内閣府食品安全委員会
平成15年度食品安全確保総合調査

食品の安全に係る緊急事態に備えた英国における
ｖＣＪＤの疫学に関する調査報告書

平成１６年３月

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1. 背景

クロイツフェルト・ヤコブ病（Creutzfeldt-Jakob Disease[CJD]）は、1921 年にクロイツフェルトとヤコブによって報告された大脳皮質、基底核、視床、小脳や脊髄の神経細胞の変性脱落、高度のグリオーシスならびに海綿状変化を特徴とする主として中年期以降に好発する疾患である。原因については 1968 年に Gibbs CJ 等がチンパンジーに患者の組織の一部を接種した実験に成功し、何らかの感染性疾患であることが判明した。その後長い間、感染因子は不明であったが、1982 年にカリフォルニア大学の Prusiner SB がタンパク性の感染因子プリオンがこの発症に重要な係わりを有していることを報告した。

このことが明らかになるにつれて、これまで原因不明とされていたクールー病や致死性家族性不眠症などいくつかの疾患の発病にプリオンが関係していることが判明した。さらに他の動物にも海綿状脳症をきたす疾患として 250 年以上前からヒツジのスクレイピー（Scrapie）や北米に局在するシカ類に発症する慢性消耗疾患（Chronic Wasting Disease[CWD]）などが知られていたが、これらもプリオンが発病に関係していることから、ヒトや動物のプリオン関連疾患はプリオン病と総称されるようになった。

CJD には以前から孤発性クロイツフェルト・ヤコブ病（sporadic Creutzfeldt-Jakob Disease[sCJD]）、家族性 CJD、ならびに医原性 CJD が存在することが知られていた。さらに英国で新しいタイプの CJD として変異型クロイツフェルト・ヤコブ病（variant Creutzfeldt-Jakob Disease[vCJD]）が 1996 年に報告された。vCJD は牛海綿状脳症（Bovine Spongiform Encephalopathy[BSE]）がヒトへ感染して発症する可能性が示唆され、それが 1996 年に英国議会において報告された。

2. 英国におけるBSE及びvCJDの歴史

英国におけるBSE及びvCJDの歴史について、簡潔に述べる。

1986年11月　中央獣医研究所（Central Veterinary Laboratory[CVL]）で、ヒツジに発生するスクレイピーがウシにも発生することがわかった（BSE感染牛の始まり）。

1987年　疫学調査開始、感染ルートが肉骨粉（Meat and Bone Meal[MBM]）であることが判明した。

1987年　South Wood Working Party 設置、ヒトへの感染について、神経リンパ組織等のリスクのある部位の接触、医療用具による感染、職業曝露によるリスクの可能性が指摘された。

1988年7月　農業水産食料省（Ministry of Agriculture, Fisheries and Food[MAFF]）は、反芻動物（ウシ、ヒツジ、ヤギ）を MBM の原料とすることを禁止した。BSE感染疑いの牛すべてをと殺し、焼却処分した。

1989年　Tyrrell報告書に基づき国立CJDサーベイランスユニット（National CJD Surveillance Unit[NCJDSU]）が設置された。

1989年2月　South Wood Working Party が「BSE のヒトへの感染リスクは低い」と報告した。

1989年11月　脳、脊髄、脾臓、胸腺、扁桃腺、腸管を特定部位牛臓物（Specified Bovine Offal[SBO]）と指定して、ヒトの食物への使用を禁止した（Human SBO Ban）。動物、家禽への餌を目的として販売、供給、使用停止、欧州連合(EU)への輸出を停止した（Animal SBO Ban）。

1990年　英国保健省(Department of Health[DH])とMAFFが、継続的討論を行うための海綿状脳症諮問委員会（Spongiform Encephalopathy Advisory Committee[SEAC]）を設置した。

1990年5月　ウシ科動物以外(ネコ)にもBSE類似症状が報告された（ブリストール大学）。

1992～93年　この頃、牛より毎月3500頭のBSEが発生した。

1993年　畜産農家の15歳少女にCJD症例が報告された。

1993～94年　畜産農家における3例目の症例では、BSE感染牛が2頭いた。4例目の発症は1991年に感染牛発症の畜産農家であった。

1996年1月　SEACにおいてNCJDSUから、1970～89年では30歳以下のCJD患者は報告されていないが、1990年以降4例発生の疑い、1例の確定診断の報告があった。

1996年2月　LancetにCJDが若年者に増加していることが報告された[1)]。

3. BSE及びvCJDの発生状況について

BSEは1986年にはじめて英国に発生した。その3年後にはアイルランドに飛び火し、1990年にはポルトガルやスイスに、さらに1991年にはフランスへと拡がった。その後ヨーロッパ各地で発生し、2001年には日本で、2003年には北米で発生が見られ、2003年までには世界24か国にまで拡大した。表1に示すようにvCJDについては2004年3月1日現在、全世界で156人であり、英国以外においては10人となっている。

さらに図1に示すように、1995年頃からヨーロッパ各地で発生件数は増加している。

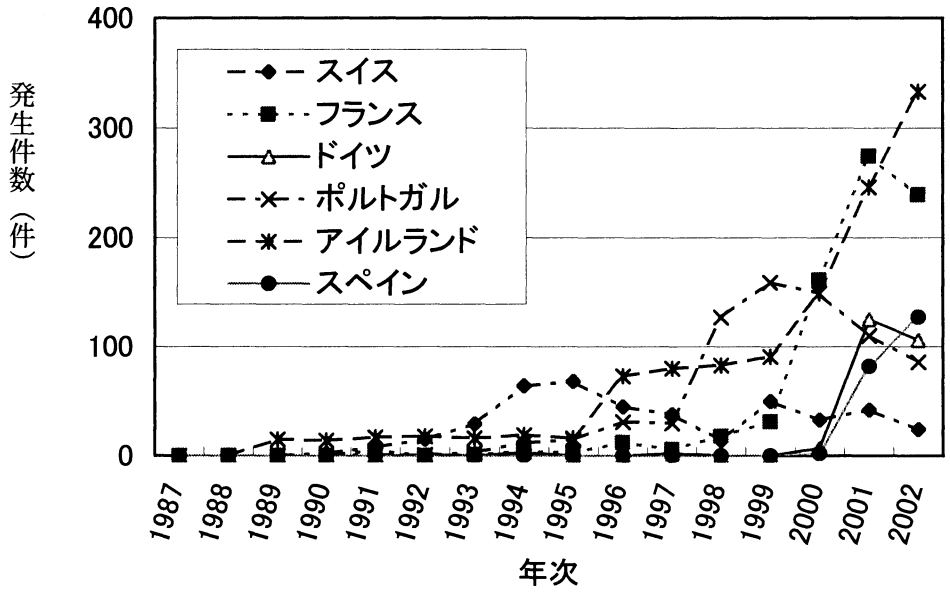
表1　BSE発生総数とvCJD患者数

国名	BSE発生総数(頭) 2004年3月11日 (OIE調べ等)	vCJD患者数(人) 2004年3月1日 (DH調べ等)
英国	183,803	146
アイルランド	1,377	1*
フランス	891	6
ポルトガル	866	0
スイス	453	0
スペイン	403	0
ドイツ	305	0
ベルギー	121	0
ルクセンブルク	2	0
オランダ	73	0
リヒテンシュタイン	2	0
デンマーク	13	0
オーストリア	1	0
チェコ共和国	9	0
フィンランド	1	0
ギリシャ	1	0
イタリア	117	1
日本	11	0
スロバキア	14	0
スロベニア	3	0
イスラエル	1	0
ポーランド	11	0
カナダ	2	1*
米国	1	1*
合計	188,481	156

*:英国滞在歴のある患者

資料1：国際獣疫事務局（Office International des Epizooties[OIE]）提供(2004.3.11)
資料2：DH提供（2004.3.1）

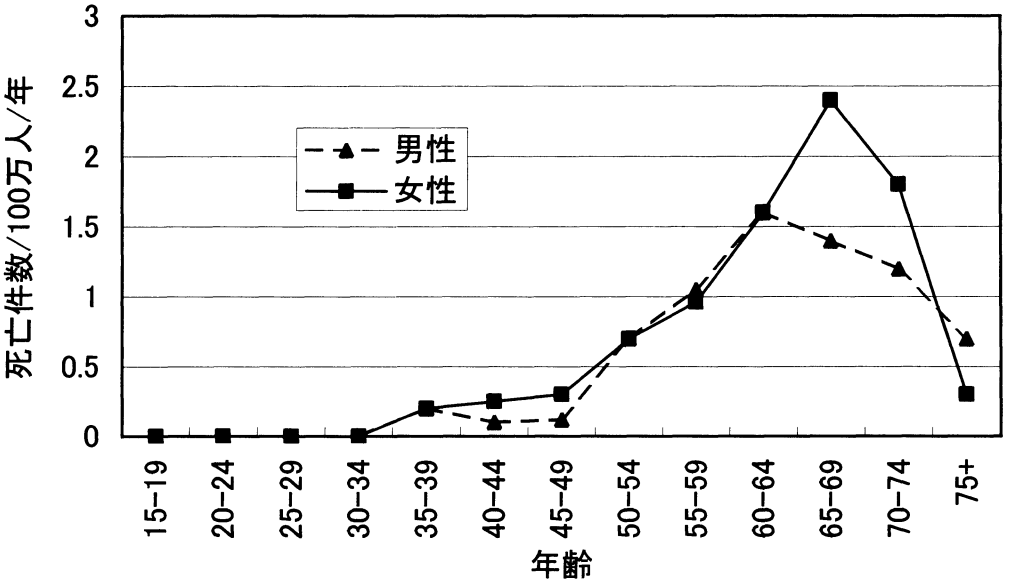
図1　主要ヨーロッパ諸国における BSE 発生件数の推移



資料 3：Smith PG 提供（2004.3.8）

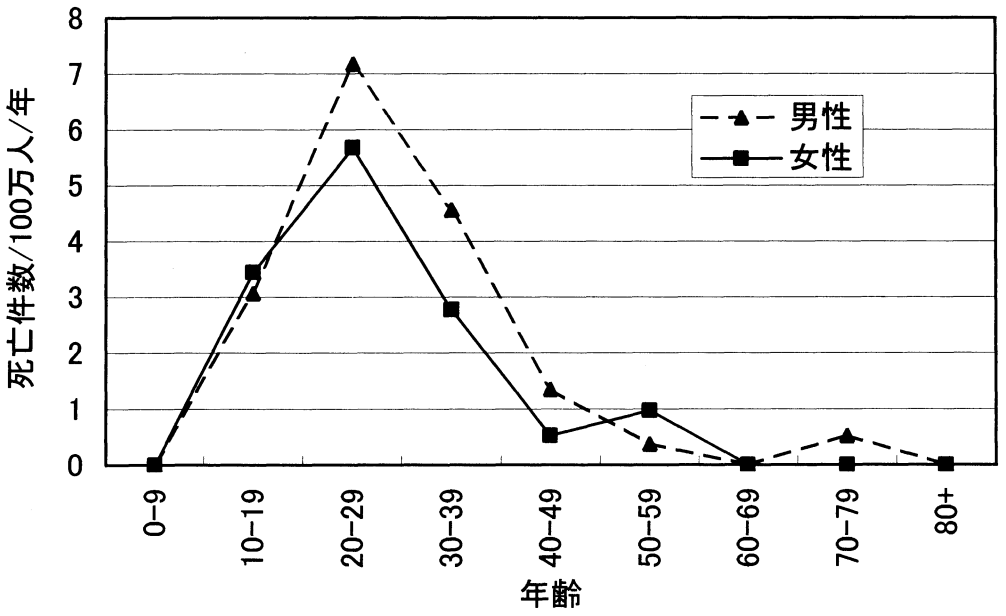
sCJD と vCJD においては、好発年齢に違いがみられる。sCJD は、図 2 に示すように中年期以降に好発する。一方、vCJD は、図 3 に示すように 10 歳代から 30 歳代の若年層に多発している。また vCJD の症状などの特徴は、1996 年に Will RG 等によって報告された症例については表 2 に示す通りである。今日までに sCJD と vCJD の相違点として認められている所見を表 3 に示す。

図 2　英国における sCJD の年齢分布



資料 3：Smith PG 提供（2004.3.8）

図 3　英国における vCJD の年齢分布



資料 3：Smith PG 提供（2004.3.8）

表 2　若年に発生したCJD症例（10例、後にvCJDと強く疑われた）の主症状[1)]

発病年齢	性	発病年	死亡年	罹病期間	症状	精神症状	失調	痴呆	ミオクローヌス
16歳	女	1994	生存	>22月	傾眠	＋	＋	＋	＋
18	男	1994	1995	11	行動変化	＋	＋	＋	＋
19	男	1995	1996	13	人格変化	＋	＋	＋	－
26	女	1994	1996	22.5	傾眠	＋	＋	＋	＋
28	女	1995	1995	10	記憶障害	＋	＋	＋	＋
28	女	1994	1996	11	行動変化	＋	＋	＋	＋
29	女	1994	1996	17	憂鬱	＋	＋	＋	－
29	男	1995	1995	7.5	足痛	＋	＋	＋	＋
31	男	1995	生存	>6	記憶障害	＋	＋	＋	－
39	女	1994	1996	21	傾眠	＋	＋	＋	＋

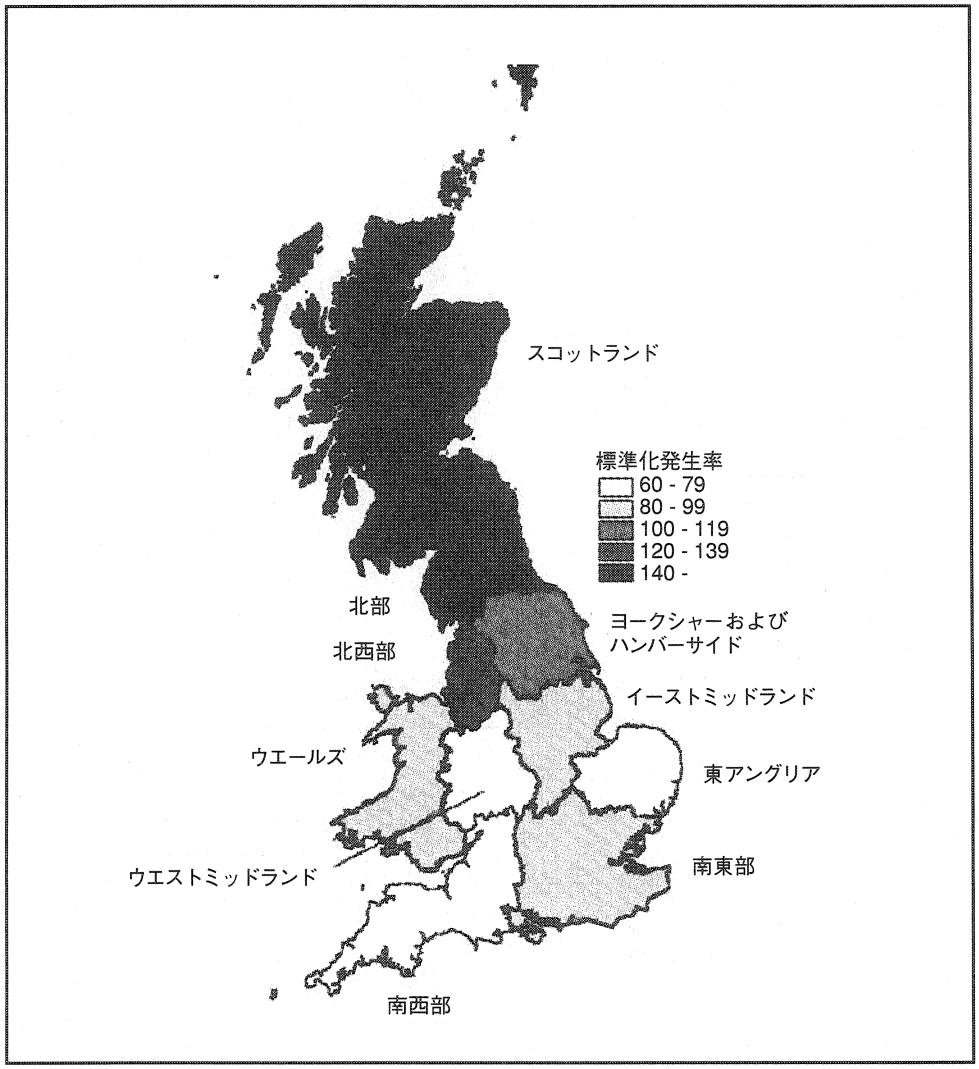
表3　sCJDとvCJDとの比較

		sCJD	vCJD
平均発症年齢（歳）		65	26
平均罹病期間（月）		5	13
主な臨床的特徴	初期症状	痴呆 失調	精神症状 行動変化 異常感覚
	臨床経過	ミオクローヌス 視覚異常 無動性無言	失調 不随意運動 痴呆
脳波		PSD	非特異的異常（PSDを欠く）
MRI		皮質や基底核の異常信号	視床枕徴候
脳病理（海綿状変化＋）		まれにアミロイド斑	クールー斑
PrP （ウエスタンブロット法解析）		タイプ1，時に2A	タイプ2B
PrP遺伝子コドン129多型		MM/MV/VV	MM*

*：現在まではMM型のみ確認され、MV、VVの患者は認められていない。

図4に示すように英国のNCJDSUによると、vCJDは中部から北部にかけて多発している。

図4　英国におけるvCJDの標準化発生率



資料3：Smith PG提供（2004.3.8）

BSEは動物の種の壁を越えた人獣共通感染症であり、現在、英国では、総合的にヒト伝達性海綿状脳症（Transmissible Spongiform Encephalopathy[TSE]）に対する対策として取り組んでいる。

