表3. アルカリ処理と複合処理

Treatments	affected / implanted	Incubation period (mean days)	Pathology	
			positive (days)	Negative (days)
Rinsed in dH$_2$O and dry	6/6	206.8 ± 18.8	188,188,195, 218,221,231	
1M-NaOH (RT.[#], 1h)	6/6	256.0 ± 44.1	211,222,237, 250289,327	
1M-NaOH (RT., 1h) + AC.[##] (121℃、20min.)	2/6	279.5 ± 119	208,351	495,691,790, >800
1M-NaOH (RT., 1h) + AC. (134℃、20min.)	0/6	>800		545,611,736, 772,796
2M-NaOH (RT., 1h)	1/6	>360	203	
2M-NaOH (RT., 1h) + AC. (121℃、20min.)	0/6	>360		
2M-NaOH (RT., 1h) + AC. (134℃、20min.)	0/6	>360		
3.0%SDS / NaOH (pH8.0, boiling, 5min.)	0/6	>360		
3.0%SDS / NaOH (pH12.8, boiling, 5min.)	0/6	>360		

RT.: room temperature
AC. : autoclaving

F．健康危険情報
なし

G．研究発表
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H．知的財産権の出願・登録状況
（予定も含む。）
1．特許取得

2．実用新案登録

3．その他

５％次亜塩素酸ナトリウム　1N 水酸化ナトリウムで消毒後に超音波洗浄の有無による鋭敏な器具の形状変化について

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研究要旨

プリオン病感染後の二次対策として、鋭利な先端の手術器具を５％次亜塩素酸ナトリウム、1N 水酸化ナトリウム消毒後の形状変化を室温（25℃）にて各々２時間、１時間浸透静置させ、５分間の超音波洗浄に有無についても検討した。手術で頻用されるメス刃、カヌラ針を用いて、電顕での形態変化を観察したところ、５％次亜塩素酸ナトリウム、1N 水酸化ナトリウム共にカヌラ針先端、メス刃の洗浄効果を認めており、カヌラ針内腔は 1N 水酸化ナトリウムで高頻度に内腔堆積物が除去されており、超音波洗浄付加により針、メス刃共に先端の鈍化傾向を認めた。また 1N 水酸化ナトリウムを用いた場合メス刃は先端がより丸く変化した。

A．研究目的

プリオン病感染後の二次対策として、特に感染者手術時に使用された場合でも再利用する可能性の高い持針器、メスホールダに直接接する、メス刃、カヌラ針の５％次亜塩素酸ナトリウム、1N 水酸化ナトリウム消毒後、超音波洗浄付加後の形態変化について電子顕微鏡を用いて観察検討する。

B．研究方法

５％次亜塩素酸ナトリウム、1N 水酸化ナトリウムを用いて室温（25℃）消毒後各々２時間、１時間浸透静置させ、５分間の超音波洗浄に有無についても検討した。メス刃、18 ゲージ、22 ゲージ、23 ゲージ　カヌラを各条件にて検討した。カヌラ、刃は各々①NN-1838R　刃の形状 R・B　針の長さ 1 1/2　(1.20×38mm)、テルモ社製、②NN-2238R　刃の形状 R・B　針の長さ 1 1/2(0.70×38mm)、テルモ社製、③No.11 メス、Feather 社、25 Gy gannma irradiated、④JMS　注射針　23 G　R.B (0.6×25mm)であった。

静置消毒後、直ぐに水洗・乾燥させたものと直ちに超音波洗浄（シャープ社 UT-106、37kHz、30±3℃）5 分間したものを比較検討した。

電顕試料ホルダーにセットアップのためメスの刃、及び注射針は適切な長さに切断する。検鏡位置の損傷を回避するため切断位置の両端をクランプ固定し切断した。また、実体顕微鏡で事前に表面を確認し、切断位置の確認、切断する衝撃による表面付着物の剥離を無くすため慎重に切断した。

検鏡には走査電子顕微鏡（FIELD EMISSION SCANNING ELECTORON MICROSSOPE）

型式：JSM-6700F/Ⅳ（JEOL,日本電子）：高電圧 15kV、エミッション電流 10μA 使用した。

（倫理面への配慮）

本研究はプリオン病感染後の手術器具を５％次亜塩素酸ナトリウム、1N 水酸化ナトリウムを用いて室温（25℃）消毒後及び超音波洗浄後の形態変化を検討しており、研究対象は手術時に使用する鋭利

