCJD (3). Again, the recipient patient was free of vCJD symptoms. Modelling studies imply that the infection was most likely to have come from the plasma products (4).

In a paper published in Transfusion, American Red Cross authors reported on the absence of evidence of transmission of classic CJD from donors who subsequently developed the disease. The study involved a lookback on 436 recipients of donations from a total of 36 donors who developed the disease subsequent to their donation, finding no cases of CJD among the recipients. A subset of recipients with exposure histories comparable to the UK cohort of patients exposed to vCJD was shown to be at lower risk of developing CJD: a statistically significant (p = 0.012) observation. This supports the absence of infectivity of classic CJD via transfusion (5).

Risk modeling for recipients of plasma derivatives in the US:

As a result of the finding of the vCJD prion in a hemophilia patient (described above), and the findings of vCJD prions among non-MM individuals, the US FDA has revised its model of the vCJD transmission risk for recipients of US-derived plasma derivatives. The new models were presented at a meeting of the Transmissible Spongiform Encephalopathies Advisory Committee in June, 2009. Although the lowest estimated annual per-person risk has risen 5 to 18-fold, it may still be as low as 1 in 12 million and the maximal estimated risk remains unchanged at 1:12,000, the FDA still regards the risk to US patients to be "extremely small".

Implications of findings of vCJD prions in non-MM individuals:

There are several variations at codon 129 of the human PrP gene, resulting in 3 main genotypes, MM, MV and VV, where M signifies methionine and V, valine. To date, all symptomatic cases of vCJD who have been evaluated have been MM homozygous at the 129 codon. Approximately 40% of the UK population has this genotype. However, there have been a number of circumstances (some described above) in which the pathologic prion has been found in asymptomatic individuals with the MV or VV genotype. This has raised two questions. The first is whether there will be a "second wave" of vCJD among individuals with a non-MM genotype, perhaps resulting from a much extended incubation period. Second is the question of whether non-MM individuals can be infectious carriers of the vCJD prion. This latter concern was included in the newer FDA infectivity model for US-derived plasma derivatives. Both questions await resolution.

Status of interventions against transfusion transmission of TSEs:

No significant progress has been reported in the development of any pre-mortem test that could be used for blood donors or donations, although one of the tests under development has undergone some preliminary clinical evaluation. Currently, one manufacturer has an available, CE-marked affinity filter intended for use with leukoreduced red-cell concentrates. The procedure has been evaluated in the UK and Ireland, but no decision has been made with respect to

its implementation. A process has also been developed for use in the manufacture of solvent-detergent treated plasma for transfusion.

References:

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3. Health Protection Agency. Asymptomatic vCJD abnormal prion protein found in a haemophilia patient. [cited June 2009]. Available from: [http://www.hpa.org.uk/web/hpaweb/hpaweb/Standard/HPAweb\\_C/11957336186817236](http://www.hpa.org.uk/web/hpaweb/hpaweb/Standard/HPAweb_C/11957336186817236)
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5. Dorsey K, Zou S, Schonberger LB, Sullivan M, Kessler D, Notari E 4th, Fang CT, Dodd RY. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. Transfusion 2009;49:977-84.