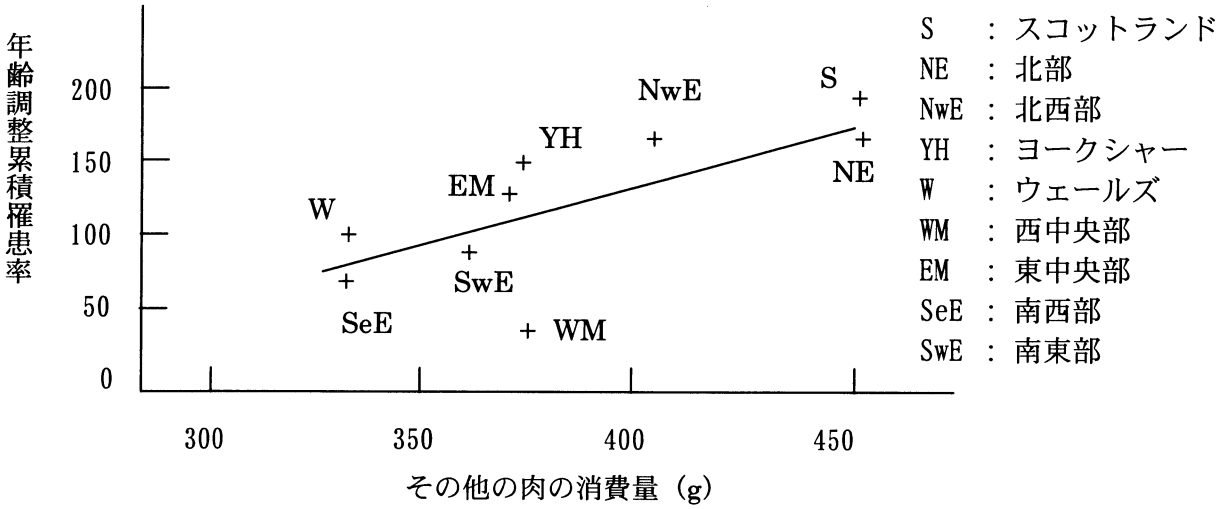
4. vCJDとBSEとの疫学的な関連について

従来、英国においてBSEがヒトに感染しvCJDを引き起こすことについては意見が分かれていたが、1996年に当時の保健大臣はBSEがヒトに感染する恐れがあることを表明した。Lancetに掲載された論文にその可能性が言及されたことがその根拠になっている[1)]。その後、レスター州におけるvCJDの集団発生例も報告され、ヒトへの感染の可能性を支持するものとなった[2)]。

地域ごとに標準化して累積罹患率を計算し（1991年国勢調査人口を標準）、それぞれの地域における1週間のその他の肉製品（通常の肉やベーコン以外の肉、機械回収肉（Mechanically Recovered Meat[MRM]）や中枢神経からの high-titer BSE agent material を含む、図5では「その他の肉」と表現）と平均消費量との相関をみると、図5に示すように北部の地域で罹患率および１週間の消費量がともに高く、両者の間に正の相関関係が観察された（相関係数0.72, p=0.03）。

このように、地域差に関連する要因として、牛肉の特定危険部位の消費量や社会経済因子が考えられるが、いずれもvCJD発生率の地域差を十分説明できるものではない、と述べている[2)]。

図5　地域別にみたその他の肉の1週間の平均消費量とvCJD累積罹患率との相関関係[2)]



これまで（2003年）英国でBSEであったと考えられる牛は100万頭を超えるといわれている。事実、英国で飼育されている牛の数は1974年から1996年に1360万頭から1020万頭へと減少している。

現在まで英国でvCJDに罹患した患者数は146例となっている。これらの感染牛がすべて食用として消費されたと仮定すれば、もっと多数の患者発生が予想されるという見方も英国にはある。過去に汚染牛肉を摂取した人達が長い潜伏期間を経て今後vCJDを発症する可能性があるが、英国の専門家たちの多くは、今後患者数が飛躍的に増加するよりは、むしろ減少していくという推計をしている。

vCJDの症例については若年者に多いことや表4に示したようにコドン129の多型でメチオニン／メチオニン（MM）にしか発病していないことが判明している。

表 4　vCJD と PrP 遺伝子の多型性

コドン 129 の型	人口全体	sCJD	vCJD
MM	37%	82%	100%
VV	12%	8%	0%
MV	51%	10%	0%

(M:メチオニン　V:バリン)

資料 3：Smith PG 提供（2004.3.8）

CJD の年間罹患率が人口 100 万人に 1 人程度であるのに対して、表 5 に示したように、vCJD が特定の地域に多発したことが、BSE と vCJD との関連を疑う根拠の一つになっている。

表 5　英国における vCJD の地域別発生状況

地域	人口（16-54 歳）	vCJD 患者数（人口 100 万対）
スコットランド	268.4 万人	8（2.98）
北部	159.2	5（3.14）
北西部	329.4	6（1.82）
ヨークシャー	256.8	7（2.73）
ウェールズ	146.1	2（1.37）
西中央部	275.0	1（0.36）
東中央部	212.2	4（1.89）
東アングリア	107.2	1（0.93）
南西部	237.9	3（1.26）
南東部	947.0	14（1.48）
計	2939.3	51（1.74）

資料 4：Will RG 提供（2004.3.5）

疫学研究以外でも、プリオンタンパク質の解析や動物実験により、vCJD と BSE の関連を支持する所見が得られている。2003 年 11 月に公表された vCJD GAC Investigation Working Group の見解では、ヒトの vCJD は、BSE からヒトに伝播する科学的証拠があることを表明している[3)]。しかし、これまでも英国の専門家の意見はあくまで「ヒトに感染するおそれがある」という表現にとどまっている。現在でもプロトコルに基づいてヒトのプリオン病に関するサーベイランスを続けている（資料 5）。

5. 疫学による vCJD の原因追求について

1) レスター州の集団発生

レスター州の人口は 870,000 人である。2000 年 11 月 10 日までに、レスター州から 5 人の vCJD が発生した。その発生頻度は人口 100 万人あたり 5.7 となり、英国の年間 1.5 に比較して 3.8 倍の高頻度である。疫学調査の結果から 5 人の全ての症例がいずれもたびたび牛肉を食べていたこと、5 人のうち 4 人は特定の 1 軒の肉屋から肉を購入しており、その店は牛肉を自家処分し、脳の解体などによる感染の可能性が高かったことが指摘されている。さらに、この牛はフリーシアン地方で飼育され、36 か月前後の牛であることなどから、脳の解体によって汚染された肉を食したとの仮説が考えられている。

他の 6 つの地区を対照とした症例対照研究によるオッズ比は 15（95%信頼区間：1.6-139）と有意に高い発生頻度となっている。この場合の潜伏期間は 10 年から 16 年間ということになる。ただし問題点として思い出しバイアス（過去のことをさかのぼって調査すると、忘れていたり、本人にとって都合の良いことだけを思い出すなど記憶についてのバイアスがあること[recall bias]）や面接によるバイアス（面接者が予め期待するように被面接者の回答を誘導するために生ずるバイアス[interview bias]）があることも考慮する必要がある。さらに牛の脳から人の手を介して汚染された肉を食べて発病したという可能性も考えられることを Will RG が指摘している。

2) 症例対照研究

これまでに収集された vCJD の症例 51 例と一般対照 116 例について、食事、外科手術の有無、職業に関する症例対照研究を実施した結果、一部の食事の摂取頻度に有意差が認められた。ここでいう一般対照とは、英国で最大の独立した社会研究機構である、国立社会研究センター（National Center for Social Research）により設定された一般集団から抽出された人々を指す。すなわち、「ソーセージの消費が週 1 回以上」のオッズ比が 8.4（95%

信頼区間:2.2-32.5)と「MRM の消費が週 8 回以上」のオッズ比が 4.4(95%信頼区間:1.5-12.7)と有意であった。また、この場合も思い出しバイアスを避けることができない。また症例の頻度が低いことや、すでに本人が死亡しているために代理人の証言であること、倫理上の問題などがあり症例対照研究の結果の解釈にあたっては、これらの点も考慮して判断する必要がある。今後、さらに例数を増して症例対照研究を行う必要があることも英国では指摘されている。

3) 地理的分布

vCJD の地域集積性をみるために、vCJD 地域研究班[4] (vCJD Geographically Associated Cases Investigations Working Group) によりマップ化が試みられた (資料 4)。レスター州以外では、いずれの地域においても集積性は認められなかった。これは、もともと発生頻度が低いことと、同じ地区 (5km の範囲) から 2 例以上の発生事例が 10 地区以下で、疫学的解析にたえられないことによると推測される。外科手術や肉屋による集積性は認められなかった。

地域的には同じ肉の販売ルートにあるものが認められたのが 6 州、同じ学校が 3 州、共通の社会的接触が 2 州、共通の家庭医、病院、歯科医が 4 州、同じ予防接種が 1 州に認められた (資料 4)。これらについては今後詳細な疫学的な追求が必要であると、地域研究班は述べている。

4) 輸血による伝播

英国において輸血による感染が疑われる 1 症例の報告があり、vCJD に罹患した患者が罹患前または潜伏期間中に輸血を受けていたことが判明した。2004 年の Lancet での報告によると、vCJD の症例から輸血を受けたのは 48 例で、そのうち 1 例が vCJD を発症していた[5]。この事実から輸血を介しての伝播の可能性が疑われ、大きな社会的問題となった。

DHが医学的侵襲によるCJDについて検討を行うために設置したCJD Incidents Panelでは、患者が過去において受けたと考えられる外科治療、歯科治療ならびに献血等についての追跡調査を行った[6]。その結果、48例は感染の疑いのある血液の輸血を受けたと推察された。しかし、現在までに判明した範囲では、その内の大部分は輸血を必要とした病気のためにすでに死亡しており、生存者の15人からのvCJDの発症者はいなかった。現在、残りの症例について追跡調査中である。

この問題は社会的にも大きな反響をよび、議会でも大きく取り上げられた。しかし、現在のところ検査方法も確定しておらず情報収集および通報システムなどの体制も十分でないことから、確実な場合を除いてはCJD Incidents Panelで追跡することにしている[7]。この症例についても、潜伏期間を考慮すると確実に血液を介して感染したとは言いきれないことから、予防的な見地から「感染のおそれがあるので」という表現にとどめている。この他、これらの血液から作られた新鮮凍結血漿（FFP）から曝露したと考えられる人数は数千人に達すると考えられるが、追跡の実施が困難である。輸血に関連すると思われるvCJD症例の同定は、輸血医薬品疫学レビュー（Transfusion Medicine Epidemiology Review[TMER]）研究によって行われている[8]。進行中の症例対照研究では、輸血に関して有意なオッズ比は得られていない。血液感染の可能性は偶然であることも否定しきれない。食品からの感染の可能性もある。このように、現時点では輸血が感染源となった科学的根拠はないものの、この報告は血液を介しての伝播の可能性についての重要な事実と受け止められている。

現在英国では血漿製剤は米国から輸入したものを使っている。また血液の白血球除去処理（ろ過による白血球の除去）の検討システムではヒツジを使っての感染モデルはすでに完成しており、現在これを用いて血液成分毎の研究が行なわれている。英国において血液は最大の問題であるが、これについては、血液安全委員会（Blood Safety Committee）で検討している。DHのStephenson Jは、同委員会は一般国民の献血は制限していないし、輸血による感染の危険性についてそれほど高くないと国民に伝えていると、述べている。

組織感染性については動物モデルを使って組織株特異的病理学研究（Strain Specific Pathology）を実施することとしている。現在、プロテアーゼ抵抗性のプリオンタンパクに対する研究、プリオン抗体に関する研究、レトロスペクティブに扁桃と虫垂の標本収集による解析を行っている。

5）その他の vCJD の危険因子

このほかに可能性は低いとしても、vCJD が伝播する可能性のある要因としては、食事、職業、社会経済要因、2 次感染、薬剤、予防接種、ヒト間の直接伝播などが考えられる（資料 4）。これらの要因を取り上げた症例対照研究を行っている。これらについて、現在までに判明した事柄を表 6 に示したが、いずれも可能性は著しく低いものと推察される（資料 4）。

表 6　vCJD の感染経路として疑いのある要因

1	食事	BSE に汚染された肉の摂食
2	職業	vCJD 検査、肉の取扱い業者
3	社会経済要因 （社会的地位、都市居住か農村居住か）	不明
4	2 次感染（血液、外科手術）	輸血、外科手術器具
5	薬剤	不明
6	予防接種	不明
7	ヒト間の直接伝播	不明

資料 4：Will RG 提供(2004.3.5)

6. vCJD 患者発生の将来推計について

vCJD の患者発生の将来推計については、表 7 に示すように、どのような要因を推計式に入れるかによって推計値は異なってくる（資料 6)。これまでの推計では将来患者数は増加することが前提になっていた[9]。現在は、図 6 に示すような Huillard J の推計式により、図 7 に示すように死亡者数が推定されている[10]。この方法によれば今後減少してくるものと推計されている。

表 7　定常モデルをあてはめた場合と二次指数モデルをあてはめた場合の 2004 年の推計患者数[10]

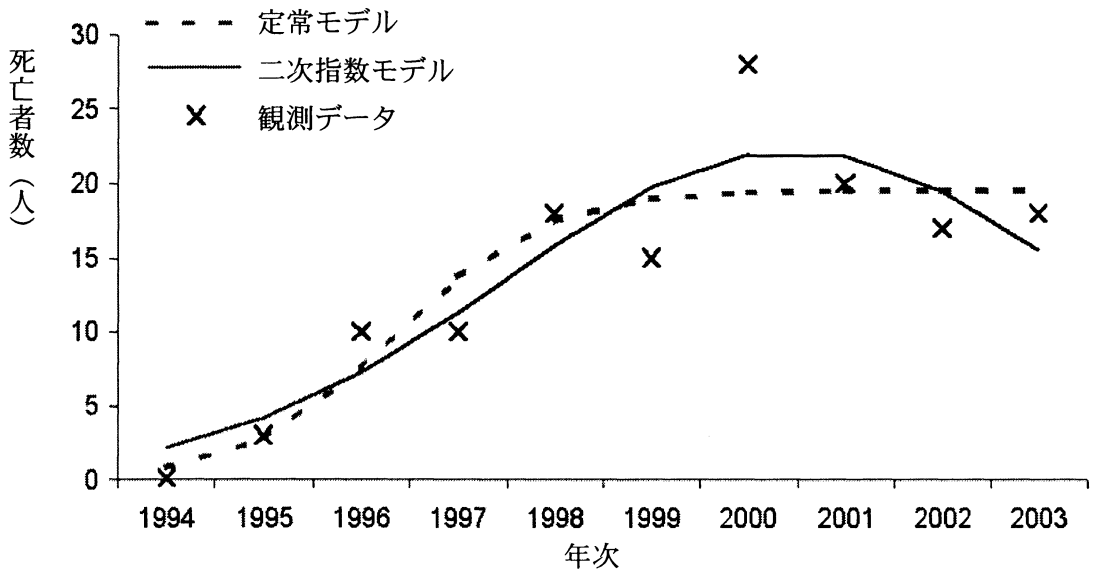
	死亡（95％信頼区間）	診断（95％信頼区間）
定常モデル	19（10-29）	20（11-30）
二次指数モデル	11（ 4-19）	11（ 4-19）

図 6　vCJD の患者数の推計式（Huillard J 等による）[11]

推計モデル式　$$n(t \mid \rho,\theta) = \int_a^b i(s \mid \rho) f(t-s \mid \theta) ds$$

$n(t \mid \rho,\theta)$ ：t 時点の発病した患者数
$i(s \mid \rho)$ ：s 時点で新たに罹患した患者数
$f(t-s \mid \theta)$ ：潜伏期間の分布
ρ と θ ：上記の潜伏期間と罹患した患者数の未だ知られていない変数
$\int_a^b$ ：流行が起こってから感染の危険がなくなるまでの期間

図 7 vCJD による死亡者数の推移についての定常モデル及び二次指数モデル [10)]



確かに英国における BSE の年間発生数は 1992 年の 37,488 頭をピークに減少し [11)]、2002 年には 445 頭になっている（資料 3)。これまで届け出られた BSE 感染牛の数は約 18 万頭であるが、Smith P は 100 万頭にも及ぶかもしれないと述べている。

また英国では当初は vCJD と BSE の因果関係を否定してきたことから当然、これらの牛肉は食用に供せられてきたことは想像に難くない。もちろんこのような推計をもたらした原因は種の違いなど生物学的な根拠もあるが、早期に対策を講じてきた英国の関係者の努力も大きくかかわっているものと推察される。しかし vCJD が BSE 感染牛の摂食のみによって起こるとしたら、患者発生数は潜伏期間を考慮しても、相当数の患者数があっても不思議はない。つまり推計が正しいとしたら、患者の PrP 遺伝子コドン 129MM 多型以外にも、vCJD の発病には未だ判らない他の要因がかかわっている可能性がある。また将来推計に用いた数字が 160 例と少ないことから、推計値の 95%信頼区間が幅広いと考えられる。

7. 英国で行っている研究の概要について

DHにおいてはTSEについて2002年において4,674,000英ポンドを確保し、6つの分野に分けて研究を進めた[12]。

①疫学とサーベイランス	787,000英ポンド	(約1億5,740万円)
②血液の安全性	47,000英ポンド	(約 940万円)
③感染性と分類	198,000英ポンド	(約3,960万円)
④診断と検査	2,277,000英ポンド	(約4億5,540万円)
⑤治療薬の開発と評価	335,000英ポンド	(約 6,700万円)
⑥汚染除去	1,030,000英ポンド	(約2億 600万円)

※) 1英ポンドは200円で換算

1) 疫学とサーベイランス

2002年度までに報告されたvCJDの症例数の数学的な解析を行い、vCJDの流行は1999年にピークに達していると考えられた。今までに報告された症例においては、PrP遺伝子のコドン129のメチオニンについてはホモ接合体であったことが判明している。

高齢者の非定型痴呆と若年小児の進行性知的神経学的退行症(Progressive Intellectual and Neurological Deterioration[PIND])についてはvCJD症例が誤診されていないか調査を行っているが、いずれもvCJDの症例が見逃されていたという事実はなかったと報告されている。

vCJDに関する症例対照研究の結果については、SEACの下に設置された疫学部会において検討を2002年に行い、新しいプロトコールを作成した上で再調査することとしている。

虫垂におけるPrP^{SC}の検出が報告されたことにより、英国民のvCJD罹患率についての関心が高まった。イングランド及びウェールズにおいて扁桃除去術を行った症例について、PrP^{SC}の検査を行うこととしている（資料7）が、健康保護庁（Health Protection Agency[HPA]）においてこの調査は行われており、2006年までに1万検体を目標としている。

2）血液の安全性

輸血によるスクレイピーの伝播に関するヒツジの実験では、その知見が集積されつつある。血液製剤から白血球を除去し、分画することにより、スクレイピーの感染を防ぐ可能性について調査を実施している。

vCJD 症例に関して献血歴を調査し、輸血者において vCJD が発症するか否かの追跡調査を行う TMER が行われている。この調査が続けられることにより、輸血による vCJD の発症の可能性の検証ができる。輸血用血液のスクリーニングに利用できるプリオン検出法は確立していないが、その実用化に向けて研究を進めている。

3）感染性と菌株分類

脊髄、脳脊髄液、虫垂、リンパ節、末梢神経、後根神経節、三叉神経節、骨髄の感染性に関する分析が行われている。今後その対象を広げ眼、歯髄、歯肉、遠位回腸、骨格筋、腎臓、副腎、心臓、肝臓、肺などに対して調査を進める計画を DH はもっている。

4）診断と検査

CJD 関連研究における vCJD 臨床症状発現前の診断方法の確立は、なかでも、DH において重要なものと考えられている。しかし診断方法の確立はされていないのが現状である。また、vCJD 診断用モノクローナル抗体開発を進めているが、医学研究会議(Medical Research Council[MRC])においてプリオンの研究として支援されることとなっている。

一方、TSE 全般にわたる診断方法として核磁気共鳴画像の確立を行うことが、NCJDSU において研究されている。

CJD に感染したが臨床徴候を示していない患者についてスクリーニングが可能となる医学的侵襲のない方法の確立は重要な位置づけとなっている。手法の確立に先立ち利用方法の検討が医監（Chief Medical Officer[CMO]）の指示によりはじめられており、HPA においてまず CJD スクリーニングに関連する倫理問題を検証することとしている。

5）治療薬の開発と評価

英国政府では従来から治療薬の開発を進めているが、MRC においても CJD の治療薬として検討されているキナクリンに対する臨床試験プロトコールの作成について検討を行った。作成されたプロトコールは MRC みずからピア・レビューを行っている。

また、臨床試験を開始する前に、既に CJD 治療にキナクリンを使用した症例で得られた知見について再検討を行うこととしており、その知見の回収作業が進められているところである。

6）汚染除去

この分野についても従来から研究を進めている。Jeffris D が議長を務める、外科用機器汚染除去研究作業部会（Working Group for Research into the Decontamination of Surgical Instruments）において汚染除去に関する研究を指揮している。主な研究としては、オートクレーブによるプリオン除去方法、オゾンを用いたプリオン除去方法、磁気共鳴センサー（Magnetic Resonance sensors[MARS]）を用いたプリオン検出等がある。

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文献 1

A new variant of Creutzfeldt-Jakob disease in the UK

A new variant of Creutzfeldt–Jakob disease in the UK

R G Will, J W Ironside, M Zeidler, S N Cousens, K Estibeiro, A Alperovitch, S Poser, M Pocchiari, A Hofman, P G Smith

Summary

Background Epidemiological surveillance of Creutzfeldt–Jakob disease (CJD) was reinstituted in the UK in 1990 to identify any changes in the occurrence of this disease after the epidemic of bovine spongiform encephalopathy (BSE) in cattle.