な刃物などであり、倫理的問題はないと思われる。

C．研究結果

　5％次亜塩素酸ナトリウム、1N 水酸化ナトリウムを用いて室温（25 ℃）消毒後カヌラ針、メス刃ともに洗浄効果を認めた。カヌラ針内腔は 1N 水酸化ナトリウムを用いた場合より効果的に内腔堆積物を洗浄除去可能であった。先端は針、メス刃ともに超音波洗浄により損傷をうけることが多かった。1N 水酸化ナトリウム消毒の際にはメス刃は先端が丸く変化していた。

D．考察

　5％次亜塩素酸ナトリウム、1N 水酸化ナトリウムを用いた消毒は前年度まで検討した 3％ドデシル硫酸ナトリウム(SDS)煮沸消毒法と比較してにより、メス刃、18, 22, 23 ゲージ針の形状は付着物、堆積物の沈着は少なく、刃および針先の摩耗程度も軽度であった。但し、1N 水酸化ナトリウム消毒後の超音波洗浄ではメス刃先端の鈍化を認め、融解などの影響を考慮する必要があると考えられた。機械的損傷定量検討と共に消毒薬種類、煮沸の有無、超音波洗浄などにより先端微細な器具の耐久性についても検討する必要があると推定された。

E．結論

　5％次亜塩素酸ナトリウム、1N 水酸化ナトリウムを用いて室温（25 ℃）消毒後カヌラ針、メス刃ともに洗浄効果を認めた。カヌラ針内腔は 1N 水酸化ナトリウムを用いた場合より高頻度に器具先端への損傷の可能性が高まる事が推測された。

F．健康危険情報

　特記事項なし

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H．知的財産権の出願・登録状況
（予定も含む。）
１．特許取得
　なし
２．実用新案登録
　なし
３．その他
　なし

厚生労働科学研究費補助金（難治性疾患克服研究事業）
プリオン病２次感染に対する現実的滅菌法の開発研究
平成２１年度　分担研究報告書

プリオン病
滅菌における海外情報収集

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研究要旨
国内におけるプリオン病２次感染対策は，難治水澤班研究成果のひとつである「プリオン病感染予防ガイドライン（2008 年版）」によって専門委員会等により策定されたプリオン病２次感染対策が周知されるなど対策がとられている。これに関連して、ハイリスク手技における手術機械の現実的滅菌法開発研究の必要があり、本分担班では海外での二次感染対策情報収集の必要性に鑑みこれに応じた情報収集研究を行った。継続的な海外情報収集により本邦における対策を検証することの重要性があらためて認識されることとなった。

A．研究目的

CJD サーベイランスによって現在まで130 例を超える硬膜移植後の CJD の存在が明らかになっているところだが，更に迅速なサーベイランスによりプリオン病発病直前に脳外科手術等を受けた事例が次々と判明している．これに対して，難治水澤班研究成果のひとつである「プリオン病感染予防ガイドライン（2008 年版）」によって専門委員会等により策定されたプリオン病２次感染対策が周知されるなど対策がとられている。この状況を踏まえて本研究班では最新の知見に基づいた手術機械の滅菌方法の研究開発および詳細な分析を行っているところである。本分担研究では、海外でのプリオン病二次感染対策情報収集の方法を模索し、それにより情報を共有することをめざした研究を行う。この情報を通じて、本邦におけるプリオン病２次感染対策に反映させることにより、医療現場における安全性を担保するのが本研究の目的である。

B．研究方法
1）国際会議出席（クローズミーティング）
2）国際研究者間情報
3）その他
のそれぞれの方法により、情報収集を行った。

（倫理面への配慮）
　個人情報等の漏洩に配慮する必要があるが今回の方法で対象となる個人が特定されることはなく、特別な倫理面への配慮は不要である。

C．研究結果
1）スェーデン王国ストックホルムにおける　　EuroCJD　Meeting (200900604-20090605)に参加した。本邦からは、小職の他に　金沢大学神経内科山田正仁教授・自治医科大学公衆衛生中村好一教授・厚生労働省疾病対策課中田課長補佐が参加した。今回の本会議における話題のひとつは、英国で発覚した血友病患者剖検例に偶発的にみつかった、脾臓における CJD 陽性例である。血液製剤使用歴との因果関係が注目される。このケースについては各国から活発な質疑

があったものの、機密情報として取り扱いのため殆ど情報が明らかにならなかった。のちに入手した本症例に関する資料を（巻末資料1）（巻末資料2）として添付した。

2）前項（1）の研究会出席により明らかとなった情報は、EUROCJD諸国を中心としてEUROCJD guidance projectの存在である。この責任者はDr. Jesu's de Pedro-Cuesta（