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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 2009. 9. 16	新医薬品等の区分 該当なし	総合機構処理欄
<b>一般的名称</b> 抗HBs人免疫グロブリン	<b>研究報告の公表状況</b>	FDA, CBER. Available from: <a href="http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095070.htm">http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095070.htm</a>	<b>公表国</b> 米国	
<b>販売名(企業名)</b> 抗HBs人免疫グロブリン「日赤」(日本赤十字社) 抗HBs人免疫グロブリン筋注200単位/1mL「日赤」(日本赤十字社) 抗HBs人免疫グロブリン筋注1000単位/5mL「日赤」(日本赤十字社)				
<b>研究報告の概要</b>	OFDA: 米国承認血漿由来第Ⅷ因子製剤によるvCJD感染リスクの可能性: 概要 ・近年、米国承認血漿由来第Ⅷ因子製剤 (pdFVIII, Antihemophilic Factor) の投与を受けた血友病Aおよびフォン・ヴィレブランド (vW) 病患者の変異型クローンフェルト・ヤコブ病 (vCJD) 感染リスクに関する疑問が提起されている。 ・リスク評価に基づき、FDA、CDC、NIHを含む米国の公衆衛生総局 (PHS) は、pdFVIII製剤の投与を受けた血友病AとvW病患者のvCJD感染リスクは、はっきりとはわからないものの、非常に小さい可能性が最も考えられる。第IX因子製剤を含む他の血漿由来製剤からのvCJD感染リスクは同程度か、更に小さいようである。 ・新たな情報を得るためには、血友病治療センターの血友病またはvW病の専門家に連絡するのが良い方法である。 (追加情報) 2003年11月～2007年4月に英国で、赤血球輸血によりvCJDに感染したと考えられる患者4名が発生し、血液製剤のvCJD伝播の可能性について懸念が高まった。このためFDAは、vCJDとBSEの発生率が米国と比べて非常に高い国に渡航した人の供血延期を勧告した。米国では、これまでvCJDを発症した人の血漿から作られたpdFVIII製剤はなく、製剤を投与された人がvCJDを発症したこともない。pdFVIII製剤は、他の血漿由来製剤と比べてvCJD感染因子を多く含むと考えられる。また、血漿由来製剤の製造工程における処理でvCJD感染因子は減少すると考えられる。FDA、CDC、NIHの認識している限り、リスクの最も高い英国を含め、血友病、vW病、その他の血液凝固障害患者がvCJDを発症したという報告はない。FDAはvCJD伝播の可能性低減のため、欧州渡航歴のある人の供血延期など様々な対策を実施している。FDAはpdFVIII製剤のvCJD感染リスクを分析したが、有病率について不明な点が多く正確なリスク評価は不可能である。リスクは非常に小さい可能性が最も考えられるが、ゼロではない。			<b>使用上の注意記載状況・その他参考事項等</b> 抗HBs人免疫グロブリン「日赤」 抗HBs人免疫グロブリン筋注200単位/1mL「日赤」 抗HBs人免疫グロブリン筋注1000単位/5mL「日赤」 血液を原料とすることに由来する感染症伝播等 vCJD等の伝播のリスク
	<b>報告企業の意見</b> 米国食品医薬品局が、米国承認血漿由来第Ⅷ因子製剤の投与を受けた血友病Aおよびフォン・ヴィレブランド病患者のvCJD感染リスクの可能性について、はっきりとはわからないものの、非常に小さい可能性が最も考えられるとの見解を示したとの報告である。生涯反復使用する血漿分画製剤の感染リスクが小さいことは、献血者を米国以上に規制してきた国産製剤はより感染リスクが低いと期待される。	<b>今後の対応</b> 日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980～96年に1日以上英国滞在歴のある人の献血を制限している。今後もCJD等プリオン病に関する新たな知見及び情報の収集に努める。		



## Vaccines, Blood & Biologics

### Potential vCJD Risk From US Licensed Plasma-Derived Factor VIII (pdFVIII, Antihemophilic Factor) Products: Summary Information, Key Points

#### Summary Information

#### Key Points:

- In recent years, questions have been raised concerning the risk of variant Creutzfeldt-Jakob disease (vCJD) (a rare but fatal brain infection) to hemophilia A and von Willebrand disease patients who receive US licensed plasma-derived Factor Eight (pdFVIII, Antihemophilic Factor) products.
- Based on a risk assessment, the US Public Health Service (PHS), including FDA, CDC, and NIH, believes that the risk of vCJD to hemophilia A and von Willebrand disease patients who receive US licensed pdFVIII products is most likely to be extremely small, although we do not know the risk with certainty. vCJD risk from other plasma derived products, including Factor IX, is likely to be as small or smaller.
- Contacting a specialist in hemophilia or von Willebrand disease at a Hemophilia Treatment Center is a good way to learn about new information as it becomes available.