Methods Case ascertainment of CJD was mostly by direct referral from neurologists and neuropathologists. Death certificates on which CJD was mentioned were also obtained. Clinical details were obtained for all referred cases, and information on potential risk factors for CJD was obtained by a standard questionnaire administered to patients' relatives. Neuropathological examination was carried out on approximately 70% of suspect cases. Epidemiological studies of CJD using similar methodology to the UK study have been carried out in France, Germany, Italy, and the Netherlands between 1993 and 1995.

Findings Ten cases of CJD have been identified in the UK in recent months with a new neuropathological profile. Other consistent features that are unusual include the young age of the cases, clinical findings, and the absence of the electroencephalogram features typical for CJD. Similar cases have not been identified in other countries in the European surveillance system.

Interpretatlon These cases appear to represent a new variant of CJD, which may be unique to the UK. This raises the possibility that they are causally linked to BSE. Although this may be the most plausible explanation for this cluster of cases, a link with BSE cannot be confirmed on the basis of this evidence alone. It is essential to obtain further information on the current and past clinical and neuropathological profiles of CJD in the UK and elsewhere.

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Introduction

Because of the epidemic of bovine spongiform encephalopathy (BSE) in cattle, surveillance of Creutzfeldt– Jakob disease (CJD) in the UK was reinstituted in May, 1990. The purpose of the surveillance is to identify changes in the pattern of CJD which might indicate an association with BSE. We report ten cases of CJD in the UK with clinical onset of disease in 1994 and 1995. These cases all have neuropathological changes which, to our knowledge, have not been previously reported. They are also unusual in that they occurred in relatively young people, and the clinical course was not typical of cases of sporadic CJD in the UK.

Methods

Since May, 1990, cases of CJD have been identified to the CJD Surveillance Unit, usually by direct referral from professional groups, which include neurologists and neuropathologists. All death certificates in the UK on which CJD is mentioned are obtained and some cases are identified retrospectively in this way; some are identified from other sources. Clinical details are obtained for all cases, and information on potential risk factors for CJD is obtained with a standard questionnaire, usually administered to a close relative of the case. After obtaining informed consent from the relatives or patients, blood is obtained for DNA analysis in most patients. Information on all known cases of CJD in England and Wales since 1970 and in Scotland and Northern Ireland since 1985 is also available from previous surveys of CJD[1]. Parallel studies of CJD have been carried out in France, Italy, Germany, and the Netherlands between 1993 and 1995 with similar methods[2].

Whenever possible, neuropathological examination is carried out on cases and suspect cases notified to the CJD Surveillance Unit. Such examinations have been done on about 70% of cases notified since May, 1990, either by referral for necropsy in Edinburgh or in cooperation with neuropathologists in other centres who refer cases after diagnosis. Blocks from the frontal, temporal, parietal, and occipital cortex; basal ganglia; thalamus; hypothalamus; cerebellum midbrain; pons; and medulla are fixed in formalin. Blocks are immersed in 96% formic acid for 1 hour before routine processing into paraffin wax. Sections are cut at 5um and stained by conventional histological techniques and immunocytochemistry for prion protein (PrP). Pretreatments for immunocytochemistry with two monoclonal PrP antibodies (KG9 and 3F4)[3] include incubation in 96% formic acid for 5 min, then 4 mol/L guanidine thiocyanate for 2 hours, and hydrated autoclaving at 121deg.C for 10 min.

Results

Patients

Of the 207 cases of CJD examined neuropathologically since May, 1990, ten have neuropathological findings that clearly distinguish them from other cases examined by the CJD Surveillance Unit (two have been reported previously [4,5]).

	<30	30–34	35–39	40–44
1970–79	0	2	3	2
1980–84	1	1	3	1
1985–89	0	0	3	3
1990–94	0	0	1+	2
1995–96++	5(1)	2(1)	0	1

*Excludes known iatrogenic and inherited cases. **England and Wales only for the period 1970 84. ++Numbers in brackets indicate patients alive. +Died before May 1990.

Table 1: Known cases of sporadic CJD* in the UK, **1970–96, dying aged less than 45 years

These ten cases (four male) had disease onset from February, 1994, to October, 1995. One came to the attention of the CJD Surveillance Unit in March, 1995, and the other nine between October, 1995, and January, 1996. The ages at death of the eight patients who have died range from 19 to 41 years (median 29). Two patients remain alive at ages 18 and 31 years. Intervals between disease onsets and death range from 7.5 to 22.5 months (median 12). Surviving patients in March, 1996, have disease durations of 6 and 22 months. These patients are relatively young compared with most patients with CJD and their disease duration is relatively long. Among 185 cases of sporadic CJD identified since May, 1990, average age at onset was 65 years and median duration of disease four months; for half of these patients, duration was 2.5 to 6.5 months. Since May, 1990, only two other sporadic cases of CJD with age less than 45 years have been identified, both aged 44 years. These cases had disease onsets in 1993 and 1994; neither showed the neuropathological changes described.

Table 1 shows the cases of CJD dying in England and Wales between 1970 and 1984 and in the UK from 1985 to 1996 at age less than 45 years. Six cases of CJD aged less than 30 years and three aged 30 to 34 years have been identified since 1990—all these cases were identified within the last 10 months. In comparison only one case of CJD aged less than 30 years and three aged 30 to 34 years were identified between 1970 and 1989. We have been able to examine pathological material from one of these earlier cases which did not show the neuropathological pattern described in this report and in the three other cases review of neuropathological reports did not suggest this pattern.

Clinical course

The clinical course of disease in the ten patients was distinct from that usually seen in sporadic CJD (table 2). Nine had behavioural changes as an early clinical feature and were referred to a psychiatrist. In four patients, an early symptom was dysaesthesiae and in another, pain in the feet persisted throughout the illness. Nine patients developed ataxia early in the course of the disease. While all patients developed progressive dementia, in only two was memory impairment part of initial clinical presentation. Seven of the patients developed myoclonus, often late in the course of the disease, and three had choreoathetosis. None of the cases had the electroencephalographic (EEG) features usually associated with CJD.

With established diagnostic criteria for CJD[6] none of these cases would have been classified as "probable" cases of CJD on clinical grounds. At the time of initial referral to the CJD Surveillance Unit, two patients were classified as definite cases (after brain biopsy) and another as a possible case, while the remaining seven did not fulfil the criteria for even "possible" CJD.

Information on PrP genotype is available for eight cases. All were methionine homozygotes at codon 129 of the PrP gene and none of the known mutations associated with the inherited forms of CJD was identified. In a study of codon 129 genotypes in sporadic CJD in the UK, 1990– 93, 83% of cases (n=111) were methionine homozygotes.

Neuropathological features

Neuropathological examination in all ten cases showed spongiform change and PrP plaques confirming the diagnosis of CJD[6]. In two cases investigated by cerebral biopsy and in the eight necropsy cases, neuropathological features were uniform, with spongiform change in a relatively sparse distribution throughout the cerebral cortex (although all areas were involved to a variable extent in each case who came to necropsy). Spongiform change, neuronal loss, and astrocytosis were most evident in the basal ganglia and thalamus, and were present focally in the cerebrum and cerebellum, most evidently in areas with confluent spongiform change.

The most striking and consistent neuropathological abnormality in all cases was PrP plaques. In the eight necropsy cases, plaques were extensively distributed throughout the cerebrum and cerebellum, with smaller numbers in the basal ganglia, thalamus, and hypothalamus. Many of these plaques resembled kuru-type plaques with a dense eosinophilic centre and pale periphery and, unusually for this type of lesion, were surrounded by a zone of spongiform change (figures 1 and 2). This unusual feature was not seen in any of the other 175 sporadic CJD cases investigated. Similar lesions have, however, been described in scrapie, where they have been referred to as "florid" plaques[7]. Immunocytochemistry for PrP showed strong staining of these plaque-like lesions, but also showed many other smaller plaques, which appeared both as single and multicentric deposits. PrP deposition was also seen in a pericellular distribution in the cerebral cortex and in the molecular layer of the cerebellum, the pattern of which suggested deposition around small neurons (figure 3). Plaque and pericellular PrP deposits occurred throughout the cerebrum and cerebellum, and were clearly visible in the absence of confluent spongiform change in the surrounding neuropil. In the

basal ganglia and thalamus, a perivacuolar pattern of PrP staining was also seen, with linear tract- like deposits within the grey matter. PrP plaques were also noted in these regions although there were fewer than in the cerebrum and cerebellum (figure 4).

Age at onset	Sex	Year of onset	Year of death	Duration of illness (months)	Presenting symptom	Psychiatric symptoms	Ataxia	Dementia	Myoclonus
16*	F	1994	Alive	>22	Dysaesthesiae	+	+	+	+
18*	M	1994	1995	11	Behavioural change	+	+	+	+
19	M	1995	1996	13	Personality change	+	+	+	
26	F	1994	1996	22.5	Dysaesthesiae	+	+	+	+
28*	F	1995	1996	10	Memory impairment	+	+	+	+
28	F	1995	1995	11	Behavioural change	+	+	+	+
29	F	1994	1996	17	Depression	+	+	+	
29	M	1995	1995	7.5	Foot pain	+	+	+	+
31	M	1995	Alive	>6	Memory impairment	+	+	+	
39	F	1994	1996	21	Dysaesthesiae	+	+	+	+

*Already published (references 4, 5, and 18).

Table 2: Characteristics of ten cases of CJD in the UK

These qualitative differences in the nature of the neuropathological lesions and morphology of PrP deposits were matched by an apparent increase in the amount of PrP deposited in all grey- matter regions compared with sporadic cases, 12 iatrogenic cases, six cases of inherited CJD, and in four cases of Gerstmann-Straussler-Scheinker syndrome.

Risk factors

Information on potential risk factors for CJD is available for nine cases. None had a history of potential iatrogenic exposure to CJD through neurosurgery or human-pituitary-derived hormones, and none had had a blood transfusion. Four cases had no history of any operation, four had undergone minor surgery (two tonsillectomy in 1975 and 1991, one a foot operation in 1984, one a dilatation and curetage in 1989), and one had had a caesarean section (1974), colonoscopy (1992, 1994), and laparoscopy (1986). One patient had worked as a butcher from 1985 to 1987 and another had visited an abattoir for two days in 1987. None had ever worked on farms with livestock, although one patient had spent 1 week's holiday a year on a dairy farm between 1976 and 1986. There was no record of BSE in this herd. All nine cases were reported to have eaten beef or beef products in the last 10 years, but none was reported to have eaten brain. One of the cases had been a strict vegetarian since 1991.

Discussion

The ten cases of CJD in this report are remarkable in that they have a specific neuropathological profile which, to our knowledge, has not been described previously[6,8] and which is so consistent that neuropathological samples from the cases are virtually indistinguishable. The cases are further characterised by having remarkably low ages at onset for CJD and other atypical features, including a generally protracted and unusual clinical course and absence of EEG changes typical of CJD. These findings raise the possibility that the cases represent a new clinicopathological variant of CJD.

Effect of age

It is possible that the unusual neuropathological profile of these cases is due to their young age. Review of published reports on previous young patients worldwide did not reveal any descriptions of neuropathology similar to these UK cases. In 14 cases of CJD aged less than 30 years previously reported outside the UK, plaques are described in only one, and in this report the possible diagnosis of Gerstmann- Straussler- Scheinker syndrome was raised. In four of these cases,[9-12] pathological reports have been reviewed and there was no evidence of PrP plaques (Paul Brown, personal communication). We did immunocytochemical staining on another of these cases of CJD aged 27 years from Poland (courtesy of Professor Kulczycki) and on a 16- year- old patient from the UK dying of CJD in 1980, and there was no evidence of plaque formation in either case. We also did immunocytochemical staining on 11 cases of CJD developing after administration of human growth hormone (mean age 27.5 years) and although PrP plaques were present predominantly in the cerebellum, the neuropathological features in these cases'3 were otherwise quite distinct from the young patients in this report. We emphasise that plaque distribution and spongiform change in these ten young cases were clearly apparent on routine light microscopy. Current evidence suggests, therefore, that the pathological

profile in these cases is unlikely to be simply an age- related feature.

CJD has been described previously in young patients, but these are usually isolated case reports[9-12] and in systematic surveys the identification of CJD in patients aged less than 30 years old is exceptional. In the UK, only one such case was identified between 1970 and 1989. In France, between 1968 and 1982[14], only two patients aged less than 30 years old were identified; only one was identified in Japan between 1975 and 1977; and none at all in Israel between 1963 and 1987. Additional cases aged less than 40 years have been identified through the European surveillance project on CJD (1993- 95); two cases aged 22 and 34 years old were found in the Netherlands; two aged 31 and 33 years old in Germany; two aged 26 and 37 years old in France; and one aged 37 years old in Italy. Six of these cases are judged on clinical evidence not to be similar to the cases described in this report. Neuropathological information is available on two of these six cases, neither of which showed the characteristic changes. In the remaining case, full neuropathological information will be available shortly.

Case ascertainment

The overall incidence of CJD has risen in the UK in the 1990s[15], although this is due mainly to an increase in the incidence of CJD in those aged over 75 years (these cases have a typical clinicopathological profile). The most likely explanation for this is improved ascertainment of CJD in the elderly, with the possible implication that the identification of young cases of CJD may be due to similar improved case ascertainment due in part to the publicity surrounding the BSE epidemic. It is noteworthy that three of the ten cases in this report were notified to the CJD Surveillance Unit as suspect cases of CJD only after biopsy samples had been examined. In the absence of neuropathological examination, these cases might not have come to the attention of the CJD Surveillance Unit. It seems likely, however, that patients of this age dying of a progressive neurological condition would have undergone necropsy in the past. Two cases came to the attention of the CJD Surveillance Unit through unconventional means (through a newspaper report and after a clinical presentation of other cases) which led to their notification earlier than would otherwise have been the case. All of the ten cases were identified over 10 months and although there was extensive publicity surrounding two young cases in late 1995, there has been considerable publicity regarding CJD and BSE since 1990. Other European countries have undertaken systematic surveillance of CJD over a similar period and there has been no obvious increase in the incidence of CJD in young patients despite detailed investigation.

There is a possibility that the diagnosis of such atypical cases may previously have been previously missed. Three of the 14 cases discussed above were from Poland, aged 19, 23, and 27 years, and were identified in the course of a study of subacute sclerosing panencephalitis (SSPE)[16] A recent review of the clinical details of suspect but unconfirmed cases of SSPE held by the SSPE register in the UK has provided no evidence that cases of CJD were misdiagnosed as SSPE in the UK. Although improved ascertainment remains a potential explanation for the identification of the young patients we report, such information as is available does not support this interpretation.

Possible link with BSE

The first aim of the CJD Surveillance Unit has been to identify any changes in CJD that might be attributable to the transmission of BSE to the human population. Although the small number of cases in this report cannot be regarded as proof, the observation of a potentially new form of CJD in the UK is consistent with such a link. The common neuropathological picture may indicate infection by a common strain of the causative agent, as in sheep scrapie in which strains of the disease have been identified which can be distinguished on the basis of diseaseincubation period and distinctive neuropathological profile in mouse models[17]. Exposure of the human population to the BSE agent is likely to have been greatest in the 1980s, and especially towards the end of that decade, before the ban on the use of specified bovine offal was introduced. This would be consistent with an incubation period of between 5 and 10 years for these cases.

If the present cases are due to exposure to the BSE agent and this accounts for the distinctive neuropathological appearance, it is not clear why this previously unrecognised variant of the disease has been found only in persons under the age of 45 years. The absence of this variant in older persons could be due to age- related exposure to the agent; to reduced susceptibility among older persons; or to misdiagnosis of this variant of the disease in older age-groups, especially in those in which dementia is more common.

We were alerted earlier to a possible link between CJD and BSE by our finding of an apparent excess of CJD among cattle farmers[15]. Our interpretation of this was tempered by observations of high rates among cattle farmers in other European countries in which BSE was either very rare or had not been reported. None of the four farmers showed the neuropathological features described here, and all were consistent with previous experience of sporadic cases of CJD.

Conclusions

We believe that our observation of a previously unrecognised variant of CJD occurring, to date, only in persons under the age of 45 years is a cause for great concern. That it is due to exposure to the BSE agent is perhaps the most plausible interpretation of our findings. However, we emphasise that we do not have direct evidence of such a link and other explanations are possible. That these cases have been observed now because of improved ascertainment cannot be completely dismissed. It seems unlikely, however, that such a distinctive neuropathological pattern would have been missed previously, especially among persons dying at a young age. It is essential to obtain information on the clinical and neuropathological characteristics of young patients with CJD in Europe and elsewhere, and historically in the UK, but proof of an association between BSE and CJD may depend on animal transmission studies and continued epidemiological vigilance. If there is a causal link then, given the potentially long and widespread exposure to the BSE agent, further cases of this new variant of CJD are likely to arise.