Centero Nacional de Epidemiologia, Instituto de Salud Carlos III, Spain）である。本プロジェクトの動向は、今後の本邦におけるＣＪＤ二次感染対策においても重要なソースとなりうるため、今後もタイムリーな解析が必要であると考えている、

3）vCJDの全世界発症数をモニターした。最新情報を巻末資料（巻末資料3）として添付した。

D．考察

本邦においては、CJDと診断された患者に対するハイリスク手技において使用された機器は①可能な限り焼却廃棄②どうしても不可能なものは3%煮沸SDS法により処理するものとされている（プリオン病感染予防ガイドライン2008年版）。これに対して、英国(Dr RG Will)・オーストリア(Dr H Budka)等では原則廃棄の方針であり、本邦における方針との若干の差異があるようであることは前年度報告した。また通常脳神経外科手術機器の廃棄規定が定められているのは前述の調査（巻末資料2，14ページ）によれば15カ国であることに対して神経内視鏡についての廃棄規定を設けているのは9カ国であり、神経内視鏡に対する対応の混乱がみられている国際的現状が浮き彫りとなった。EuroCJD guidance projectはこれに呼応する形でのアクションプランである。

国際的にみても、硬膜移植歴があるCJD(dCJD)患者が130例を超える数で判明しているのは日本だけであり、諸外国では十数例―1桁台の発症である。変異型CJD(vCJD)に関しては英国における160例以上、という数にほぼ匹敵するものであり、残念ながら日本はdCJD大国と言わざるを得ない。国民感情を鑑みれば、本邦独特ともいえるdCJDの再発防止に万全の対策を立てることは必須であり、今回の英国における血友病患者におけるCJD陽性例に対する対策を継続的にモニターすることと呼応する。EuroCJD guidance projectの今後の動向が注目される。

E．結論

プリオン病の各国対策については英文公式文書等が公表されていないことも多く、また現状で公表されているガイドラインにおける将来的改変を見据えた各国状況等の個々の公式文書による検索は殆ど不可能と言ってよい。また、英国血友病患者における新知見を例にとっても、新たに生じた問題点については当該患者担当医の研究対象でもあるため、発症早期には公表される情報量・質ともに限界がある。したがって特に研究者間の個人的関係による情報は有用であった。

本研究班における研究成果が『現時点において単独で有用な手術機械の滅菌方法は見当たらない』であることを考えれば、プリオン病に纏わる安全性を担保し続けるためには今後とも海外情報の継続的アップデートを行う必要性ならびに研究者間情報交換を拡張継続することの必要性が認められたと考えている。

F．健康危険情報

特になし。

G．研究発表

1．論文発表

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2) Takumi I, Akimoto M. One-stage reconstruction using a vascularized calvarial flap for intractable scalp ulcers in relation with cranial implants without removing the whole prosthesis.Neurosurg Rev. 32(3), 363-368 , 2009.
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3) Takumi I, Akimoto M. Advantage of Catcher's mask cranioplasty for post-surgical infectious skin trouble. Childs Nerv Syst. 25: 493-495, 2009. (E pub 2009 Jan 17, DOI: 10.1007/s00381-008-0793-3)

4) 児玉南海雄, 太組一朗. プリオン病感染予防ガイドライン(2008 年版), p11－13, p84－91

H．知的財産権の出願・登録状況
（予定も含む。）
1．特許取得
　　なし
2．実用新案登録
　　なし
3．その他
　　なし

(**DH**) *Department of Health*

vCJD Risk Assessment Calculations for a Patient with Multiple Routes of Exposure

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Preface

This paper was developed in response to a request from the CJD Incidents Panel following the finding of abnormal prion protein in the spleen of a patient with haemophilia. Assuming that the abnormal protein represents a marker of vCJD infection, the paper sets the various possible routes through which such infection could have occurred, and considers their relative likelihood in various scenarios. As well as dealing with this specific "incident", the paper sets out a more general methodology for assessing multiple possible infection routes. The analysis was considered by the Panel at its meeting on 20th May 2009. The Panel concluded that there was no evidence to change its current advice to those patients treated with UK sourced pooled plasma products between 1980 and 2001 already notified as being "at risk of vCJD for public health purposes", or to notify any new groups of patients. This version of the paper repeats the analysis presented to the Panel, while giving slightly more background information for other readers, and is placed here for public record.

Introduction

1.   This paper offers an analysis of the recent finding of abnormal prion protein in the spleen of a haemophilic. This involves a patient exposed to multiple potential vCJD infection routes (including multiple blood component transfusions, repeated receipt of UK-sourced fractionated plasma products including some units linked to a donor who later went on to develop clinical vCJD, and several invasive biopsies) who was found at post mortem to have abnormal prion protein in one spleen sample.