#### Additional Information:

- Between December 2003 and April 2007, there have been four reports of people, all in the UK, who probably acquired the vCJD agent through red blood cell transfusions. This has increased concern about the potential transmission of vCJD by blood products.
- Principal concerns are whether persons infected with vCJD could donate plasma in the U.S., and whether clotting factor products made from their plasma donations might transmit the disease.
- To address these concerns FDA recommends the deferral of donors who may have lived in or traveled extensively to countries with a higher prevalence of vCJD and bovine spongiform encephalopathy (BSE) than in the U.S.
- In the United States, pdFVIII products have not been made from the plasma of anyone known to have developed vCJD, and no one who received any of these products is known to have developed vCJD.
- FDA conducted a risk assessment for pdFVIII because the plasma fraction from which it is made is likely to contain more of the vCJD infectious agent, if present, than plasma fractions from which other plasma-derived products are made, such as Factor IX, (used to treat hemophilia B), albumin, and immune globulins. The FVIII-containing fraction is further processed using a variety of methods that are likely to reduce or

potentially eliminate vCJD from the final pdFVIII product. Methods likely to reduce or potentially eliminate vCJD are also used in the manufacture of other plasma-derived products.

- FDA, CDC, and NIH are not aware of any cases of vCJD having been reported worldwide in patients with hemophilia, von Willebrand disease, or other blood clotting disorders. This includes those who have received, over a long period of time, large amounts of blood clotting factor products manufactured from plasma donations from the UK where the risk of vCJD is highest because of a previous higher risk of potential exposure to BSE-infected beef in the UK diet.
- The FDA has taken a number of steps to further reduce the potential vCJD risk from blood components. These steps include donor deferral recommendations, and quarantine and withdrawal of products at increased vCJD risk. Donor deferral guidance, first issued in August 1999 and subsequently updated, includes, among other things, deferral of donors who visited or resided in Europe where BSE prevalence is higher than in the US. Also, blood components and plasma derivatives are to be withdrawn if a donor is later diagnosed with vCJD. The potential spread of vCJD through red blood cell or plasma transfusion is limited by these deferral and quarantine measures that are in place.
- Additional steps FDA is taking to reduce potential vCJD risk from plasma derivatives include gathering, evaluating, and disseminating information about manufacturing processes that potentially could reduce the vCJD infectious agent in blood products. FDA is helping to develop donor screening and diagnostic tests for vCJD, and to inform patients and physicians about the current scientific understanding of vCJD risk from blood products.
- Using a computer model, FDA assessed the potential risk of vCJD infection from the current use of pdFVIII products. However, because so much is unknown about vCJD and its prevalence, the risk assessment performed by FDA has a lot of uncertainty, making it impossible to precisely estimate the risk of vCJD in general, or of the actual risk to individual hemophilia A or von Willebrand disease patients. Meaningful distinctions also could not be made among specific products. There is no test yet available to detect vCJD infection in healthy donors or recipients.
- Although the risk of vCJD exposure from US pdFVIII products is most likely to be extremely small, it may not be zero, and FDA is encouraging physicians and patients to consider this risk, in the context of all remaining real or potential risks and the known benefits of product use, when making treatment decisions.
- At this time, the PHS does not believe there is a need for hemophilia A and von Willebrand disease patients who receive pdFVIII to inform their surgeons or dentists about their potential exposure to vCJD. Also, there is no recommendation for surgeons and dentists to take any special precautions based on such potential exposures. This belief is based on the results of the FDA risk assessment, as well as on the lack of known cases of vCJD transmitted by plasma-derived clotting factor products in the UK or anywhere else in the world. PHS agencies will continue to monitor and reevaluate the situation as new information becomes available.
- vCJD originally came from a disease in cattle called "mad cow disease" or

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- BSE (bovine spongiform encephalopathy) . Transmission of the BSE agent to humans, leading to vCJD, is believed to occur primarily from eating beef and beef products contaminated with the BSE agent. Both BSE and vCJD are invariably fatal brain diseases with incubation periods typically measured in years.
- From 1995 through April 2007, 202 individuals with vCJD were reported worldwide, with 165 in the United Kingdom (UK), and three in the United States. Two of the individuals in the United States had lived in the UK from 1980-1996 during a key exposure period to the BSE agent. The third US individual with vCJD most likely acquired the disease in Saudi Arabia. The reported incidence of vCJD in the UK based on disease onset peaked in 1999 and has been declining thereafter. In the UK, where most cases of vCJD have occurred, the current risk of acquiring vCJD from eating beef and beef products appears to be negligible.
- More information about vCJD is available on these government websites:
  - FDA: Potential Risk of Variant Creutzfeldt-Jakob Disease (vCJD) From Plasma-Derived Products
  - Centers for Disease Control and Prevention: vCJD (Variant Creutzfeldt-Jakob Disease)
  - US Department of Agriculture