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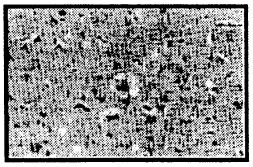

Figure 1: Large kuru- type plaque surrounded by a zone of spongiform change in a cerebral cortical- biopsy

specimen (centre). A smaller plaque is also present (right) but spongiform change is sparse Haematoxylin and eosin.

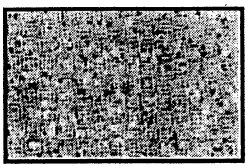

Figure 2: Cerebral cortex in a case at necropsy with a large kuru- type plaque surrounded by spongiform change (centre) with smaller lesions present in the surrounding neuropil (right and below) Haematoxylin and eosin.

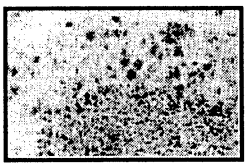

Figure 3: Immunocytochemistry for PrP in the cerebellum shows strong staining of a kuru- type plaque (centre) with multiple smaller plaques in the granular layer and abundant pericellular deposition in the molecular layer

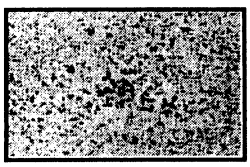

Figure 4: Immunocytochemistry for PrP in the thalamus shows several large multicentric plaques (centre) with perivacuolar and synaptic deposition in the surrounding neuropil

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Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994-2000

Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994–2000

Simon Cousens, P G Smith, H Ward, D Everington, R S G Knight, M Zeidler, G Stewart, E A B Smith-Bathgate, M-A Macleod, J Mackenzie, R G Will

Summary

Background Geographical variation in the distribution of variant Creutzfeldt-Jakob disease (vCJD) might indicate the transmission route of the infectious agent to man. We investigated whether regional incidences of vCJD were correlated with regional dietary data.

Methods The National CJD Surveillance Unit prospectively identified 84 people with vCJD up to Nov 10, 2000, in Great Britain. Their lifetime residential histories were obtained by interviews with a close relative. Cumulative incidences of vCJD by standard region were calculated. Grid references for places of residence in 1991 were identified and evidence of geographical clusters were sought. Data on diet in the 1980s were analysed for regional correlations with vCJD incidence. The socioeconomic status of the places of residence of people with vCJD was compared with that of the general population.

Findings vCJD incidence was higher in the north of Great Britain than the south. The rate ratio (north *vs* south) was 1·94 (95% CI 1·27–2·98). The mean Carstairs' deprivation score for areas of residence of people with vCJD was −0·09 (−0·73 to 0·55), which is close to the national average of zero. Regional rates of vCJD were correlated with consumption of other meat or meat products as classified and recorded by the Household Food Consumption and Expenditure Survey (r=0·72), but not with data from the Dietary and Nutritional Survey of British Adults. Five people with vCJD in Leicestershire formed a cluster (p=0·004).

Interpretation Regional differences in vCJD incidence are unlikely to be due to ascertainment bias. We had difficulty determining whether regional variations in diet might cause these differences, since the results of dietary analyses were inconsistent.

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Introduction

Variant Creutzfeldt-Jakob disease (vCJD) was first identified in the UK in 1996,[1] and there is strong evidence that it is caused by the same agent as bovine spongiform encephalopathy (BSE).[2–5] The main route of infection in cattle was probably contaminated feed.[6,7] The route by which people were infected with vCJD remains uncertain. The National CJD Surveillance Unit (CJDSU) in Edinburgh prospectively identifies people with vCJD. Methods of case ascertainment have been described.[8] Definite cases are those confirmed neuropathologically. Criteria for identification of individuals as probable cases have been published,[9,10] and all those so identified for whom neuropathological data have become available have been confirmed as having vCJD. People with suspected vCJD are, whenever possible, visited by a CJDSU neurologist and a research nurse who, with informed consent, interviews a close relative of the patient about a wide range of factors, including lifetime residential history.

The geographical distribution of people with vCJD might provide clues to its transmission routes. From such data we have previously reported an apparent excess of cases in the north of Great Britain.[11] This excess was difficult to interpret without an a priori hypothesis for the regional distribution of vCJD. We therefore aimed to look at the present distribution of vCJD and examine whether it was related to dietary data. Reports of a cluster of people with vCJD in an area of Leicestershire have provoked much interest. We therefore investigated vCJD clustering on the basis of place of residence in 1991.

Methods

We noted the place of residence on Jan 1, 1991, of each person with the disease. We chose this date because accurate small-area census data by age are available for Great Britain for 1991. Specified bovine offals were banned in 1989. 1991 is likely to have been close to the time of peak exposure; the peak would have occurred in 1989 if the ban on specified bovine offals had been effective, or 1992–93 if it had not. We calculated crude cumulative incidences of vCJD for the ten standard regions of Great Britain, with the population aged 10 years and older at the 1991 census as the denominator. We used data based on the 1991 census (source: the 1991 Census, Crown copyright, Economic and Social Research Council purchase). We did a statistical comparison of rates in the north and south, which took account of age and sex, on the assumption that cases had a Poisson distribution.

We located two sources of regional data on diet in the 1980s: the Dietary and Nutritional Survey of British Adults;[12] and the Household Food Consumption and

Figure 1: **Map of Great Britain showing place of residence in 1991 of 84 people with definite and probable vCJD, identified up to Nov 10, 2000**
vCJD=variant Creutzfeldt-Jakob disease.

Expenditure report for 1998.[13] The Dietary and Nutritional Survey of British Adults was done in 1986–87. A weighed, 1-week dietary record was obtained for 2197 adults aged 16–64 years. For regional analyses, Great Britain was divided into four areas: Scotland; north England; Wales; the midlands and southwest England; and southeast England.[12] The Household Food Consumption and Expenditure report covered 1984–86, and was based on 1-week records from about 20 000 households of all foods that entered the home for human consumption. Great Britain was divided into nine areas that corresponded with the ten standard regions, but with southeast England and East Anglia combined.[13] We compared dietary data with regional vCJD incidence by use of Spearman's rank correlation coefficient.

We identified the grid reference of each person with vCJD's place of residence in Great Britain at the beginning of 1991 by postcode (AFD Postcode Plus version 4.1.17). We also used the postcode to identify the census enumeration district and ward in which the person lived. An enumeration district is the smallest managed census area, typically 150–250 households. Each enumeration district is the responsibility of one census employee. A ward is a group of enumeration districts. We used the Carstairs' index to compare the affluence or deprivation of the placesof residence (enumeration district) of people with vCJD with that of the general population. The indexis a composite measure available at enumeration district level, and is based on overcrowding, unemployment, social class, and car ownership.[14] The index has a mean of zero with negative values indicating relative affluence and positive values indicating relative deprivation.

We used Kulldorff and colleagues' method[15,16] to look for clusters of cases. This method uses a spatial scan statistic that can detect clusters of any size anywhere in the study region, whether or not they cross administrative borders. Circles of continuously varying size centred on many different locations are examined. For each circle, a likelihood ratio is calculated for the hypothesis that there is an increased risk of disease inside the circle against the null hypothesis that there is not. The most likely cluster is that with the largest likelihood ratio. Statistical significance of the cluster is assessed with a likelihood ratio test, whose distribution under the null hypothesis is obtained by Monte Carlo simulation, which takes account of the multiple testing inherent in the procedure.

Results

By Nov 10, 2000, we had identified 85 people with vCJD in the UK, 75 of whom had died. 68 cases had been confirmed neuropathologically. The other 17, ten of whom remained alive, were classified as probably having vCJD. Median age at onset was 26 years (range 12–74) and 42 (49%) were female. One person, who had lived in Northern Ireland all their life, was excluded from the subsequent geographical analyses—which are thus based on 84 cases.

Figure 1 shows the geographical distribution of people with vCJD. Table 1 and figure 2 show cumulative regional rates of vCJD. We previously analysed the geographical distribution of the first 51 cases, distinguishing two areas.[11] The north was four standard regions: Scotland, north England, Yorkshire and Humberside, and northwest England. The south was the remaining six regions: Wales, West Midlands, East Midlands, East Anglia, southwest

Standard region	Number of people aged 10 years and older at the 1991 census (million)	Number (cumulative incidence per million) of people with vCJD by place of residence in 1991
Scotland	4·4	13 (2·98)
North England	2·6	7 (2·66)
Yorkshire and Humberside	4·2	10 (2·38)
Northwest England	5·4	13 (2·41)
East Midlands	3·4	7 (2·03)
West Midlands	4·5	2 (0·45)
East Anglia	1·8	1 (0·56)
Wales	2·5	4 (1·62)
Southeast England	15·0	21 (1·40)
Southwest England	4·1	6 (1·48)
Total*	47·8	84 (1·76)

vCJD=variant Creutzfeldt-Jakob disease. *Does not add up exactly due to rounding.

Table 1: **Distribution of 84 people with vCJD by standard region of residence on Jan 1, 1991**

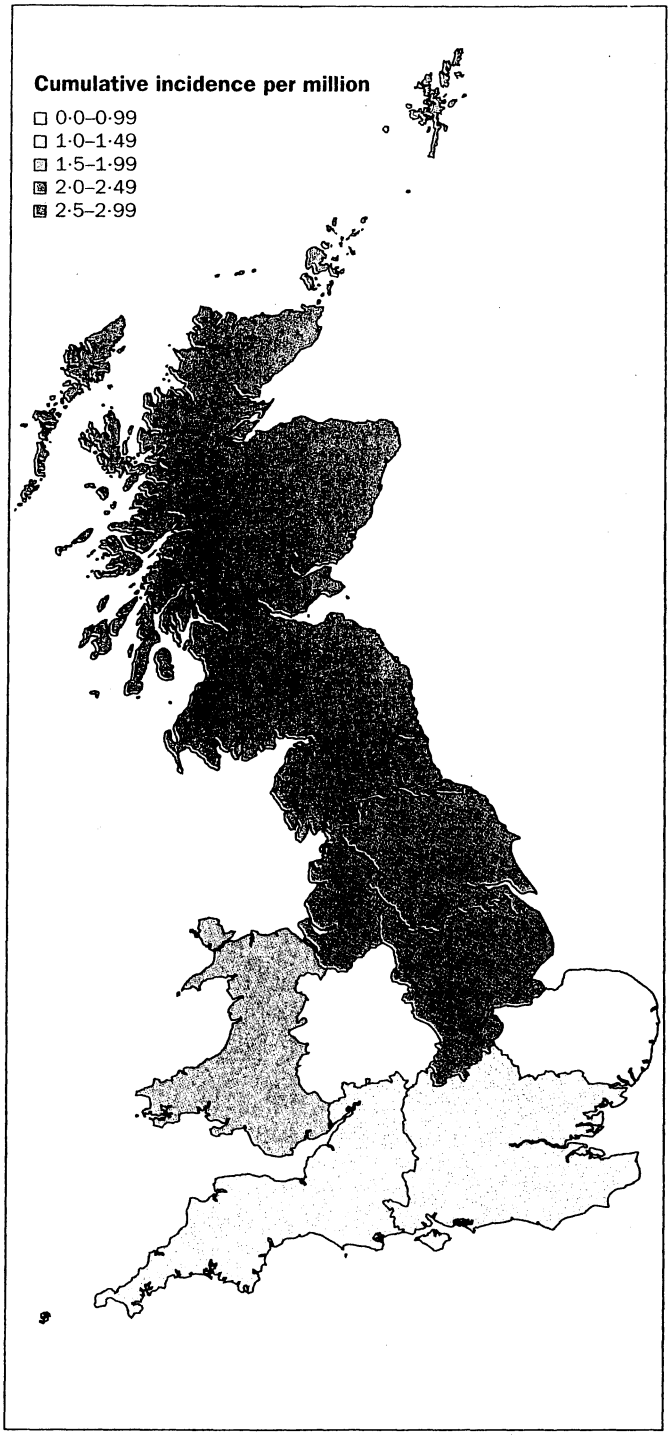

Figure 2: **Cumulative incidence up to Nov 10, 2000, of vCJD per million people aged 10 years and above, by place of residence on Jan 1, 1991**
vCJD=variant Creutzfeldt-Jakob disease.

England, and southeast England. Table 2 shows the distribution of people with vCJD between the north and the south, distinguishing between those cases included in the previous analysis and those classified as cases subsequently (under an a priori hypothesis). The excess of people with the disease previously identified in the north (rate ratio, adjusted for age and sex=1·94; 95% CI 1·12–3·36) seems to have continued in subsequent cases (1·95; 0·99–3·86). The estimated rate ratio for all 84 cases together was 1·94 (1·27–2·98).

We examined data on sporadic CJD cases since May, 1990 (when the CJD Surveillance Unit was set

Region	Number of people aged 10 years and older at the 1991 census (million)	Number (cumulative incidence per million) of people with vCJD by place of residence on Jan 1, 1991		
		First 51 cases	Subsequent cases	Total
North*	16·6	26 (1·57)	17 (1·02)	43 (2·59)
South†	31·2	25 (0·80)	16 (0·51)	41 (1·31)
Total (rate ratio)‡	47·8	51 (1·94)	33 (1·95)	84 (1·94)

vCJD=variant Creutzfeldt-Jakob disease. *North=northwest England, Yorkshire and Humberside, north England, and Scotland. †South=southwest England, southeast England, Wales, West Midlands, East Midlands, and East Anglia. ‡North versus south, adjusted for age and sex.

Table 2: **Comparison of cumulative vCJD incidence between the north* and south† of Great Britain**

up), to see whether rates of sporadic CJD were higher in the north than the south. Up to 31 Dec, 1999, 151 sporadic CJD cases had been identified in the north (population 19·1 million, annual mortality per million=0·82) and 270 in the south (population 35·8 million, annual mortality per million=0·78). We also looked at the regional distribution of individuals who were referred to the unit as suspected cases of vCJD but who were subsequently shown to have some other condition or who are currently thought unlikely to have vCJD. There were 15 such individuals from the north (0·9 per million people aged 10 years and older) and 35 from the south (1·1 per million people aged 10 years and older).

Northern people with vCJD were slightly older at onset than those in the south (median [range] of 27 [12–74] *vs* 24 [14–52] years, respectively, p=0·24) and more were male people (25 of 43 *vs* 17 of 41, p=0·13). The mean Carstairs' score for the enumeration districts of the 84 cases was −0·09 (95% CI −0·73 to 0·55), which is close to the national average (zero), and to the average adjusted for regional distribution (0·11). The cases were evenly distributed across the five quintiles of the index (data not shown).

Table 3 shows data from the Dietary and Nutritional Survey of British Adults[12] on consumption of food items most relevant to putative transmission of BSE. Those items most likely to have contained mechanically recovered meat or high-titre BSE agent material from the central nervous system (burgers and kebabs, sausages, meat pies and pastries, and other meat products) showed no consistent pattern of higher consumption in northern regions. People in the north ate more meat pies and pastries than those in the south, but those in southeast England consumed the most burgers and kebabs and other meat products.

Food type	Mean quantity per person (g) by region			
	Scotland	North England, northwest England, and Yorkshire and Humberside	East Midlands, East Anglia, West Midlands, southwest England, and Wales	Southeast England
Beef and veal	351	342	319	362
Burgers and kebabs	170	166	139	205
Sausages	147	136	142	143
Meat pies and pastries	251	284	243	237
Other meat products	170	201	197	215
Total	1089	1129	1040	1162

*From the Nutritional Survey of British Adults.[12]

Table 3: **Regional variations in quantities of foods consumed per week from 1986 to 1987***

Food type	Mean quantity per person (g) by region								
	Scotland	North England	Yorkshire and Humberside	Northwest England	East Midlands	West Midlands	Southwest England	Southeast England and East Anglia	Wales
Carcass meat	325	362	359	377	373	392	395	382	355
Bacon	102	119	113	121	110	122	89	88	113
Poultry	158	192	174	199	175	212	196	205	191
Other meat and meat products	455	456	369	408	367	376	362	338	339
Total	1040	1129	1015	1105	1025	1102	1042	1013	998

*From Household Food Consumption and Expenditure: 1988.[13]

Table 4: **Regional variations in quantities of foods per week brought into the home from 1984 to 1986***

Table 4 shows data on meat consumption from the Household Food Consumption and Expenditure report for 1988,[13] for 1984–86. Four categories of meat or meat products were distinguished. Carcass meat included: joints; steaks; chops; and mince of beef, pork, and lamb. The products most likely to have contained bovine mechanically recovered meat or high-titre BSE agent material from the central nervous system were classed as other meat and meat products. Consumption of other meat and meat productsshowed some correlation with vCJD incidence (r=0·72, p=0·03) (figure 3), whereas for both carcass meat and poultry the correlation was negative (r=−0·70, p=0·04; and r=−0·68, p=0·04, respectively), and bacon consumption was not correlated (r=0·12, p=0·77).

We identified a group of five people with vCJD in Leicestershire as the most likely cluster (p=0·004). There were no other significant (p<0·05) clusters. In particular, the cases in Kent which have been much debated[17] were not identified as a cluster. The population of Leicestershire at the 1991 census was about 870 000, which gave a local cumulative vCJD incidence of about 5·7 per million, whereas overall cumulative incidence in Great Britain was about 1·5 per million. Four of the five Leicestershire people lived in the district of Charnwood. Charnwood had a population of about 142 000 in 1991, which gave a cumulative incidence for this district of about 28·2 per million. The fifth person lived a few km outside Charnwood District; the greatest distance between any two of the Leicestershire cases was less than 10 km. Apart from the closeness of place of residence, these cases did not seem different from others from elsewhere in the country. Two were women and ages at onset ranged from about 17 to 33 years. All five people were reported to have eaten beef products and one had worked as a farm labourer.

Four of the Leicestershire people with vCJD lived in the area from birth until onset. The fifth person lived in the area from birth until mid-1991, then moved to the south coast but returned regularly to their previous home. When the cluster analysis was repeated with this person's place of residence not recorded as Leicestershire, the four remaining Leicestershire cases still formed the most likely cluster (p=0·02). None of the other 79 people with vCJD had ever lived in Leicestershire.

Figure 3: **Scatterplot of cumulative, age-standardised vCJD incidence against weekly consumption of other meat and meat products by region**

Dietary data are from Household Food Consumption and Expenditure: 1998.[13] vCJD=variant Creutzfeldt-Jakob disease.

Discussion

When we first reported[11] an excess of people with vCJD in the north compared with the south of Great Britain, we were cautious about interpretation in the absence of an a priori hypothesis that incidence of vCJD might be higher in the north. Our results show that a similar excess has been maintained in subsequent cases, which suggests that the original observation was not a chance finding. We also showed that five people with vCJD in Leicestershire (which is in the south in our classification) formed a cluster. Both these findings are based on analyses of place of residence on Jan 1, 1991. Our findings are not, however, sensitive to this choice of date; distribution of cases in 1985 (46 in the north of Great Britain, 37 in the south, and one overseas) and at onset (45 in the north *vs* 39 in the south) also suggest higher incidence among individuals living in the north.