2.   If this finding is interpreted as an instance of asymptomatic vCJD infection, this raises questions as to the operational meaning of the "prevalence" of infection. The discovery of abnormal protein in a single spleen sample was the only positive result after exhaustive investigation of tissues taken at autopsy of an elderly haemophilia patient who died of other causes with no symptoms of vCJD or other neurological condition. All other tissues from this patient tested for the presence of abnormal prion protein – fixed samples of brain, heart, liver, blood vessel, appendix, spleen and lymph node and frozen samples of frontal lobe, occipital lobe, cerebellum, lymph node and 23 other samples from the spleen – were negative. This individual would *not* have tested "positive" on any of the vCJD prevalence tests conducted so far, and possibly not even in a post mortem spleen survey (depending on the size of spleen sample used). Nor do we know whether someone with this limited distribution of abnormal prion protein would be infective - and if so, by what routes of transmission.

3.   For present purposes, however, these issues of interpretation are ignored. We simply assume that the abnormal prion protein found in this patient is a marker for asymptomatic vCJD infection: the task is then to investigate the relative likelihood of the infection having come from the various possible routes. This is done in order to inform discussion by the CJD Incidents Panel ("the Panel") as to the implications of the finding, and in particular whether the new evidence warrants any change to the "at risk" status of any individuals or groups.

4.   The ideal would be to quantify these likelihoods in a robust way. However, this is not possible due to the multiple uncertainties involved. These are well-rehearsed. We do not know the prevalence of infectious donors – and in this instance, some of the potential routes are dependent on prevalence while others are not, so the relativities change. The probability of an infected blood component (e.g. a unit of Red Cells) transmitting infection is uncertain - though on the precautionary approach adopted by the Panel, it is presumed to be substantial. The risks of plasma derivatives transmitting infection are even more uncertain. However, they can be estimated using methods suggested in an existing assessment by independent consultants DNV (DNV, 2003), which have been used in drawing up Panel recommendations to date. These calculations have also been regarded as "precautionary", i.e. giving a pessimistic view of the levels of infectivity likely to be present.

5.   Given these unknowns, we make no attempt at definitive probability calculations, though illustrative examples are provided. Instead, we concentrate on the more limited task of determining whether different groups in the complex chain of contacts associated with the index patient can be robustly placed under or above

the additional 1% (over the UK population risk derived from consumption of beef and beef products) "risk threshold" used by the CJD Incidents Panel to trigger decisions on notification of increased risk status. We also consider the wider implications for groups that are or might be classed as "at risk". Although the analysis does throw some light on these questions, it also highlights some conundrums for our understanding of vCJD prevalence and transmissibility. We note that there have been no clinical cases of vCJD amongst people with haemophilia treated with UK-derived pooled plasma products or UK-derived coagulation factors.

Summary of findings

6. Specifically, we conclude that on the evidence available:

    (i) **The chance of this patient having been infected via an endoscopic procedure is very small,** probably comparable to that of having been infected via primary (dietary) exposure. The potential risk associated with the endoscopies can be disregarded in assessing the risks associated with the possible blood-borne transmission routes. No specific action is called for with regard to patients who underwent endoscopies, and where the endoscope was subsequently used on the haemophilia patient.

    (ii) Comparing the blood-borne routes, **the patient is much more likely to have been infected through receipt of plasma products, rather than any of the 14 units of red cells known to have been received.** The implied risk of each of these 14 donors being infected appears to lie below the 1% threshold that would trigger "at risk" status.

    (iii) Given the large pool sizes involved (20,000 or more donations per pool), **the risk differential between "implicated" and "non-implicated" batches of blood product is not marked.** Unless the prevalence of infection is very low, there is a strong possibility of *any* given batch of blood products prepared from large pools sourced from UK donors in the period 1980-2001 containing at least one infected donation. This reinforces the logic of the CJD Incidents Panel's 2004 decision to consider all haemophilia and blood disorder patents exposed to such UK-sourced plasma products as an "at risk" group for public health purposes. On present evidence, there is no strong case for differentiating between sub-groups.

    (iv) DNV's 2003 risk assessment contains "pessimistic" (precautionary) assumptions regarding the levels of infectivity liable to be present in plasma products. These imply that a patient receiving many units of higher-risk UK-sourced products could be exposed to a significant risk of infection *whether or not* any of the batches were "implicated" (i.e. traceable to a donor known to have developed clinical vCJD later). It was for this reason that these recipients have been considered as an "at risk" group for public health purposes, and notified of this status. On balance, this individual patient may have been more likely to have been infected by receipt plasma product from of "non-implicated" batches, than by the much smaller quantities derived from "implicated" batches.