• Information also may be obtained from these non-government sources:

- Committee of Ten Thousand
- Hemophilia Federation of America
- National Hemophilia Foundation and/or HANDI
- World Federation of Hemophilia

**Contact Us**

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• **Consumer Affairs Branch (CBER)**

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医薬品  
 医薬部外品 研究報告 調査報告書  
 化粧品

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一般的な名称 人ハプトグロビン	研究報告の 公表状況	Vox Sanguinis 2009; 97: 207-210	公表国 イギリス	
販売名 (企業名)	ハプトグロビン静注 2000 単位「ベネシス」 (ベネシス)			
研究報告の概要	(背景) 輸血や血液製剤の投与を介して変異型クロイツフェルト-ヤコブ病 (vCJD) が伝播することの公衆衛生上の危険性は、特に血友病患者の体内で異常プリオンタンパク質が検出されたことが最近報告されたことから、現在でも懸念されている。 (目的) 英国の vCJD 臨床症例について過去に血漿分画製剤への暴露があったか説明すること。 (方法) 国立 CJD サーベイランスユニット (National CJD Surveillance Unit) に保管されている記録 (親族、開業医、および病院からのもの) を調査する。 (結果) 英国の 168 例の vCJD 症例のうち 9 例が、血漿分画製剤の投与を介して 12 回を受けたことがあった (その 12 回のうちの 1 回は 1970 年で vCJD の危険性以前であったが、残りの 11 回は 1989~1998 年であった)。UK CJD Incident Panel の危険性評価基準によれば、11 回は低危険度製品の投与であり、1 回は低もしくは中等度危険度製品の投与であった。 (結論) 現在までの英国の vCJD 臨床症例のうちのいずれの例についても、血漿分画製剤への暴露を介して感染したものと考えられない。しかし、将来的にそのような伝播が vCJD 感染例をもたらす可能性は排除し得ない。			使用上の注意記載状況・その他参考事項等 2. 重要な基本的注意 (1) 略 1) 略 2) 現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病 (vCJD) 等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全に排除できないので、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		
英国の vCJD 臨床症例について過去に血漿分画製剤への暴露があったかについて、国立サーベイランスユニットに保管されている記録を調査した報告である。 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られるので、特段の措置はとらない。		

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## ORIGINAL PAPER

## Variant Creutzfeldt–Jakob disease and exposure to fractionated plasma products

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**Background** The risk to public health of onward transmission of variant Creutzfeldt–Jakob disease (vCJD) via blood transfusion and plasma product administration is of on-going concern, particularly with the recent reported detection of abnormal prion protein in a person with haemophilia.

**Objectives** To describe the history of fractionated plasma product exposure in clinical cases of vCJD in the UK.

**Methods** Through examination of records held at the National CJD Surveillance Unit (from relatives, general practices and hospitals).

**Results** Nine out of 168 UK vCJD cases had a history of receipt of fractionated plasma products on 12 different occasions (1 pre-vCJD risk in 1970, the remaining between 1989–1998). According to the UK CJD Incident Panel risk assessment criteria, 11 were low-risk products and one was low or medium risk.

**Conclusion** It is unlikely that any of the UK vCJD clinical cases to date were infected through exposure to fractionated plasma products. However, the possibility that such transmission may result in vCJD cases in the future cannot be excluded.

**Key words:** fractionated plasma products, public health, transfusion, vCJD.

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## Introduction

The risk of onward transmission of variant Creutzfeldt–Jakob disease (vCJD) via blood transfusion and plasma product administration is of on-going concern. This has been highlighted by the recent announcement by the UK's Health Protection Agency of the post-mortem finding of abnormal prion protein in the spleen of a patient with haemophilia who died from a cause unrelated to vCJD [1]. This individual had received UK-sourced fractionated plasma products before 1999, when safety measures were put in place in relation to vCJD, including importation of plasma, mainly from the USA, to manufacture plasma products. There has been no previous

documentation suggesting transmission of any type of CJD by fractionated plasma products. On the other hand, variant CJD has been shown to be transmissible via blood component transfusion, with four instances of transfusion-transmitted vCJD infection to date associated with non-leucodepleted red cells [2–5].