Such regional differences could have arisen if ascertainment of people with vCJD is more complete in the north, perhaps because the CJD Surveillance Unit is located there (in Edinburgh, Scotland). However, the similarity of the regional rates for sporadic CJD and for vCJD referrals who do not have the disease does not lend support to the hypothesis that there are major differences in ascertainment of CJD between the two regions.

The socioeconomic profile of the places of residence of individuals with vCJD was close to that of the whole population, suggesting that the difference in cumulative incidence between north and south cannot solely be explained by regional variations in socioeconomic circumstances. The leading hypothesis for the mode of transmission of the BSE agent to the human population is that infection occurred through dietary exposure to contaminated bovine products. Data from the Dietary and Nutritional Survey of British adults,[12] showed no clear pattern of higher consumption in the north of Great Britain of food items thought most likely to contain high BSE agent titre material. Data from the Household Food Consumption and Expenditure report,[13] on the other hand, showed a correlation between consumption of other meat and meat products and vCJD incidence. Consumption of poultry and carcass meat showed an inverse relation with vCJD incidence, perhaps because of an inverse correlation between the consumption of poultry and carcass meat and that of other meat and meat products.

The positive regional correlation of vCJD incidence with other meat and meat products is difficult to interpret. Because the analysis was ecological, the correlation could be attributable to some confounding factor which is, or was, more prevalent in the north. Furthermore, no clear correlation was identified between vCJD incidence and the data from the Dietary and Nutritional Survey of British Adults.[12] Regional rates of vCJD have not correlated with BSE incidence, which has tended to be higher in the south than in the north.[18] These findings might indicate merely that beef and beef products were generally consumed far from the place where the cattle were raised.

Exposure routes that might distinguish cases at a national level have not yet been established—eg, all people with vCJD had eaten beef and beef products at some time during their lives, but then so have most of the population. Recent results[19] from an investigation of a cluster of people with vCJD in Leicestershire, led by the local public health department, indicate that most of these individuals were probably infected through their diet. Beef carcass meat was unwittingly cross contaminated with the BSE agent in local butchers' shops where cattle heads were split. The proportion of other people with vCJD who might have been infected in a similar way is as yet unknown.

We think the regional differences in cumulative vCJD incidence are not likely to be attributable to ascertainment bias. Although the general view is that there are regional differences in diet, do these differences cause the variations in incidence of vCJD? First, we are unsure about which food items carried the highest risk, if indeed the BSE agent was transmitted to human beings through their diet. Second, the limitations of ecological analyses, including the difficulty of controlling confounding, are well known even when they provide consistent results. Our analyses with two independent data sources do not provide consistent results. A national case-control study of vCJD is presently underway, which includes an investigation of potential dietary risk factors in individuals. However, unbiased dietary data from years past will be difficult to obtain. Relatives rather than the person with vCJD will have to provide the information and there has been substantial media coverage of a possible link between diet and risk of vCJD. Results from the Leicestershire investigation suggest that it might not be only the type of food consumed that determines risk of vCJD, but also where and how items were prepared.

Contributors

P Smith, S Cousens, H Ward, R Knight, and R Will initiated the study. M Zeidler, G Stewart, M-A Macleod, and R Knight obtained data. J Mackenzie coordinated the study. S Cousens and D Everington did statistical analyses. S Cousens wrote the first draft and all authors contributed to subsequent drafts of the manuscript.

Acknowledgments

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The uses of error: Quality control

It was the first day of my medical house job and we were on take; no induction period, straight in the deep end. The man in his forties was in coma and sweating profusely. At the hand-over, I was assured by the outgoing houseman that it was a stroke case and there was nothing to be done. Twenty-four hours later he was dead for want of a glucose drip for his hypoglycaemic coma. During this time my feet hadn't touched the ground and the duty senior never appeared.

The lessons are self evident so that by the time I reached consultant status, on call meant regular ward rounds by the specialist registrar and consultant and monthly morbidity and mortality meetings. How many lives were lost in vain so that the chief could have a good night's sleep?

As an arrogant young surgical registrar I was called to see a young girl with asthma and an acute abdomen. In spite of the anaesthetist's protestations I insisted that I open her belly. It was a negative laparotomy and she died in status asthmaticus. There was no forum to discuss this case and I got off without being called to task so that others might learn of pseudoperitonitis in acute asthma.

As a lecturer/senior registrar I was doing a difficult vagotomy in a man with a duodenal ulcer and concurrent Crohn's disease which had involved his oesophagus. Without recognising at the time I pushed my index finger through the intra-abdominal portion of his oesophagus with disastrous consequences. Perhaps I could be forgiven for that mistake but no one else learnt from it apart from myself.

Finally as a professor of surgery I was attempting a very low anterior resection in a woman with an early carcinoma of the rectum. It all went badly wrong and she developed a rectal vaginal fistula and ended up with a colostomy for life. At this point I realised I was becoming de-skilled in this branch of surgery and simply didn't have the time for retraining or for learning the emerging new techniques of large bowel anastomosis. I never allowed myself to do another case and capitulated to my ultimate full-time specialisation as a breast surgeon.

In fairness to my generation and myself this was all a long time ago. Since then I've been involved in monthly audit and morbidity and mortality meetings and have introduced weekly clinical-pathological audit meetings into my breast cancer practice. As this has been over more than a decade it can not have been a defensive response to current frenzy of self-recriminations. Let us continue to learn from each other's mistakes.

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Investigation of geographically associated cases of variant Creutzfeldt-Jakob disease

SUMMARY

vCJD GAC Investigations Working Group
25th November 2003

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1. Investigation of all cases of CJD

Scientific evidence suggested that vCJD is caused by transmission of the BSE agent to humans. Clinicians suspecting a diagnosis of CJD, including vCJD, are encouraged to refer patients to the National CJD Surveillance Unit (NCJDSU), Edinburgh for confirmation of diagnosis and further investigation. Following referral the NCJDSU undertakes a medical assessment of the patient and seeks detailed risk factor information through interviews with a close relative (diet, medical procedures and possible occupational, educational, social and recreational exposures).

2. Geographically associated cases of vCJD

Geographically associated cases are cases of probable or definite vCJD with a geographic association either through proximity of place of residence or through another link to the same location (occupational, educational or social/recreational). Such cases are of considerable interest since it may be possible to identify shared local exposures to the BSE agent and hence identify transmission routes of the BSE agent.

Geographical associations are identified principally by detection of cases resident within 5km of at least one other since 1980 for any common period up to 2 years before disease onset. Additional cases including those otherwise linked to the same location, and near outliers in geographic space and time, which ought to be considered for inclusion in any local investigation, may be identified by further examination of data by staff at the NCJDSU, or local sources.

3. Investigations of geographically associated cases of vCJD (vCJD GAC Investigations)

Following an investigation in North Leicestershire (see http://www.leics-ha.org.uk/publics/cjdrep.pdf) a protocol has been developed to facilitate vCJD GAC investigations (see http://www.doh.gov.uk/cjd/cjdguidance.htm). In the event of an association becoming apparent a local investigation will be conducted, lead by the public health department/health protection unit representing the locality(s) involved and supported by a national steering group. Consent to share available information is sought from the relatives of each of the cases involved; this is reviewed in confidence and further investigations agreed and actions undertaken.

The purpose of these investigations is to establish common factors linking the cases through geographic location, that might be related to their becoming infected with the BSE agent and plausibly explain their local occurrence. As well as identifying risk factors for local transmission, the

investigations will seek to determine whether the risk is continuing, and inform control measures. Information obtained following referral to NCJDSU may need to be clarified, and further "additional" and "beef-purchasing" questionnaires may be completed through interviews with relatives. Medical and dental records may be reviewed to assess the possibility of iatrogenic transmission of vCJD. An environmental investigation may also be undertaken, in which information pertaining to local butchery practices and beef supply chains, waste management procedures and water supplies, as well as the occurrence of BSE and other TSEs in the area, may be collected from key local informants.

A full report of any vCJD GAC investigation will be produced by the local investigation team. To date reports of 4 investigations are available in the public domain, listed below:

vCJD-GAC Investigation Reports*

North Leicestershire

Monk, P. and Bryant, G. *Final report of the investigation into the North Leicestershire cluster of variant Creutzfeldt-Jakob disease.* Leicester: Leicestershire NHS Health Authority, April 2001. Available online at http://www.leics-ha.org.uk/Publics/cjdrep.pdf.

Southampton

Southampton and South West Hampshire Health Authority. Report of the investigation into the geographically associated cases of variant Creutzfeldt-Jakob disease in Eastleigh and Southampton. Southampton: Southampton and South West Hampshire NHS Health Authority, February 2002. (Requests for information should be directed to Dr Mike Barker, CCDC **(Michael.barker@sswh-ha.swest.nhs.uk)).**

North East

North East vCJD regional investigation team. ***Investigation of geographically associated cases of variant Creutzfeldt-Jakob disease in the North East. Summary report.*** Durham: Communicable Disease Surveillance Centre, July 2002. (Requests for information should be directed to Dr Vivien Hollyoak, Regional Epidemiologist **(vivien.hollyoak@hpa.org.uk)).**

Anonymous. Investigation of geographically associated cases of variant CJD in north east England. *CDR Weekly,* 2002, 12, 3202. Available online at http://193.129.245.226/publications/cdr/archive02/News/news3202.html

* reports available in the public domain

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Protocol for the investigation of Geographically Associated Cases of variant Creutzfeldt-Jakob Disease

Title **Protocol for the investigation of Geographically Associated Cases of variant Creutzfeldt-Jakob Disease**

Version **Final version**

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Date **9th April 2001**

1 Background

Variant Creutzfeldt-Jakob Disease (vCJD) was first recognised in 1996. The disease is thought to be caused by the same agent that causes Bovine Spongiform Encephalopathy (BSE) in cattle, but the route(s) by which transmission to humans occurs remains to be established.

Cases of vCJD have been identified that appear to be associated with one another geographically. This may be by virtue of geographical proximity of residence or another link with the same area e.g. attending the same school or work place. The geographical association may be current or historic. Individuals with vCJD who appear to be associated in these ways are referred to here as geographically associated cases.

The association between these cases may reflect a common experience that is related to their having become infected with the BSE agent. Investigating cases that are associated geographically may therefore help to identify risk factors for transmission of infection.

An understanding of how the infectious agent is transmitted is important for a number of reasons:

- It allows the design of appropriate control strategies.
- It will permit more accurate estimates of how many people are likely to have been exposed to the agent causing vCJD.
- It will improve predictions of how the epidemic will develop and thereby facilitate appropriate planning.

In addition to the reasons outlined above, when geographically associated cases of vCJD are identified, the Director of Public Health (DPH) of the Health Authority or Health Board involved will to want to determine if there is a continuing risk to public health. The DPH of a Health Authority or Board has a statutory duty to ensure that effective arrangements are in place to control communicable diseases.

However, it is important to recognise that cases of vCJD that are geographically associated may have acquired their infection through a different route to cases that are not geographically associated. Hence any hypotheses generated for geographically associated cases will also need to be tested in cases that have no apparent geographical association with other cases.

2 Investigation framework

All suspected cases of vCJD should be referred to the National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU) for confirmation of diagnosis. As soon as possible after referral the NCJDSU will carry out a medical examination of the individual and interview a close family member. The interview seeks detailed information on diet, medical procedures, occupation, and educational and residential histories. Since individuals from the NCJDSU are amongst the first to become aware of new cases of vCJD and have early contact with the families of cases, the NCJDSU is most likely to identify an association between cases.

All suspected cases of vCJD referred to the NCJDSU will be reported to the Public Health Department of the Health Authority or Board where the case is resident (see guidance on local reporting of CJD). Local public health teams may therefore identify geographical associations between cases.

The detailed investigation of geographically associated cases of vCJD requires a co-ordinated and consistent approach that incorporates local and national expertise, knowledge and information.

A National Steering Group will provide guidance on the appropriate response to geographically associated cases of vCJD (Appendix 1). This National Steering Group will be composed of representatives from the NCJDSU, the Scottish Centre for Infection and Environmental health (SCIEH), the Department of Health, the London School of Hygiene and Tropical Medicine (LSHTM), the Public Health Laboratory Service, Communicable Disease Surveillance Centre (CDSC) and the Public Health Medicine Environmental Group (PHMEG).

When a decision is required on whether to undertake a detailed investigation of geographically associated cases of vCJD, a Working Group of the National Steering Group will be convened. This Working Group will comprise the relevant Consultant(s) in Communicable Disease Control (C(s)CDC) from the Health Authority or Board where the cases currently reside, the relevant Regional Epidemiologist (RE), a representative from the NCJDSU, a representative from LSHTM and a representative from CDSC. To avoid delays, this group may convene by teleconference. An individual known as the Investigation Co-ordinator will act as the Secretary to the Working Group.

If the Working Group recommends detailed investigation of an apparent association, the Investigation Co-ordinator will be appointed to act on behalf of the National Steering Group and provide support to local agencies.

The agency that should lead the local investigation of geographically associated cases of vCJD is the Public Health Department of the Health Authority or Board in which the cases live. The relevant CCDC will lead the local Investigation Team on behalf of the DPH.

This protocol will be updated as information from these investigations accumulates.

3 Aim of investigation

To identify, through a series of co-ordinated and standardised investigations of geographically associated cases of vCJD, routes of transmission of the BSE agent to humans.

4 Objectives of investigation

1) To combine and co-ordinate local and national expertise and information.

2) To investigate geographically associated cases of vCJD in a standardised way.

3) To identify if geographically associated cases of vCJD share any common factors which may represent a plausible route of transmission of the BSE agent to humans.

4) To determine whether there is any continuing risk of transmission of infection.

5) To document the circumstances, methods and findings of these investigations in a standardised way.

6) To inform the relevant local and national agencies of the findings of investigations in a timely and consistent way.

5 Identifying geographically associated cases of vCJD

5.1 Definition

Because knowledge of vCJD is currently rudimentary, a useful definition of geographically associated cases will necessarily be loose.

Definition of geographically associated cases

Two or more cases of probable or definite vCJD where preliminary investigations suggest there is an association between the cases because of:

a) Geographical proximity of residence at some time either now or in the past.
b) Other link with the same geographic area e.g. attending the same school or work place, or attending functions in the same area.

There are a number of mechanisms by which geographically associated cases may be identified:

1) When the NCJDSU is first notified of a suspected case of vCJD staff will be aware of earlier cases from the same area and therefore may identify a close geographical association.

2) An association may be picked up during the interview of family members of a case. The interviewer may identify a link with a previous case or the family may be aware of a link with a previous case.

3) Information on lifetime residential addresses of each case is collected by NCJDSU. The LSHTM in collaboration with the NCJDSU performs a monthly systematic check of the residential database to identify all pairs of cases who have lived within 5 km of each other at any time since 1980.

4) The NCJDSU regularly reviews data held at NCJDSU in order to identify other possible associations between cases e.g. school, occupational addresses.

5) As all cases of vCJD will be reported to local public health departments, local agencies may be the first to identify an association between cases.

6) On occasions the press may be the first to uncover a link between cases.

5.2 Initial action if the NCJDSU becomes aware of an association between cases

- The agreed national procedure will apply for reporting of all cases of vCJD.

- If the NCJDSU becomes aware of a geographical association between probable or definite vCJD cases they will as a first step inform the CCDC of the Health Authority or Board where the cases live and also the relevant RE. If the associated cases live in different Health Authorities or Boards then each CCDC will be informed. The CCDC will be responsible for informing other relevant individuals in the locality such as the DPH.

- The decision to undertake further investigation of an association should be jointly taken by a Working Group made up of; the relevant C(s)CDC, RE, and representatives from the NCJDSU, LSHTM and CDSC (See section 6).

5.3 Initial action if local agency becomes aware of an association between cases

- The agreed national procedure will apply for reporting of all cases of vCJD.

- The agency that should lead the local investigation of geographically associated cases of vCJD is the Public Health Department of the Health Authority or Board in which the cases live. If any other person or agency becomes aware of an association between cases of vCJD they should as a first step contact the CCDC of the Health Authority or Board where the cases live. If the associated cases live in different Health Authorities or Boards then each relevant CCDC should be informed.

- If the NCJDSU have not already informed the Health Authority or Board of the cases or the apparent association, then the C(s)CDC should as first step contact the NCJDSU (Tel: 0131 537 2128).

- The NCJDSU will confirm if the individuals are probable or definite cases of vCJD. If the individuals are not probable or definite cases then further investigation is not warranted at this time.

- If the individuals are probable or definite cases of vCJD the CCDC should inform the RE. A decision then needs to be taken on whether further investigation is required. The decision should be jointly taken by a Working Group made up of the C(s)CDC, RE and representatives from the NCJDSU, LSHTM and CDSC (See section 6).

6 Deciding to initiate further investigations

A Working Group of the National Steering Group should be convened by telephone to review available evidence including that already gathered by the NCJDSU. The membership of this working group should include:

a) The relevant C(s)CDC
b) Regional Epidemiologist
c) NCJDSU representative
d) LSHTM representative
e) CDSC representative [SCIEH representative in Scotland]

In deciding whether further investigation is necessary, the Working Group will consider the following information:

a. The total number of cases, the certainty of diagnosis and the dates of onset of illness.

b. The proximity, duration and nature of the geographical association between the cases.

c. The reliability of information on the geographical association. There may be a need to corroborate the information through other sources before embarking on a detailed investigation.

d. The influence of population density and chance on apparent geographical clustering of cases. However, statistical confirmation that a geographical association is unlikely to be due to chance is not a pre-condition for investigation.

e. Whether further information, in addition to that already collected, is required.

f. The local context and how it may influence the feasibility of particular courses of action.

If the decision is taken not to initiate further investigations this should be documented along with the rationale for this decision. All decisions will have to be re-visited if further associated cases are identified.

6.1 Notifying national agencies

Once the decision to initiate further investigations has been taken, the Working Group will inform the relevant Department(s) of Health. The Department of Health will consider cascading the information to other national agencies if necessary e.g. Food Standards Agency, Ministry of Agriculture Fisheries and Food.

As Secretary to the Steering and Working groups, the Investigation Co-ordinator will be responsible for ensuring that the Department of Health is kept informed of decisions made by these two groups.

6.2 Biennial review of geographically associated cases

The Working Group will meet every six months to review all geographically associated cases. At this meeting the group will review:

1) Findings of completed investigations.
2) Progress of ongoing investigations.
3) Changes to the investigation protocol.
4) Recently identified geographically associated cases.

The six monthly review meetings will be timetabled to take place approximately one month before the six monthly meeting of the Spongiform Encephalopathy Advisory Committee (SEAC) Epidemiology sub-group. This will allow the Working Group to prepare a summary report for the SEAC Epidemiology sub-group.