    (v) The lack of any clinical vCJD cases to date amongst patients with haemophilia may suggest that the DNV infectivity scenario is overly-

pessimistic. Risk assessments carried out elsewhere assume that a greater proportion of the infectivity would be removed during the manufacturing processes. This raises issues beyond the scope of this paper. Nevertheless, we have re-run the analysis using a markedly lower infectivity assumption with regard to plasma products, and the conclusions listed in (i) – (iii) still hold.

Method

7. The following analysis starts from the "reverse risk assessment" previously used by the Panel to assess the implied risks of donors to vCJD clinical cases being infected (DH, 2005a; Bennett, Dobra and Gronlund, 2006), and extends it to deal with this much more complex incident. We start with a simple example and then build up the analysis step-by-step. This is both to demonstrate how the conclusions are reached in this case, and to show how the same approach can be used to handle other complex incidents that may arise.

Example 1

8. We therefore start with a simple incident as shown in Figure 1(a). Here, a patient has received two single-unit Red Cell transfusions, one from each of two donors. The recipient goes on to develop vCJD, and the timing of the transfusions does not rule either of the donors out as the route of infection. What is the chance of each of these donors carrying vCJD infection?

Figure 1 (a) Two component donors, neither known to be infected
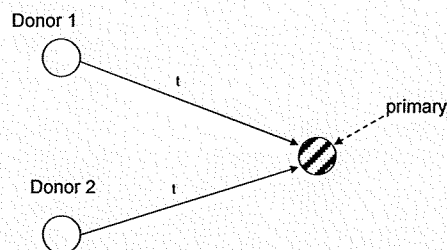
9. The answer to this depends primarily on the chance of transmission occurring *if* one of the donors were to be infected – i.e. the transmission probability, t. By definition, this lies between 0 and 1: if t = 1, transmission would be certain. In

that case, and all else being equal[1], the patient's disease would be equally likely to have come from primary infection, or from either of the two donors having been infected. So by implication, each donor would have a 1 in 3 chance of being infective.[2] More generally, if there are n donors, the chance of each being infective would be $1/(n+1)$.

10. The implied risks to the donors clearly diminish if $t < 1$. However, the CJD Incidents Panel has used a precautionary approach, concentrating on scenarios in which t is at least 0.5. With t in this range, the implied risk to donors remains high unless the number of donors to the vCJD case is large. For example, if $t = 0.5$, then with two donors the chance of either being infected would be roughly 0.25. Note that none of these calculations depend on the underlying prevalence of infection, provided this is the same for donors and recipients.

Example 2

11. The situation would clearly be very different if one of the donors was later diagnosed with vCJD, as in Figure 1(b).

Figure 1 (b) Two component donors, one known to be infected
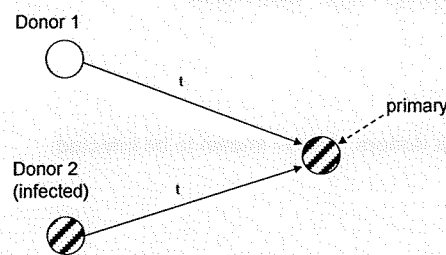
This creates a marked asymmetry between the infection routes, dependent on the prevalence of infection in the donor population. Whilst Donor 2 is now known to be infected, Donor 1's prior probability of infection is simply the prevalence of infection (p), unknown but assumed to be small. This situation provides an

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[1] "All else being equal" essentially means that there is no prior reason to suppose that donors or recipient were particularly likely or unlikely to have been infected with vCJD, e.g. through "high risk" surgery, or conversely not having lived in the UK during years of high BSE exposure.

[2] The arguments expressed here can be expressed more formally using Bayes' Theorem to update probabilities in the light of new information. However, this is presentationally more clumsy, especially in the more complex examples considered below.

exemplar for analyses in which some routes are prevalence-dependent and others are not.

Let:

P(D1) be the probability of the recipient's infection having come via Donor 1

P(D2) be that of the infection having come via Donor 2

and P(prim) be the probability of the recipient having a primary infection

- For simplicity, suppose that the chance of the patient being infected by more than one route is negligible. Then (given that infection has occurred) P(D1), P(D2) and P(prim) must add up to 1.