Laboratory studies in animal models have shown that infectivity may be present in plasma both during clinical illness and in the incubation period [6]. Although there is experimental evidence that significant infectivity may be cleared during the production process for fractionated plasma products [7], there are doubts about the interpretation of studies that have been largely based on spiking of plasma with brain-derived material rather than endogenous infectivity [8]. In addition, there are varieties of manufacturing processes used in production of plasma products. These findings have drawn attention to the important public health implications of potential secondary transmission of vCJD.

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In addition to recipients of vCJD-implicated labile blood components, more than 4000 UK-sourced plasma product recipients have been classified and notified by the UK CJD Incidents Panel as 'at risk for public health purposes', in part on the basis of a risk assessment [9]. In 2004, the UK CJD Incidents Panel advised that patients who were treated with UK-sourced fractionated plasma products between 1980 and 2001, and who were exposed to a 14% risk of infection in addition to the background risk of the UK population through diet, should be contacted and advised to take public health precautions. Fractionated plasma products were categorized into three groups according to the number of treatments that were likely to result in a patient reaching this risk threshold: high risk (one treatment with factor VIII, factor IX or anti-thrombin), medium risk (several infusions of intravenous immunoglobulin or 4–5% albumin) and low-risk (intramuscular immunoglobulins or 20% albumin) [1, personal communication]. An exercise was undertaken to trace recipients, estimate individual risk and inform all those who reached this threshold that they were 'at risk of vCJD for public health purposes'. The amount of potential infectivity in the low-risk category was estimated to be so small that the likelihood of surpassing the threshold was extremely unlikely and so individual recipients did not need to be traced or notified.

Data from actual cases of vCJD are important in attempting to determine the potential risk from fractionated plasma products. This paper describes a number of UK vCJD cases reported to have received such products before the onset of illness. The characteristics of the specific plasma products involved suggest that these exposures are most unlikely to have been the source of vCJD in these cases.

## Methods

The UK National CJD Surveillance Unit (NCJDSU) routinely collects information on potential risk factors for all cases of vCJD referred to the unit [10], including data on blood transfusion, plasma product administration, vaccination and 'injection' histories. The information is obtained from interviews with relatives of cases and, when available, primary care and hospital records. Where possible, batch numbers of fractionated plasma products were obtained for vCJD cases found to have received such products and compared with the list of product batches derived from plasma donated by individuals who later went on to develop vCJD. Eleven of the 168 cases of vCJD referred to the NCJDSU up to end of March 2009 are known to have made 25 plasma donations which had been used to manufacture 191 batches of fractionated products, prior to the UK importing plasma from abroad in 1999.

## Results

To examine whether any of the 168 vCJD cases had received fractionated plasma products, we examined records held at NCJDSU. One hundred and fifty-eight had data available from relatives only, two from general practice records only and in one case there was minimal information available (this patient was investigated in another country).

Nine cases of vCJD, with onset of symptoms between December 1994 and April 2006, had recorded receipt of fractionated plasma products on 12 occasions (Table 1). Five

Table 1 Variant CJD clinical cases reported to have received plasma products

vCJD case	Plasma product	Year given	Year clinical onset of vCJD	Batch number known (country of plasma origin, if known)
1	Human normal immunoglobulin* (gammaglobulin for travel)	1990	1994	✓ (non-UK)
2	Rh(D) immunoglobulin*	1992	1995	✓ (non-UK)
	Human normal immunoglobulin* (gammaglobulin for travel)	1993		
3	Rh(D) immunoglobulin*	1991	1996	✓ (UK)
4	Albumin	1993	1998	✓
	Rh(D) immunoglobulin*	1989	1998	✓ (UK)
	Rh(D) immunoglobulin*	1993		
5	Rh(D) immunoglobulin*	1998	1998	✓
	Rh(D) immunoglobulin*	1993		
6	Human normal immunoglobulin* (gammaglobulin for travel)	1993	1999	✓ (non-UK)
	Human normal immunoglobulin* (for travel)	1991	2000	✓ (UK)
7	Rh(D) immunoglobulin*	1970 <sup>b</sup>	2001	✓
8	Rh(D) immunoglobulin*	1997	2006	✓