The full National Steering Group will meet annually, alternately in London and Edinburgh.

7 The Local Investigation

7.1 Membership of Local Investigation Team

The investigation will be undertaken by a Local Investigation Team. The chair and lead investigator should normally be the CCDC of the Health Authority or Board in which the majority of the cases reside. Suggested membership of the Local Investigation Team includes:

1) C(s)CDC (Chair)
2) Senior Environmental Health Officer
3) Regional Epidemiologist
4) Director of Public Health
5) Representative of local MAFF Veterinary Investigation Centre
6) Investigation Co-ordinator supported by:
   a) NCJDSU representative
   b) CDSC (national) representative

7.2 Operational issues

The Local Investigation Team should deal with the following issues as a priority at their first meeting:

- Terms of reference of the Local Investigation Team
- Remit of the investigation
- Roles and responsibilities of members of the Team
- Likely duration of investigation and resources required
- Communications strategy
- Liaison with the families and possibility of press injunction

7.3 Design issues

The investigation can be divided into a number of phases.

7.3.1 Preliminary phase

- Review all the available information
- Establish working definitions

Population at risk

In order to investigate geographically associated cases it is important to try to define a population from which the cases have arisen. This helps provide parameters to the investigation and also will allow the appropriate selection of controls if this should become necessary.

Time
Exposure period. Exposure of the UK population to the BSE agent is likely to have been greatest between 1980 and 1996. However, earlier or later exposure cannot be ruled out.

Place
Can a meaningful geographic area be defined which contains the population at risk?

Person
Can a social network be defined which contains the population at risk?

Case definition

Individuals from the *population at risk* diagnosed with probable or definite vCJD.

- Consider hypotheses

  An agreed checklist of hypotheses to consider (Appendix 2) will drive the investigations. This checklist will not be fixed and items may be added as further hypotheses are generated.

7.3.2 Descriptive phase

This phase is likely to be important whilst hypotheses for transmission are being developed. This phase may involve the use of more qualitative techniques to gather information to guide the investigation. Whilst novel hypotheses may be explored, it is envisaged that a 'minimum information set' will be generated which provides essential details relating to the most likely hypotheses (Appendix 3). Steps in the descriptive phase may include:

- Interviews with relatives of the cases to develop hypotheses further. The NCJDSU will have already undertaken interviews and careful consideration will be needed as to how valuable additional information will be.

- Interviews with key local informants – farmers, butchers, vets etc. (See environmental investigation below)

- Review of medical and dental records to gather information on certain hypotheses e.g. immunisation or surgery. Primary care notes are likely to be the most

accessible and comprehensive records. Note that for any individual case of vCJD a review of medical and dental records may be necessary to assess the risk of iatrogenic transmission of vCJD.

Environmental investigation
E.g. meat trading and butchering practices, agricultural practices, herd structure (beef/dairy, breed), history of BSE, water supply etc. Routine data sources will provide some information but interviews are also likely to be necessary.

7.3.3 Review phase

Once all the relevant descriptive information has been gathered it should be reviewed. Certain hypotheses may be discarded at this stage. Others may appear more plausible or new hypotheses may present themselves. At this stage the Investigation Team need to decide whether a formal epidemiological study is required to test specific hypotheses.

7.3.4 Analytic phase

This phase may become more important as information from investigations accumulates and hypotheses need to be tested.

7.4 Reporting findings

As is normal practice, the Chair of the Local Incident Control Team will be responsible for producing a full report of the investigation. Due to the lengthy delays that can occur in writing and agreeing final reports, the Investigation Co-ordinator will compile a standardised interim report for each investigation. This will be agreed by the local team and reviewed by the Working Group. The National Steering Group will present a summary of all investigations to the SEAC Epidemiology Sub-group biennially.

8 Roles and responsibilities

8.1 National Steering Group

a) To establish and develop an informative and acceptable process for the detailed investigation of geographically associated cases of vCJD.

b) To provide members for the Working Group deciding whether to undertake detailed investigation of geographically associated cases of vCJD.

c) To review and interpret the results of the investigations.

d) To present a biennial summary of the investigations to the SEAC Epidemiology Sub-group.

8.2 Working Group

a) To decide if further investigation of geographically associated cases of vCJD is necessary.

b) To document the circumstances, methods and findings of these investigations in a standardised way.

c) To provide operational guidance to the Local Investigation Team on the investigation of geographically associated cases of vCJD.

d) To support the Investigation Co-ordinator.

e) To review and interpret the results of the investigations.

f) To report to the National Steering Group

8.3 Local Investigation Team

a) To undertake investigation of geographically associated cases of vCJD when agreed by the Working Group.

b) To adhere to standard 'good practice' in local outbreak investigation.

c) To address community concerns and to keep relatives and the local community informed of the progress of the investigation.

d) To control any ongoing risk after taking national advice.

e) To write an incident report.

8.4 CCDC

a) To inform the NCJDSU and RE of geographically associated cases of vCJD of whom the CCDC becomes aware.

b) To serve as a member of the Working Group deciding whether to undertake further investigation of geographically associated cases of vCJD.

c) To chair the Local Investigation Team.

d) To co-ordinate the local investigation of geographically associated cases of vCJD.

8.5 Investigation Co-ordinator

a) To provide direct support to the Local Investigation Team in the field investigation.

b) To ensure a standardised approach to the investigation of geographically associated cases of vCJD.

c) To write an interim investigation report agreed by the Local Investigation Team for review by the Working Group.

d) To liaise between the Local Investigation Team and members of the Working Group.

e) To act as Secretary for the National Steering Group and the Working Group.

8.6 NCJDSU

a) To provide a representative for the National Steering Group and Working Group.

b) To attempt to ascertain if cases of vCJD referred to NCJDSU are geographically associated, working in collaboration with statistical & epidemiological support from the LSHTM.

c) To inform local CCDC, RE, & CDSC of any geographically associated cases of vCJD that are identified by NCJDSU.

d) To provide epidemiological advice and more general advice on all aspects of vCJD to the local investigation team.

8.7 LSHTM

a) To provide a representative for the National Steering Group and Working Group.

b) To perform statistical analysis, in collaboration with the NCJDSU, which will help to inform the decision as to whether geographically associated cases merit detailed investigation.

c) To perform monthly checks of the vCJD residential database to identify pairs of cases who have lived within 5 km of each other.

d) To inform local CCDC, RE, & CDSC of geographically associated cases on behalf of NCJDSU if necessary.

e) To provide epidemiological and statistical guidance to the Local Investigation Team.

8.8 CDSC

a) To provide a representative for the National Steering Group and Working Group.

b) To inform the NCJDSU of geographically associated cases of vCJD that CDSC becomes aware of.

c) To provide epidemiological guidance and assistance to the Local Investigation Team.

8.9 Department of Health

a) To provide a representative for the National Steering Group.

b) To provide policy guidance to the Local Investigation Team.

c) To cascade information to other relevant Government Departments.

d) To provide generic press support to the Local Investigation Team.

If you have any questions or comments on this protocol please contact Dr Hester Ward at the NCJDSU (h.ward@ed.ac.uk) or Dr Noel Gill at CDSC (ngill@phls.org.uk).

Appendix 1.

Membership of National Steering Group

Dr N Connor – Department of Health, Communicable Diseases Branch
Mr A Harvey – Department of Health, Communicable Diseases Branch
Dr N Gill – PHLS Communicable Disease Surveillance Centre (convenor)
Dr R Salmon - PHLS Communicable Disease Surveillance Centre
Dr H Ward – National CJD Surveillance Unit
Mr S Cousens - London School of Hygiene and Tropical Medicine
Dr D Walker – Durham HA / Public Health Medicine Environmental Group
Dr P Horby – PHLS Communicable Disease Surveillance Centre (secretary)

Appendix 2.

Checklist for investigation of Geographically Associated Cases of vCJD

1 DIET

Rationale: Large numbers of BSE infected cattle were slaughtered for human consumption.

Specific hypothesis of interest: local butchering practices, particularly butchering of the head on the same premises as the butchering of the rest of the carcass, may have led to consumption of material with a high infectious titre.

1.1 Meat/ meat product purchase

Where did cases purchase meat/ meat products, especially mince, burgers, meat pies, sausages during the period 1980-1996? A detailed questionnaire on the purchase of meat products is now part of routine data collection that takes place during the initial visit by the NCJDSU to all cases of vCJD.

1.2 Butchering practices

Did any of these outlets butcher cattle heads on the same premises as they butchered other parts of the carcass?

1.3 Local cattle

Where did these cattle come from? What were they used for? What age were they? What breed were they? Was BSE reported in these herds?

1.4 Take- away/ restaurant purchasing

Did the cases purchase meat products such as burgers, sausages or meat pies regularly from the same fast-food/takeaway outlets, restaurants or pubs?

2 Medical

Rationale: a large number of medical products were produced using bovine materials including a wide range of medicines, some vaccines and catgut sutures. Surgical procedures also carry the theoretical risk of secondary transmission from an infected individual to another individual.

Specific hypotheses of interest:
(i) Individuals may have been infected by exposure to a common batch of medical products contaminated with BSE infected bovine products.
(ii) Infection may have been transmitted from one infected individual to other, previously uninfected individuals, through medical procedures.

2.1 General practice

Did cases share the same general practitioner at any time between 1980 and 1996? If so, did they undergo minor procedures at the GP's surgery at around the same time? Did they receive the same treatments at the same time?

2.2 Vaccination

When and where were the cases vaccinated during the period 1980 to 1996? Which makes and types of vaccine did they receive (routine and travel)? Were they vaccinated with the same vaccine batch?

2.3 Surgery

Did cases undergo surgical procedures in the same hospital at around the same time during the period 1980-1996?

2.4 Out-patients clinics (hospital, community)

Did cases attend out-patients at the same location and at the same time during the period 1980- 1996? If so, did they undergo minor procedures/ interventions in the out-patient clinic at around the same time? Did they receive the same treatments at the same time?

3 Dentistry

Did cases share the same dentist at any time between 1980 and 1996? If so, did they undergo any dental procedures (other than cleaning/dental hygiene) at around the same time?

4 Ophthalmology

Did the cases use contact lenses in the period 1980 to 1996, including those worn for social reasons (e.g. to change eye colour)? Did they undergo tonometry in the same location at around the same time during this period?

5 Water Supply

Rationale: it has been suggested that waste material from abattoirs or rendering plants, spread onto fields could lead to infectious material reaching the water course and hence the water supply.

Specific hypothesis: individuals were infected through contamination of a shared water supply.

- Were abattoirs/rendering plants discharging waste material in the catchment area of the water supply during the period 1980-1996?

- Did cases share a common water supply at any time during the period 1980-1996?

6 Social or leisure activities

Rationale: individuals may have been exposed to a common source of infection through social or leisure activities.

Specific hypothesis: individuals may have been infected through a common exposure linked to social or leisure activities.

- Did cases have any social or leisure activities in common during the period 1980-1996? For example, did they go to the same pub? Did they attend the guides/scouts/ the same youth club/night clubs? Did they go to watch the same football team? Were the cases sexual partners?

7 Occupation

Rationale: individuals may have been exposed to a common source of infection at work.

Specific hypothesis: individuals may have been infected through a common exposure to infected materials linked to work.

- Did the cases work in the same organisation at any time during the period 1980-1996?
- Did the cases work in occupations involving contact with animals or animal products? (could include leather, etc.)

8 Schooling

Rationale: individuals may have been exposed to a common source of infection at school.

Specific hypothesis:
(i) Individuals were infected through eating the same school dinners
(ii)Individuals were infected through dissecting bulls' eyes.

- Did cases attend the same school during the period 1980 to 1996?
- Did cases eat school meals during this period?
- Even if cases did not attend the same schools, were they eating school meals from the same source?
- Did they dissect bulls' eyes? If so, what was the source of the bulls' eyes?

9 Other exposure to animals

Rationale: it is known that cats get FSE. It has been suggested that transmission of BSE to humans could have occurred indirectly through transmission to other animals, such as cats.

Specific hypothesis: individuals were infected through being bitten or scratched by animals such as cats.

- Did the cases keep pets or take part in leisure activities involving contact with animals? If they had contact with cats, were any sick from an unexplained illness during 1980 to 1996?
- Did cases have a history of being bitten by pets or other small animals?
- What was the incidence of FSE in the area from 1980- 1996?

10 Needle puncture

Rationale: individuals may have been infected through cross- contamination of re-used needles for non- medical or recreational purposes.

Specific hypothesis: individuals were infected through ear piercing, body- piercing, acupuncture, intravenous drug use.

- Did the cases have ear or body piercing? When and where was this carried out?
- Did the cases undergo acupuncture? When and where was this carried out?
- Did the cases take recreational drugs? Did they ever inject them? Did they ever share needles?

Appendix 3

Information set to guide the investigation of geographically associated cases of vCJD.

The National CJD Surveillance Unit (NCJDSU) undertakes a detailed interview of every suspected case of vCJD referred to them. The interview seeks detailed information on diet, medical procedures, occupation, and educational and residential histories. However, since associations between cases will often only become apparent some time after the initial interview, the initial interview cannot probe for particular associations between cases.

When geographically associated cases of vCJD are identified the information in the following tables should be checked or collected. Given that exposure of the UK population to the BSE agent is likely to have been greatest between 1980 and 1996, it is reasonable to limit the investigation to exposures or events occurring from 1980 onwards.

Where an association is identified, further investigation may be necessary. For instance, it may be discovered that a number of cases purchased meat from the same source. Information that might then be required includes the original source of the meat, the BSE history of the particular farms that supplied the meat, where the animals were butchered and the butchering practices in the establishment that supplied the meat.

A detailed review of medical and dental records may not always be a necessary part of the investigation of associations between cases of vCJD e.g. if the cases were never registered with the same dental practice. However, such a review may be necessary for individual cases to establish if there is any risk of iatrogenic transmission of vCJD. The *CJD Incident Panel* at the Department of Health (Tel: 020 7972 5324) has been established to provide advice on the management of the possible risk of transmission resulting from medical or dental procedures in people subsequently diagnosed with CJD.

Check list

Note: Details of cases must not be disclosed to the family of associated cases unless permission to share this information has been sought and granted.

Questions	Availability of information
Educational	
Did any of the cases ever attend the same school? If yes, did the cases attend the same school at the same time?	An educational history is collected by NCJDSU.
Did any of the cases eat school meals from the same source? One supplier of school meals may supply many schools.	Local Education Authority.
Medical / dental history	
Did any of the cases ever undergo surgery at the same hospital? If yes, further investigation in partnership with the relevant Trust will be necessary.	A history of operations is collected by NCJDSU. Primary care notes. Some information may have already been collected for the CJD Incident Panel.
Did the cases ever attend the same hospital outpatients clinic? If yes, further investigation in partnership with the relevant Trust will be necessary.	The NCJDSU collects information on regular attendance at hospital outpatients. Primary care notes. Some information may have already been collected for the CJD Incident Panel.
Were any of the cases ever registered with the same GP practice at the same time? If yes, a full review of the notes will be necessary to produce a chronology of visits and the purpose of each visit, including vaccinations and minor surgery.	Primary care notes. Supplementary interview with case informant may be necessary. Some information may have already been collected for the CJD Incident Panel.
Were any of the cases ever registered with the same dental practice at the same time? If yes, a full review of the notes will be necessary to produce a chronology of visits and the purpose of each visit.	NCJDSU ask about history of dental treatment other than fillings. Supplementary interview with case informant may be necessary. Some information may have already been collected for the CJD Incident Panel.
Did any of the cases ever attend the same opticians? If yes, a full review of the notes will be necessary to produce a chronology of visits and the purpose of each visit.	Supplementary interview with case informant will be necessary.
Occupational / recreational / social	
Did any of the cases ever share the same occupation?	An occupational history is collected by NCJDSU.
Did any of the cases ever work at the same place? If yes, did the cases work there at the same time and what was the nature of their job?	An occupational history is collected by NCJDSU. Supplementary interview with case informant may be necessary.
Did any of the cases ever have tattoos, body piercing or acupuncture carried out at the same establishment? If yes, further investigation will be necessary to produce a chronology of visits and the purpose of each visit.	NCJDSU collect information on acupuncture, piercing and tattoos but not the establishment. Supplementary interview with case informant may be necessary.

Note: Details of cases must not be disclosed to the family of associated cases unless permission to share this information has been sought and granted.

Question	Availability of information
Were two or more of the cases intra-venous drug users? If yes, further investigation will be necessary to try to establish if the cases may have shared injecting equipment.	NCJDSU collect information on intra venous drug use. Supplementary interview with case informant may be necessary.
Did any of the cases know each other? If yes, what was the nature of the relationship? Close friends, casual acquaintance?	Supplementary interview with case informant will be necessary.
Did any of the cases ever belong to the same clubs or groups?	NCJDSU may have some information on social activities. Supplementary interview with case informant may be necessary.
Did any of the cases share any hobbies or sports?	NCJDSU may have some information on social activities. Supplementary interview with case informant may be necessary.
Did any of the cases regularly eat meat products purchased from the same establishment?	NCJDSU will have some information on where meat products consumed by cases were purchased. Supplementary interview with case informant may be necessary.
Did any of the cases regularly eat out at the same restaurant, pub or café?	NCJDSU may have some information on restaurants / pubs regularly visited by the cases. Supplementary interview with case informant may be necessary.
Did any of the cases suffer animal bites?	NCJDSU may have some information on bites. Supplementary interview with case informant may be necessary. Primary care notes.

Environmental	
Was there a rendering plant, abattoir or meat processing plant close (5 km) to where the cases lived? If yes, there may be a need to investigate the waste management procedures of the plant and the cases' water supply.	Local Environmental Health Department. Relevant water supply company.
What is the history of BSE and Feline Spongiform Encephalopathy in the local area?	

文献５

Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion

Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion

C A Llewelyn, P E Hewitt, R S G Knight, K Amar, S Cousens, J Mackenzie, R G Will

Summary

Background Variant Creutzfeldt-Jakob disease (vCJD) is a novel human prion disease caused by infection with the agent of bovine spongiform encephalopathy (BSE). Epidemiological evidence does not suggest that sporadic CJD is transmitted from person to person via blood transfusion, but this evidence may not apply to vCJD. We aimed to identify whether vCJD is transmissible through blood transfusion.

Methods The national CJD surveillance unit reported all cases of probable or definite vCJD to the UK blood services, which searched for donation records at blood centres and hospitals. Information on named recipients and donors was provided to the surveillance unit to establish if any matches existed between recipients or donors and the database of cases of vCJD. Recipients were also flagged at the UK Office of National Statistics to establish date and cause of death.

Findings 48 individuals were identified as having received a labile blood component from a total of 15 donors who later became vCJD cases and appeared on the surveillance unit's register. One of these recipients was identified as developing symptoms of vCJD 6·5 years after receiving a transfusion of red cells donated by an individual 3·5 years before the donor developed symptoms of vCJD.