- Furthermore, the "balance" between the three probabilities will be governed by t and p. Specifically:
    o P(D1) will be proportional to both p (prevalence of infection) and t (transmission probability)
    o P(D2) will only be proportional to t
    o and P(prim) will only be proportional to p

12. Provided p is small (e.g. 1/4,000 or 1/10,000) and t is not, P(D2) will be *much* larger than either of the other two probabilities. To a very close approximation, P(D2) = 1 and P(D1) and P(prim) are zero. We can be virtually certain that the infection came from Donor 2. In practical terms, this new information about Donor 2 means that Donor 1 need not be considered as "at risk" according to CJD Incidents Panel criteria.

Example 3

13. In the last two examples, the two secondary routes had the same transmission probability, t. But suppose now that there are routes with different values of t – e.g. transfusion of blood components and receipt of fractionated blood products. Figure 2 below shows a situation in which the calculations need to balance two contrasting secondary routes:
    o a blood component transfusion, associated with a high transmission probability (t_1) *if* the donor (D1) is infected, but with no reason to believe that this is the case, and
    o a plasma product pool with a contributing donor (D2) now known to be infected , but with a low transmission probability (t_2)

As before, the three probabilities P(D1), P(D2) and P(prim) must add up to 1, and now:
    o P(D1) will be proportional to p and t_1
    o P(D2) will be proportional to t_2
    o and P(prim) will be proportional to p

Figure 2: One component donor, not known to be infected: plasma pool, containing an implicated donation
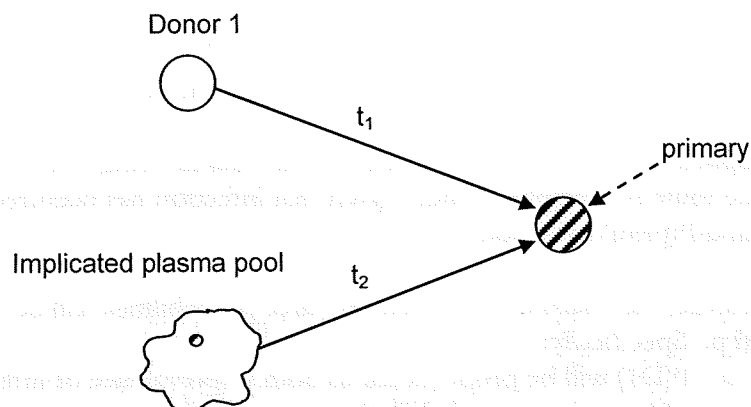
14. To illustrate numerically, suppose p is 10^{-4} i.e. prevalence of infection is 1 in 10,000, that $t_1 = 1$ and $t_2 = 10^{-3}$ (that is, transmission via the product pool is less efficient than via the transfused component by a factor of 1,000).

In that case, it can be shown that:

$$P(D1) = 1/12 \qquad P(D2) = 10/12 \qquad \text{and} \qquad P(\text{prim}) = 1/12$$

The infected plasma pool is thus clearly the most likely transmission route, by a factor of 10 over each of the other two possibilities.

15. The principles used to analyse these simple cases are now extended to consider the case of the haemophilic patient with a finding of abnormal prion protein in the spleen.

Analysis of the incident

16. Potential secondary transmission routes in this instance consisted of the following (where an "implicated" donor means one for which there is now evidence of having been infected with vCJD):

- 5 invasive endoscopic procedures (biopsies) and a larger number of endoscopies without biopsy.

- exposure to 14 units of Red Cells, each from different ("non-implicated") donors

- exposure to just over 9,000 units of Factor VIII made from two plasma pools with an "implicated" contributing donor (8,025 units from one batch and 1,000 from the other)

- exposure to many other units of UK-sourced pooled products, including nearly 400,000 units of Factor VIII, with no *known* links to "implicated" donors

To simplify the subsequent discussion, we consider the relative risks from each of these routes in turn.

Transmission risks from the endoscopies

17. vCJD transmission risks from endoscopy have been examined by an ACDP TSE WG subgroup, informed by an outline risk assessment. It is important to appreciate that these procedures involve a very small instrument (head) being passed down a very long, thin, channel. The possible "mechanics" of infection therefore differs from other surgical procedures. The group considered that any significant risk of onward transfer of infective material to a receptive site would require the procedure to be invasive, as distinct from examinations that involve the instrument sliding against the wall of the gut. On that argument, the relative risk from endoscopic procedures *not* involving biopsy would be negligible.

18. So concentrating on procedures involving biopsy, the question arises of whether the heads used would have been single-use. This would reduce the transmission risks considerably, but not eliminate them (due to the possibility of the new head being contaminated on its way down the endoscopy channel. Although we do not know whether the heads involved in these procedures were single-use, let us suppose they were not.