\*Administered intramuscularly; <sup>b</sup>before the considered start of the vCJD at risk period in 1980.

cases had received Rh(D) immunoglobulin to protect against Rh isoimmunization, four in childbirth (on six occasions) and one (case 9, Table 1) with receipt of fresh frozen plasma. Before travel, four cases had received normal human immunoglobulin for intramuscular use (three gammaglobulin, one human normal immunoglobulin), including one case (case 2, Table 1) who had received Rh(D) immunoglobulin previously. The remaining case was given albumin (unknown concentration) for 'cover' during a paracentesis procedure. One of the nine cases received Rh(D) immunoglobulin in 1970 before the considered start of the vCJD at risk period (1980) and the other eight received products between 1989 and 1998.

Batch numbers were available for only two of the seven Rh(D) immunoglobulin products, which indicated the UK as origin of the plasma in these two cases. However, batch numbers were available for all four intramuscular human normal immunoglobulin/gammaglobulin products and one of these was of UK origin. The albumin batch number was not recorded. No batch number matched any others, nor did the batch numbers match any of those from products known to have included plasma donated from individuals who subsequently went on to develop vCJD.

## Discussion

Of the nine vCJD patients who had received fractionated plasma products, the batch numbers of the plasma products, where known, did not correlate with any of the batches derived from pools containing a donation from a person who went on to develop vCJD. Eight had received products considered by the UK CJD Incidents Panel as low risk and one person had received a low-/medium-risk product (albumin of unknown concentration). It is, therefore, unlikely that administration of plasma product was the source of vCJD infection in these cases.

Thirty-two of the 74 female vCJD cases had children and, of these, four (13%) were reported to have received Rh(D) immunoglobulin. In the UK, 17% of all women are RhD negative. Approximately 10% of all UK pregnancies are in RhD negative mothers bearing RhD positive babies, and these women should all receive routine Rh(D) immunoglobulin after delivery [11]. Although less likely now, in the past RhD negative women may have been given Rh(D) immunoglobulin without the blood group of the baby being known, resulting in more than 10% receiving Rh(D) immunoglobulin. However, the median age at death in vCJD is only 28 years and the proportion of women with vCJD who received Rh(D) immunoglobulin is comparable to the likely exposure rate in the general population.

The lack of evidence of transmission of vCJD through fractionated plasma products assumes that accurate and thorough information has been obtained on relevant exposure [10]. Information was available from relatives, hospital notes at the time of admission for the terminal illness and

from primary care records in 158 of the 168 cases included in this analysis. In this group, it is unlikely that any plasma product exposure was missed and, in particular, it is unlikely that higher-risk exposures involving long-term treatment with plasma products, such as treatment of haemophilia, were undetected. This is probably also true for the seven cases in which information from relatives was the only source of data on past exposures. However, it is possible that prior treatment, for example with albumin or intravenous immunoglobulin, could have been missed and it was only possible to identify batch numbers in half of plasma products identified as having been used in vCJD cases. There is also the possibility that infection via plasma products might result in a protracted incubation period because of the relatively low dose exposure and that cases of vCJD infected through this mechanism have yet to occur.

In conclusion, it is unlikely that any of the UK vCJD clinical cases to date were infected through exposure to fractionated plasma products. However, the possibility that such transmission may result in vCJD cases in the future cannot be excluded.

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品名	製造日	ロット	メーカー	成分	性状	製剤	有効成分	添加物	有	無	
100071	2009/12/17	90805	バクスター	乾燥イオン交換樹脂処理人免疫グロブリン	人免疫グロブリンG	人血漿	米国	有効成分	無	有	無
100072	2009/12/17	90806	バクスター	乾燥イオン交換樹脂処理人免疫グロブリン	人血清アルブミン	人血漿	米国	添加物	無	有	無

## 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）。