Interpretation Our findings raise the possibility that this infection was transfusion transmitted. Infection in the recipient could have been due to past dietary exposure to the BSE agent. However, the age of the patient was well beyond that of most vCJD cases, and the chance of observing a case of vCJD in a recipient in the absence of transfusion transmitted infection is about 1 in 15 000 to 1 in 30 000.

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See Commentary

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Introduction

Human prion diseases include sporadic Creutzfeldt-Jakob disease (CJD), which is of unknown cause; hereditary forms associated with mutations of the prion protein gene; variant CJD (vCJD), which has been causally linked to the bovine spongiform encephalopathy (BSE) agent; and iatrogenic cases transmitted via human pituitary hormones, human dura mater grafts, corneal grafts, and neurosurgical devices. All instances of iatrogenic transmission of CJD to date have been due to cross-contamination with high-titre tissues in or adjacent to the CNS,[1] and findings of epidemiological and observational studies have failed to provide evidence of transmission via blood transfusion or fractionated plasma products.[2,3] This evidence may not apply to vCJD, which is caused by a novel infectious agent for human beings and in which there is evidence of a peripheral pathogenesis different from other forms of human prion disease.[4] In vCJD, prion protein is readily detectable in lymphoreticular tissues such as appendix, spleen, tonsil, and lymph nodes, whereas these tissues are negative—by comparable methods—in other forms of human prion disease.[4]

The possibility that vCJD might be transmitted by blood transfusion led us to start a study with the aim to identify whether vCJD was transmissible by this mechanism.

Methods

Procedures

In 1997, a surveillance system was set up between the UK national CJD surveillance unit and the UK national blood services. Workers at the surveillance unit notified the relevant medical director of the blood services (National Blood Authority, Scottish National Blood Transfusion Service, Welsh Blood Service, Northern Ireland Blood Transfusion Service) of vCJD patients who were old enough to have donated blood (age >17 years). On receipt of this notification, workers at the blood services began an immediate search of donor records, irrespective of whether or not the case was reported by relatives to have been a blood donor. We searched current computer databases and archived records (computerised and paper-based records where appropriate) at individual blood centres, with name, date of birth, and a full set of previous addresses as identifiers. No search took place for donations or transfusions given before 1980, the presumed earliest possible exposure date to BSE. When donor records were found we identified all blood components made and issued to hospitals, and established their fate as recorded on blood transfusion laboratory records. We then checked recipient details against the national CJD surveillance unit register to establish if any individuals had developed vCJD.

This report does not include details of the current negative reverse study, in which donors of blood transfused to vCJD cases are traced, nor of a concurrent

study of sporadic CJD. The study has not, to date, entailed tracing of recipients of fractionated plasma products produced from pools containing a donation from an individual later diagnosed as a case of vCJD.

We received ethical approval for the study, and it is noteworthy that hospitals were passed masked details with no mention of the diagnostic category. The UK Office of National Statistics flagged all identified donors and recipients to establish the date and cause of death. This component of the study also received ethical approval.

From the information provided by the Office of National Statistics, we calculated the length of time since receipt of the transfusion until death or Dec 18, 2003, for every recipient. Based on the total amount of follow-up time in the cohort of recipients, we calculated the number of vCJD cases we would have expected to record in the cohort in the absence of any vCJD transmission through blood transfusion, and hence the probability of noting one or more cases, assuming a Poisson distribution. We obtained the expected number of vCJD cases by assuming that the vCJD epidemic in the UK had been in progress for a period of 10 years (the first known case had onset at the beginning of 1994), calculating average annual crude and age-specific incidence rates in the UK population over this period, and applying these to the cohort of transfusion recipients, assuming that all recipients were susceptible (not just those methionine homozygous at codon 129 of the PrP gene, *PRNP*).

Role of the funding source

The sponsor of this study had no role in study design; in collection, analysis, and interpretation of data; in writing of the report; or in the decision to submit the paper for publication.

Results

Case report

In 1996, a patient aged 62 years was transfused with 5 units of red cells at time of surgery. One of the units had been donated by a 24-year-old individual who developed symptoms of vCJD 3 years 4 months later, and who died in 2000 of pathologically confirmed vCJD.

In late 2002, 6·5 years after the blood transfusion, the recipient became withdrawn and irritable, and within 3 months, treatment with antidepressants was started—without benefit. The depression deteriorated and was associated with a shuffling gait and repeated falls. Blurred vision, shooting pains in the face and abdomen, fidgety movements, and difficulty with motor tasks such as dressing developed over subsequent months. Admission took place 6 months after onset of symptoms, and cognitive impairment, dyspraxia, a shuffling unsteady gait, and extensor plantar responses were seen. Routine investigations were normal. Cerebrospinal fluid (CSF) was acellular with normal constituents apart from a modest rise of CSF protein of 0·67 g/L. CSF 14-3-3 immunoassay was not done. MRI brain scan was reported as normal and was not judged to show the pulvinar sign after review. The patient deteriorated rapidly, showed myoclonic jerks of the limbs, and died 13 months after onset of illness.

As a result of flagging, the death certificate, which listed dementia as a cause of death, was forwarded from the Office of National Statistics to the national CJD surveillance unit, and the link through blood transfusion to the donor case was established. Independently of this process, the post mortem had been provisionally reported as showing changes suggestive of CJD, and the case was referred to the surveillance unit after death and tissues were sent for review. Subsequent investigation showed that the patient was a methionine homozygote at codon 129 of the prion protein gene (*PRNP*), and sequencing did not show any mutation. Prion-protein typing confirmed deposition in the brain of type 2B prion protein, which is pathognomic of vCJD. The neuropathological changes were typical of those seen in vCJD, with extensive florid plaque deposition.

Year of transfusion	Blood component transfused	Number of recipients (n=48)
1980–1984	Whole blood	1
	Red blood cells	1
1985–1989	Red blood cells	1
1990–1994	Red blood cells	8
1995–1999	Whole blood	1
	Red blood cells	16
	Red blood cells, buffy coat depleted	2
	Red blood cells, leucodepleted	1
	Fresh frozen plasma	3
	Cryodepleted plasma	1
	Cryoprecipitate	1
	Platelets	1
2000–2003	Red blood cells, leucodepleted	10
	Fresh frozen plasma, leucodepleted	1

Table 1: **Number of recipients transfused, by year and blood component given**

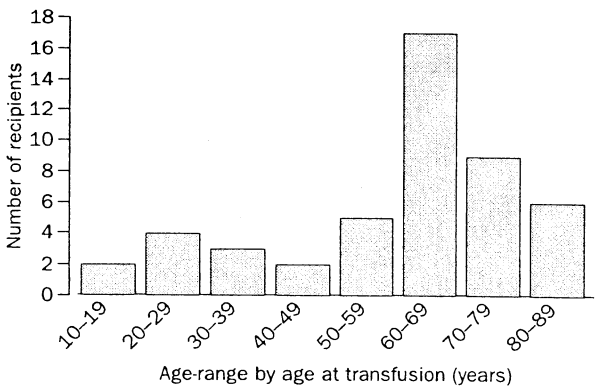
Statistical analysis, taking account of reported vCJD mortality to date and details of the recipients of vCJD donations (see below), indicated that the probability of recording a case of vCJD in this population in the absence of transfusion transmitted infection ranges between about 1 in 15 000 and 1 in 30 000. The first figure is based on crude analysis of the data, whereas the latter figure takes account of the ages of the transfusion recipients.

Review of records established that the affected donor had donated another unit of blood, the red cells of which were transfused to a patient who died of cancer 5 months after the transfusion. The platelets from this donation were included in a platelet pool, which has not been traced to a recipient. Plasma from both the donations was included in two different plasma pools for the production of fractionated plasma products.

vCJD cases with history of blood donation

As of Dec 18, 2003, 135 vCJD cases (of a total of 145 on the national CJD surveillance unit register) who were old enough to have been potential blood donors were notified to the UK blood services. 15 individuals were confirmed to have donated blood, with the number of components made and issued for use by the blood services ranging from one to eight per donor.

55 labile components originating from 15 donors were issued to UK hospitals over the period 1982–2002, most being issued between 1996 and 2000. Of these, 48 were



Age-range of recipients at transfusion

Interval from transfusion to death (years)	Number of recipients (age [years] at death)	Cause of death	Blood component transfused (single units)	Interval between blood donation and onset of clinical symptoms in donor (months)
<1	7 (68, 68, 65, 87, 88, 53, 69)	Cancer	FFP, RBC-BCD, RBC-LD, RBC-LD, RBC, RBC, WB	17, 15, 2, 18, 59, 31, 9
	1 (64)	Myocardial infarction	Cryoprecipitate	7
	2 (76 66)	Myelodysplasia	RBC, RBC	58, 7
	1 (81)	Myelofibrosis	RBC-LD	13
	1 (70)	Peritonitis	RBC-LD	10
	1 (68)	Postoperative pneumonia	RBC-LD	16
	2 (53 17)	Septicaemia	FFP, RBC	-6, 93
	2 (49 72)	Not yet available	RBC, RBC	139, 116
1 to <2	1 (52)	Acute myeloid leukaemia	RBC	34
	1 (27)	Heart disease and chronic renal failure	FFP	13
	1 (62)	Spinal haemangioblastoma	RBC	55
	1 (85)	Not yet available	RBC	127
2 to <3	1 (76)	Chronic obstructive airways disease	RBC	32
	1 (68)	Acute myeloid leukaemia	Platelets	58
3 to <4	1 (29)	Disseminated sepsis	RBC-LD	21
	1 (36)	Ischaemic heart disease	FFP	0
4 to <5	1 (80)	Ischaemic heart disease	RBC-BCD	6
6 to <7	1 (23)	Acute lymphoblastic leukaemia	RBC	93
7 to <8	1 (69)	Dementia*	RBC	40
	1 (70)	Ischaemic heart disease	RBC	112
>10	1 (99)	Bronchopneumonia	WB	141
	1 (69)	Ischaemic heart disease	RBC	191

*vCJD case. RBC=red blood cells. RBC-BCD=red blood cells, buffy coat depleted. RBC-LD=red cells, leucodepleted. FFP=fresh frozen plasma. WB=whole blood.

Table 2: **Dead recipients (n=31) of labile components from vCJD donors**

transfused to recipients. Seven components (issued between 1982 and 1996) were sent to hospitals that were unable to trace their fate. 18 units of plasma were included in pools for the production of fractionated products.

48 people were identified who received blood from 15 donors who went on to develop vCJD. Table 1 shows the number of recipients transfused by year and the type of blood component transfused. 41 (85%) received red-cell components (39 red blood cells, two whole blood), six (13%) were transfused with plasma components (four fresh frozen plasma, one cryoprecipitate, one cryodepleted plasma), and one (2%) received platelets. A third of the red-cell recipients received cells that had been leucocyte-depleted by prestorage filtration to less than 5×10^6 leucocytes per unit after introduction of universal leucocyte depletion of the UK blood supply in 1999 as a precautionary measure against vCJD transmission.

The figure shows the age-range of the 48 recipients. 32 (67%) were aged older than 60 years at the time of transfusion and thus would not have been eligible to enrol as blood donors subsequently. At Dec 18, 2003, none of the remaining recipients had themselves donated blood, although five were still young enough to be eligible as donors.

31 recipients (65%) were known to have died, with mean age at death 63 years (SD 20; range 17–99). 17 (55%) died less than 12 months after receiving their transfusion. Table 2 shows the cause of death as stated on death certificates for 28 recipients; the other three were confirmed dead, but cause of death was not available from the Office of National Statistics. No further information on clinical or neuropathological features was available for these cases.

At Dec 18, 2003, 17 (35%) recipients were alive. The mean age of these recipients was 65 years (SD 19, range 29–88). Ten patients survived for longer than 5 years after being transfused. Table 3 shows the number of living recipients according to time elapsed since transfusion, component transfused, and the interval between donation and onset of clinical symptoms of vCJD in the donor, as estimated by the national CJD surveillance unit to the nearest month after reviewing the case notes. None of these recipients have appeared on the surveillance register as vCJD cases. Most donations were made before onset of clinical illness (table 3) although two cases donated shortly after the first signs of clinical illness. These individuals would have seemed healthy when attending donor sessions and passed the normal medical checks as being fit to donate.

Time elapsed since transfusion (years)*	Number of recipients (current age in years*)	Blood component transfused (single units)	Interval between blood donation and onset of clinical symptoms in donor (months)
1 to <2	1 (88)	RBC-LD	-5
2 to <3	2 (50, 65)	RBC-LD	9, -3
3 to <4	2 (69, 73)	RBC-LD	5, 4
4 to <5	2 (40, 82)	RBC	5, 18
5 to <6	3 (71, 80, 85)	RBC	17, 13, 55
6 to <7	2 (29, 74)	RBC	20, 49
7 to <8	1 (72)	RBC	70
8 to <9	1 (31)	Plasma†	7
	2 (47, 85)	RBC	15, 82
>9	1 (65)	RBC	46

*To Dec 18, 2003. †Cryoprecipitate-depleted plasma. RBC=red blood cells. RBC-LD=red blood cells, leucodepleted.

Table 3: **Living recipients (n=17) of labile blood components donated by vCJD cases**

Discussion

The identification of a case of vCJD who received a blood transfusion from a donor who later died of vCJD raises the possibility that this infection was transfusion transmitted. Although statistical analysis suggests that coincidence is an unlikely explanation for this case, it is important to stress that this is a single case and there is a possibility that infection was due to dietary exposure to the BSE agent, the presumed route of zoonotic transmission of BSE.

The hypothesis of transfusion transmitted infection implies an incubation period of 6·5 years and that there was infectivity in the blood of the donor more than 3 years before development of clinical symptoms. The shortest incubation period in iatrogenic CJD due to human growth hormone treatment is 4·5 years,[1] which accords with the incubation period in this case. The route of administration, intramuscular rather than intravenous, and the probable amounts of infectivity in the implicated tissue—brain versus blood—suggest that a direct comparison between these iatrogenic mechanisms of prion transmission might not be valid. However, findings in experimental models show that blood may contain infective agents of prion diseases,[5,6] that no barrier to transmission exists with intraspecies transmission, and that the intravenous route of exposure to prions is fairly efficient.[7] The seminal experiments by Houston and Hunter[8,9] have shown transmission of BSE by blood transfusion in sheep, and it is noteworthy that the blood for transfusion in these experiments was obtained from sheep midway through the incubation period. Infectivity has also been noted in the incubation period and symptomatic phase in a rodent model of vCJD.[10] This evidence accords with the possibility of transfusion transmitted infection in the case reported here.

No evidence of transmission of sporadic CJD by blood transfusion exists, despite the identification of individuals who were exposed to blood donated by people who later developed this disease.[3] These data may not, however, be relevant to vCJD because this disease is due to a novel infectious agent in human beings and because the amount of disease-associated prion protein in peripheral lymphoreticular tissues is higher than in sporadic CJD,[4] indicating a different pattern of peripheral pathogenesis. In one study, infectivity in plasma and buffy coat in vCJD has not been detected,[11] but this fact, as in many previous studies of prion diseases, might be because of the severe restrictions in volumes of blood components that can be inoculated intracerebrally into experimental animals, leading to sampling errors in a tissue with low levels of infectivity and species-barrier effects.

The clinical presentation of the individual in this report is typical of vCJD,[12] and preliminary examination confirmed that the neuropathological features were identical to previous experience of this disease.[13] The MRI scan did not show the pulvinar sign, which is present in most cases of vCJD, but fluid attenuated inversion recovery sequences were not obtained, and these have the highest sensitivity.[14] The fact that the clinical and pathological phenotype was largely consistent with vCJD does not preclude the possibility that this case is caused by secondary transmission. The effects of serial transmission on phenotype are unpredictable in experimental models,[15] but it is noteworthy that the neuropathological features are stable in serial transmission of BSE and vCJD in macaque monkeys.[16] It is also of note that this case is the second oldest one of vCJD identified to date.

The red blood cells transfused in this case were not leucodepleted, although this measure was introduced during 1998 as a precaution to keep the chance of transmitting vCJD through blood transfusion to a minimum. However, uncertainty exists about the probable efficiency of leucodepletion in reducing infectivity,[6] and we cannot assume that the risk of transmitting vCJD will have been abolished by this measure.

The surviving recipients of blood transfusions donated by individuals who later developed vCJD may be at increased risk of developing vCJD and, after consideration by the Department of Health CJD incidents panel, are being informed of this risk and the need not to act as blood or organ donors. Additional measures might be considered, including exclusion of transfusion recipients from donating blood and extension of the policy of sourcing of fresh frozen plasma from outside the UK, but the most direct action to reduce risk is a careful case-by-case evaluation of the need for blood transfusion. Although the epidemic of vCJD presently seems to be in decline,[17] a proportion of the UK population could be incubating vCJD[18] and acting as blood donors.

18 units of plasma from individuals who later developed vCJD were included in pools for the production of fractionated products before 1998, at which time a policy was introduced to source plasma for fractionation from outside the UK. Before this date, many thousands of individuals may have been exposed to fractionated products derived from pools containing a donation from an individual incubating vCJD. To date, no case of vCJD has been identified with a history of exposure to fractionated blood products, and findings of experimental studies show that significant clearance of infectivity happens in several of the component steps in the plasma fractionation process.[19] The risks from fractionated plasma products to a recipient are probably less than from blood transfusion, not least because the volume of material to which an individual is exposed could be an important determinant of the level of risk.

Our report suggests that human prion diseases may be transmissible through blood transfusion and underlines the importance of epidemiological surveillance systems. Although experimental studies are important, only through the study of natural disease can evidence of an actual iatrogenic risk be identified. The risk of vCJD is not restricted to the UK, and the identification of cases of vCJD and examination of history of blood donation may be important in other European countries and elsewhere.

Contributors

C A Llewelyn, P E Hewitt, J Mackenzie, and R G Will were responsible for design, data collection, and management of this study. S Cousens did statistical analyses. R S G Knight and K Amar were responsible for the clinical data in the case report. All authors contributed to writing and amendment of the paper.

Conflict of interest statement

None declared.

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Annual Report of the CJD Incidents Panel, 2001-2002

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2001 - 2002

CJD INCIDENTS PANEL

Second Annual Report August 2001–August 2002 to the Joint Working Group on Transmissible Spongiform Encephalopathies of the Spongiform Encephalopathy Advisory Committee and the Advisory Committee on Dangerous Pathogens

CONTENTS

1 The role of the CJD Incidents Panel

The CJD Incidents Panel assists all those bodies responsible for the provision and delivery of health care to decide on the most appropriate action to take to handle incidents involving potential transmission of Creutzfeldt-Jakob Disease (CJD) between patients through clinical interventions, including via surgical instruments, tissues, organs and blood and to keep the relevant devolved administrations informed.