19. For endoscopy with re-useable heads, the best existing analogy is with the current surgical risk assessment as applied to procedures encountering lymphoid tissue. Depending on assumptions on the efficacy of decontamination, the "standard" model suggests that indefinite re-use of a set of instruments might cause $1 - 10$ secondary infections per operation on an infective patient. The infection risk to a random patient resulting from all previous re-uses of the instruments would be in the same range multiplied by the prevalence of infection (p). However, the surgical model considers the transmission risks from a set of 20 instruments, rather than just one (very small) biopsy head. For the latter, it therefore seems reasonable to reduce the estimated risk by a factor of at least 10. Even on pessimistic assumptions, therefore, the risk of infection from a "random" biopsy would be in the range $0.1p - 1p$. In other words, the chance of the patient being infected via any of 5 such biopsies would be similar to the risk of having been infected through the "primary" route of dietary exposure.

20. As will be seen below, the chance of this particular patient having been infected by the primary route are very small (in all scenarios) as compared to that of infection through a blood-borne route. On the above argument, the same applies to the endoscopic route. For simplicity, this route will therefore be disregarded in the following calculations. It should be noted that even if the risks of transmission via endoscopy were much greater than suggested here, the only effect on subsequent calculations would be to reduce the probabilities associated with all the blood-borne routes slightly.

21.   We now consider the relative probability of the patient's infection having come from the implicated plasma products, versus the 14 Red Cell transfusions. As discussed in the "methods" section, we need to balance the greater transmission probability for blood components (Red Cells in this instance) against the existence of an implicated donor contributing to the pooled plasma products. The situation is shown schematically in Figure 3, omitting for now the other "non implicated" plasma products.

Figure 3: 14 component donors, none known to be infected; 2 plasma products, each from a pool containing an implicated donation
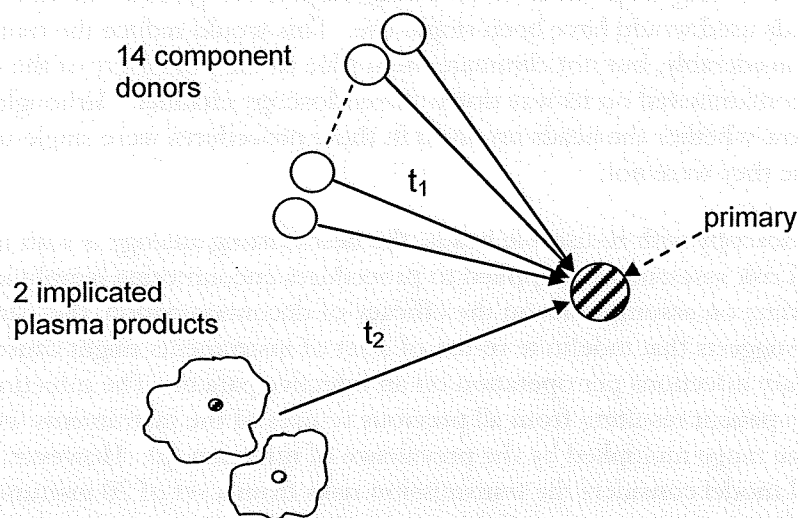
22.   The key additional variable here is t_2 – the chance of transmission from an implicated pool. This can be quantified using the infectivity assumptions originally generated in DNV's risk assessment (DNV, 2003). As discussed further below, the calculations initially use the more pessimistic of alternative infectivity scenarios considered by DNV.

23.   For the present, we also suppose that the *only* infected donation in the plasma pools came from the identified infected donor – though this is reconsidered below. As detailed in the first part of Annex A, calculations then suggest that this one infected donor would have resulted in the Factor VIII received by the patient containing a total infective dose of about 0.2 ID_{50} (0.16 via one pool and 0.05 via the other). Using the simple linear dose-response model that has informed Panel recommendations to date, this implies a transmission probability t_2 of approximately 0.1.

24.   We can then use the approach set out before to assign probabilities to the possible infection routes in different scenarios. Table 1 below shows the results, using this value for t_2 and alternatives of 1 and 0.5 for t_1 and 1 in 4,000 and 1 in

10,000 for the prevalence, p. The true value of p is unknown, but these values are consistent with the retrospective survey of stored appendix and tonsil tissue reported by Hilton *et al* (2004). The successive rows show the probability of infection having come from the implicated plasma products, from any *one* of the 14 component (Red Cell) donors, and from the primary outbreak. It can be seen that in all scenarios, the first route strongly dominates. Note that these are illustrative figures, using assumptions subject to much uncertainty. Nevertheless, they do suggest that the infection is much more likely to have come from the plasma products, with the implied risk to the component donors remaining clearly below 1%.

Table 1: Relative probabilities of potential infection routes (omitting "non implicated plasma" products)

Prevalence, p	1 in 4,000		1 in 10,000	
Transmission probability, t1	0.5	1	0.5	1
Probability implicated plasma products	98%	97%	99%	99%
Probability of each of the 14 component donors	<0.3%	<0.3%	<0.1%	<0.1%
Probability primary	<0.3%	<0.3%	<0.1%	<0.1%

Note: these are illustrative calculations only. All figures are rounded to the nearest %, or (for small probabilities) indicate an upper bound.

Implicated and "Non-implicated" plasma products

25.   Although the above analysis provides some robust conclusions about the infection routes considered so far, the calculations ignore one further factor: the chance of the infection having come from the "non-implicated" plasma products – i.e. those manufactured from plasma pools not *known to have* an infected contributing donor. The problem here is that because the pool sizes are so large (of the order of 20,000 donations each), there is a high probability that many of them did, in fact, contain infective donors even if one has not been identified. Crudely, if the prevalence were 1 in 10,000, one would expect each pool to contain about 2 infected donations.[3]

26.   This argument would not hold if the prevalence of infection amongst donors were *very* low (e.g. 1 in 1,000,000). Such low prevalence would be compatible with the results of the ongoing prospective tonsil survey reported by Clewley *et al* (2009). However, current advice from the Spongiform Encephalopathy Advisory Group (SEAC) is that the retrospective Hilton *et al* provides the most relevant indicator of sub-clinical vCJD in the general UK population. This suggests a prevalence of the order of 1 in 4,000, albeit with wide confidence intervals.

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[3]   More strictly, the expected number of infected donations in each pool will be subject to a binomial distribution. However, the distribution is not essential to the argument, especially for patients receiving high volumes of product sourced from many different pools, when these statistical fluctuations will tend to even out.

27. Even with the values of p considered here, there is still a distinction between the risks from implicated and non-implicated pools. Where there is known to be an infected contributing donor (and nothing is known about the rest), the other donors to that pool also have the same probability p of being infected. So with a prevalence of 1 in 10,000 and typical pool sizes of 20,000, one would reasonably expect a "non-implicated" pool to contain 2 infected donations and an "implicated" pool to contain 3. Nevertheless, this is not a great differential. The calculation suggests that unless the prevalence of infection is very low - much lower than considered here, there is only a modest difference in the risks posed by receipt of implicated and non-implicated plasma. This observation supports the existing policy of considering recipients of UK-sourced plasma products as a group, rather than applying additional measures to those with known exposure to implicated batches.

28. This specific haemophilia patient had received about 400,000 units of Factor VIII, the majority since 1980. On these calculations, the cumulative risk from the "non-implicated" batches may therefore have exceeded that from the smaller number of "implicated" ones. This can be illustrated by considering the expected number of ID_{50} received via each route. This is illustrated in the second part of Annex A. In summary:

   ▪ If the two "implicated" pools contained 3 infected donations, this route would have exposed the patient to a total dose of 0.6 ID_{50}.

   ▪ If the other "non-implicated" pools each contained 2 infected donations (although there is no evidence of any of the donors to these pools going on to develop clinical vCJD), this route would have exposed the patient to an expected total of 24 ID_{50}.

29. Simple application of the linear dose-response model would then suggest that whereas Factor VIII from the two "implicated" pools would have contained a dose liable to transmit infection with a probability of 0.3, the larger number of units sourced from "non-implicated" pools would have cumulatively contained more than enough infectivity to transmit. Crudely, this suggests that the "non-implicated" pools may represent the more probable source of infection, by a factor of about 3.[4]

30. This last calculation is reflected in Table 2 below, for prevalence scenarios of both 1 in 10,000 and 1 in 4,000. However, we stress that this is very simplistic. It rests on accepting the linear model uncritically, and assuming that doses received on successive occasions can simply be added together in calculating an overall risk of infection. Nevertheless, the comparison between "implicated" and "non-implicated" routes is instructive, in showing how the sheer number of exposures may come to dominate the presence of a known infection.

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[4] Note that the differential between *infectious doses* is much greater, but the practical effect is limited by infection being regarded as certain once the dose reaches 2 ID_{50}. As below, the risk differential between routes is therefore more pronounced in lower-infectivity scenarios.