The Panel also advises on what studies or follow-up of patients may be needed; on patient tracing and notification exercises where these are indicated; and on what should be done with any equipment that may have been contaminated.

2 Introduction and background to the establishment of the Panel

2.1 The nature of CJD

CJD is a rare and fatal condition that affects the nervous system, and is one of a group of transmissible diseases known as the prion diseases or transmissible spongiform encephalopathies. Three major types of CJD are recognised:

- Sporadic CJD is the commonest form of CJD, which accounts for around 85% of all cases worldwide and for which the underlying cause is unknown.

- Familial CJD (along with the Gerstmann-Sträussler-Scheinker syndrome and Fatal Familial Insomnia) is associated with a point mutation or insertion mutation in the human prion protein gene, and is inherited as an autosomal dominant condition.

- Acquired forms of CJD include iatrogenic CJD, which is caused by human-to-human disease transmission through medical and surgical procedures. Other forms of acquired human prion disease include kuru, which was confined to the Fore tribe in Papua New Guinea and vCJD, which results from the exposure to the bovine spongiform encephalopathy agent.

All forms of CJD and other human prion diseases are associated with the accumulation of an abnormal form (known as a prion) of a host-encoded protein (called the prion protein) within the central nervous system. This abnormal protein is thought to be neurotoxic and responsible for the characteristic pathology occurring in the brain. There is an increasing body of research to indicate that the transmissible agent may be composed entirely of the abnormal form of prion protein, and it is thus distinct from microorganisms. The highest level of infectivity in CJD occurs in the brain. Infectivity can be reduced, but not removed, by the currently available decontamination procedures in NHS facilities.

Between 1970 and December 2001, the National CJD Surveillance Unit (NCJDSU) identified 944 cases of sporadic CJD in the UK.[1]

Since 1970, up to 31st December 2001, 45 cases of CJD attributable to iatrogenic exposure have been identified, 6 in individuals receiving dura mater implants, 38 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN).

The figures for the number of cases familial forms of prion disease in the UK are not available.

Variant CJD (vCJD), a new disease, is believed to be caused by the same abnormal 'prion' protein that causes Bovine Spongiform Encephalopathy (BSE) and is thought to result from eating contaminated beef products. vCJD was first recognised as a distinct clinical entity in 1996. At 5th August 2002, there were a total of 125 confirmed or probable cases of vCJD (dead and alive) in the UK[2]. It is not known how many people have been infected but have not yet developed symptoms. Although there have been no documented cases of transmission of vCJD through medical interventions to date, it must be assumed that vCJD has the potential for transmission between patients as has been shown for the older, better known forms of the disease, known as classical CJD.

2.2 Minimising the risks of transmission

In order to minimise the risk of transmission of CJD in a healthcare setting, the Joint Working Group (JWG) set up by the Spongiform Encephalopathy Advisory Committee and the Advisory Committee on Dangerous Pathogens drew up guidelines on the action required to prevent the possible spread from patients who are diagnosed, suspected or considered to be at risk of developing CJD [3] (This guidance is currently being reviewed).

However, infectious prions are thought to accumulate in the tissues of patients for a long period before symptoms of disease are apparent. Such patients incubating sporadic or variant CJD cannot currently be identified. The elimination of any risk of

transmission as a result of medical procedures carried out on such individuals could only be achieved by the exclusive use of single-use equipment for all patients, or the development of a decontamination process that is shown to be completely effective against prions.

Single use tonsillectomy kits were introduced in the UK in 2001. They were withdrawn the same year in England on patient safety grounds in the light of reports of adverse incidents. Most Trusts in Northern Ireland returned to using reusable instruments in 2002. Single use instruments are still used in Wales and reprocessing is not approved. In Scotland single use instruments use recommenced in March 2002.

DH funded research projects are working on the development of novel decontamination procedures. This is overseen by the Working Group on Research into the Decontamination of Surgical Instruments, which reports to SEAC. In 2001, £200 million of special initiative funding was secured by the Department of Health to improve decontamination services in the NHS and bring them to an acceptable level.

Although good decontamination reduces the risk of transmission of CJD, it cannot be relied on to eliminate the risk entirely because abnormal prion protein is extremely sticky and can survive even the best current decontamination processes used for surgical instruments. Therefore, whilst the potential for the risk of transmission as a result of medical procedures remains, guidance has to be given on the appropriate action to take when possible exposure has occurred.

The JWG considered developing guidelines to assist healthcare providers to take the appropriate action but concluded that the issues were too complex to be addressed by a guidance document applicable to all the anticipated types of incidents. Therefore the Government's Chief Medical Officer established an expert panel to consider the details of incidents and provide the appropriate advice on a case-by-case basis. The establishment of the CJD Incidents Panel was announced by the Chief Medical Officer in his August 2000 Update (Extract.Appendix 1). The Panel is chaired by an ethicist and reports to the JWG. Local clinicians are asked to report incidents to the Panel. The Panel comprises independent experts in the field of prion diseases, a range of clinical specialities, legal and ethics advisers and members who speak for the general public. (Appendix 2). The Panel provides advice on a case-by-case basis to local clinicians on follow-up action to incidents in which individuals who develop CJD are found to have had previous surgery, or to have donated blood, tissues or organs.

3 Outline of the work of the Panel: August 2001-August 2002

There were three full Panel meetings (October 2001, April 2002, June 2002). The minutes of the Panel meetings are provided, in confidence, to the JWG. Public summaries are posted on the Department of Health website[4]

In addition to the full Panel meetings, subgroups of the Panel met to consider the details of specific incidents and individual Panel members provided the Secretariat with advice by telephone and correspondence.

A table listing the meetings of the Panel and subgroups is given at Appendix 6

3.1 Framework Document (Consultation Paper)[5]

A significant amount of time and effort has been expended by Panel members in the development of this document. At the first meeting of the Panel in November 2000, it was agreed to draw up a draft framework document setting out the principles underlying the Panel's advice on individual incidents. The draft framework document "Management of possible exposure to CJD through medical procedures. A consultation paper" was made publicly available for consultation in October 2001.

The aims of the management actions as outlined in the draft framework document are:

- To protect patients from the risk of acquiring TSEs in healthcare settings.
- To ensure that those who might have been exposed are informed in a manner appropriate to their level of risk.
- To ensure that those who might have been exposed to lower levels of risk, while not being actively informed, are able to find out about their exposure if they so wish.
- To increase our knowledge about the risk of transmitting TSEs in healthcare settings, to be better able to manage any risk to individuals and to public health.
- To ensure that the public is informed about possible risks of acquiring TSEs through healthcare.

Because the Panel recognised the need for reflection and discussion in relation to its proposals, the Panel asked the Department of Health to put the framework document out to a full consultation with stakeholders and with the general public. This consultation was launched on 10 October 2001 and concluded with a public meeting

on 17 April 2002. The consultation document and response form was made publicly available on the CJD section of the Department of Health website and was also posted to approximately 3000 people, including health professionals, patient representative groups and lay and religious groups. A total of 336 written responses (11.5% of the total mailed) were received. The open meeting was intended to provide a further opportunity to receive comments and suggestions from interested bodies, health professionals and patient groups. The public meeting attended by just over 300 individuals from throughout the UK, including a range of professional healthcare workers, patient representative groups, relatives of CJD patients, representatives of professional bodies and national organisations, and those with ethics, legal or insurance backgrounds. A report summarising the responses is available on the CJD Incidents Panel website and it is intended to put all the responses received on this site. Further discussions have also taken place with the British Medical Association and the Information Commissioner.

The framework document was revised in the light of the consultation, which made a vital contribution to thinking about the scientific, ethical and practical aspects of the Panel's proposals. The sections dealing with the general principles and surgical instruments are now complete; the section on blood and blood products is still under consideration, pending completion of the blood risk assessment and sections on dentistry and tissue and organ donations have yet to be added. Even then, the framework document will remain a working document. It is anticipated that it will need updating on an ongoing basis in the light of new developments in understanding of the disease, in decontamination methods and in the light of experience of the outcomes of the management actions advised. Changing attitudes in society may also require modifications to the balances struck.

The revised Framework Document (Consultation Paper), together with a discussion of the key issues raised will be submitted to the CMOs. There are currently three particular areas of concern to the Panel as follows:

Firstly, proposals for the management of CJD incidents represent, the Panel believe, a coherent package of measures and it is important that they are recognised as such. In particular, it is crucial that the establishment of a database and the identification of a contactable group be accompanied by an effective communications strategy regarding CJD and its management, including the proper provision and funding of appropriate counselling services.

Secondly, the Panel considers that for their proposals to be workable there are certain practical issues to be addressed, which can be tackled more appropriately by the Departments than by the Panel itself. In particular, it is vital that steps be taken to ensure that the actions taken to protect public health do not compromise the ability of individuals to obtain access to medical, dental or financial services. In addition, the Panel is aware that the precise terms under which the database could be established raises legal questions in relation to the use of confidential patient information.

Thirdly, although the Panel is charged with advising on the management of incidents arising from medical procedures, it believes it appropriate to stress how important it is that the risk of future incidents be reduced by the appropriate introduction of single use instruments and the effective implementation of the Departments' policies for improvements in decontamination. In addition, the speedy introduction of traceability

of instruments will crucially assist the Panel in providing appropriate and effective advice in the years to come.

3.2 Blood components and plasma derivatives

The Panel developed a strategy for recipients of blood components, based on the risk assessment published by the independent consultants Det Norske Veritas (DNV) in 1999[6], which it used to advise on individual incidents. The Panel however found that the risk assessment was not suitable for the Panel's work in that it was not comprehensive. It also lacked transparency and was out of date. The Panel considered that the information available on infectivity in different plasma derivatives required further analysis to reach conclusions as to the level of risk. The Department of Health therefore commissioned DNV to provide a revised risk assessment for blood products and plasma derivatives. The assessment has been considered in 2002 by SEAC, the Committee on the Safety of Medicines and the Committee for the Microbiological Safety of Blood and Tissues for Transplantation. The risk assessment is being updated in the light of the comments from these committees and other experts. The CJD Incidents Panel will use the revised risk assessment as the basis for advice on incidents involving blood and blood products. Meanwhile, the Panel continues to provide advice on a precautionary basis, to ensure the protection of public health until a more robust evaluation is available.

3.3 Other tissue and organ transplantation

Guidance on the microbiological safety of organs, tissues and cells used in transplantation sets out selection criteria for prospective donors. A theoretical risk of vCJD transmission exists, but addressing the immediate clinical need for which

organ/tissue transplantation is required is paramount. The CJD Incidents Panel will provide specific advice if an incident involving transplantation occurs and the basis for such advice will be included in the revised framework document. Whilst a full risk assessment in this area has yet to be developed, advice will be given for incidents involving tissue and organ donations on a precautionary basis.

3.4 Storage of contaminated instruments

The Panel welcomes the Department of Health's proposed arrangements for storage of instruments that may have been contaminated with CJD for research purposes and will provide advice on the information that would need to be linked to these instruments.

4 Cumulative analysis of incidents reported to the Panel (27/8/00-6/8/02)

4.1 Definitions and Procedures

Incidents arise when patients who are diagnosed or suspected of having CJD are found to have undergone a medical procedure at some time in the past. Other patients could be put at risk if CJD is transmitted through contaminated instruments and/or devices, blood or other tissues or organs donated by patients with CJD.[5]

The incidents reported and analysed in the following section, exclude certain queries which have come in to the Panel Secretariat, such as historical incidents in which actions had been taken prior to the establishment of the Panel, incidents outside the UK and incidents for which the information available was insufficient to allow follow up.

When an incident is reported to the Panel a patient incident number (PI number) is allocated and given to the person reporting the incident for use in all future correspondence. One PI number may include one or more procedures that the patient has undergone. These procedures often cover a range of specialities at various hospitals and clinics. In many incidents, additional information from the clinicians involved is required before advice can be given. In many cases, final advice on the full actions to take must await Government agreement with the Panel's proposals and establishment of the appropriate infrastructure required for their implementation.

4.2. Types of incidents reported

The CJD Panel Secretariat had received at 6 August 2002 a total of 113 incidents or requests for advice from the Panel. Of these, 77% (n= 87) involved surgery or other invasive procedures. The remaining 23% of reports almost all related to blood donations. (Table 1).

Table 1: Incidents (n=113) reported to the CJD Incidents Panel (27/8/00 – 6/8/02)

YEAR	SURGERY-RELATED	NOT SURGERY-RELATED *	TOTAL
2000 (27/8-31/12)	16	0	16
2001 (1/1-31/12)	38	16	54
2002 (1/1-6/8)	33	10	43
Total (27/8/00-6/8/02)	**87**	**26**	**113**

* These incidents are almost all related to blood donations but also include other examples such as a human growth hormone-recipient query.

Incidents not related to surgery (or other invasive procedures)

The non-surgical incidents comprise 25 blood-related incidents and one query about procedures on a recipient of human growth hormone. These non-surgical incidents are mainly requests for advice on the precautions required for invasive procedures on recipients of plasma derivatives but also include reports of a CJD diagnosis being made on people who have donated blood. The Panel has agreed that concern about blood donations is restricted to vCJD cases. No incidents involving transplantation of organs or tissues have been received to date.

At present, the Panel is only able to provide advice to clinicians caring for recipients of plasma derivatives as and when the clinicians request advice. This is the basis on which many blood-related incidents are logged. This does not necessarily mean that the patient is at special risk, only that the potential risk needs to be considered. This is done on an individual patient risk assessment based on the details of the batch of product and the number of units of the plasma-derived product each has received. The Panel is able to advise on the risks once the full details are provided.

Incidents of 9 potentially contaminated blood donations have been reported with 29 recipients of the blood (of whom 13 patients were still alive in August 2002). None of these patients have been informed but precautions have been taken to protect the blood supply.

Incidents related to surgery (or other invasive procedures)

The following tables relate to the 87 surgery-related incidents. 85% of cases were reported from England, 10% from Scotland and the remainder from Wales and Northern Ireland. (Table 2).

Table 2: Surgery related incidents reported to the CJD Incidents Panel 27/8/00-6/8/02 by country

COUNTRY	NUMBER	% TOTAL
England	74	85
Northern Ireland	2	2
Scotland	9	10
Wales	2	2
Total	**87**	**99***

* % do not add up to 100 due to rounding

Most of the incidents reported (90%) involving surgery or other invasive procedures were related to cases of either sporadic (45%) or vCJD (45%). (Table 3) Some incidents reported to the Panel related to patients eventually confirmed as a diagnosis other than CJD. In a few cases the type of CJD was unclear. The Panel Secretariat advises the local incident team to provide the opinion of the NCJDSU using their terminology and classifications for the diagnosis.

Table 3: Types of CJD involved in surgery-related incidents (n=87) reported to the CJD Incidents Panel 27/8/00 – 6/8/02

FINAL DIAGNOSIS	NUMBER	% TOTAL
Sporadic CJD (possible, probable or definite)	39	45
Variant CJD (possible, probable or definite)	39	45
Other types of CJD (including 1 familial and 1 probable GSS) or CJD type unclear	6	7
Not CJD	3	3
Total	**87**	**100**

When surgery-related incidents are reported to the Panel, information is sought about the surgical instruments used. This includes the traceability of the instruments. Where the instruments used cannot be identified, it may be advised that all the

instruments that could have been used are placed in quarantine. Lack of traceability also means that it is not possible to identify patients who may have been exposed subsequently. Some or all of the surgical instruments of concern were traceable (by tray) in only 45% of incidents reported to the Panel (Table 4). This is a matter of concern as the Department of Health has advised Chief Executives of NHS Trusts to have 'taken steps towards having systems in place to enable the tracing of surgical instrument sets to patients on whom they have been used by 31st March 2002'.[7]

Table 4: Instruments/equipment traceable/not traceable in surgery-related incidents (n=76*) reported to the CJD Incidents Panel 27/8/00 – 6/8/02

TRACEABILITY (BY TRAY)	NUMBER	% WHERE TRACEABILITY SOUGHT
Traceable (some or all)	34	45
Not traceable	18	24
Missing/awaited information	24	31
Total	**76**	**100**

* 11 of the total 87 are not included in this table because traceability was not an issue for such reasons as the instruments were disposable or the tissue was low risk.

The procedures involved contact with a range of tissues and a variety of specialities. The most common related to the gastrointestinal tract (often endoscopy). (Table 5).

Table 5 Specialities involved in incidents reported to the CJD Incidents Panel (note one incident often involves several procedures across a range of specialities)

SPECIALITY	NUMBER	% TOTAL
Gastrointestinal	29	20
Obstetrics and gynaecology	18	13
Neurology/neurosurgery	16	11
Orthopaedics	14	10
Ophthalmology	13	9
ENT (including 4 tonsillectomies)	12	8
Thoracic	11	8
Other*	18	13
Total	**143**	**100**

*including general surgery, urology, accident and emergency, anaesthesia, vascular surgery.

Panel Advice

In one surgery-related incident reported, there are 3 patients who will be 'contactable' for public health reasons as assessed by the Panel and based on the Framework Document (Consultation Paper).

The Panel is advising that these patients should be contacted as soon as adequate support is available. The Panel Chairman has written to the CMOs requesting the establishment of a communication strategy to support full implementation of the Panel's proposals.

Quarantine and withdrawal

Instruments were quarantined (either on Panel advice or already before reporting the incident) in 55% (n=48) of reported incidents involving surgery or other invasive procedures. Following consideration and receipt of further information, the Panel advised that the instruments were returned to use in 21 (44%) of these 48 incidents.

The Panel advised that a small number of instruments were to be permanently removed from use. Other instruments may have been destroyed, but not on Panel advice.

5 Issues of concern and matters of principle

5.1 Dental procedures

The Panel is concerned to obtain more information on the possible risks that could arise from various types of dental procedures and awaits the outcome of risk assessments being carried out by the Department of Health before including these procedures in its framework document. Problems have been recognised in connection with identifying which dentist(s) a CJD patient may have attended prior to the diagnosis of CJD. The name of a patient's dentist is not formally recorded in their

medical records and immediate relatives may not know this information. Dental records are kept for at least seven years for all registered patients over eighteen years of age but this will not be the case for non-regular attenders. When patients change their dentist there is no formal system for transferring their records to the new dentist. Another area of concern in dentistry is that some of the reusable instruments are extremely difficult to clean e.g. reamers and files used in root canal treatments. Questions have been asked about infection control issues in dentistry including methods of sterilisation, auditing of decontamination in dental surgeries and traceability of instruments. The JWG has been asked to consider the risks of transmission of CJD through dental procedures.

5.2 Endoscopy

Incidents involving endoscopy/fibreoptic equipment accounted for 26% of procedures reported. The endoscopic procedures involved a range of specialities e.g. gastroscopy, flexible laryngoscopy, cystoscopy.

The Panel was asked for advice on the potential risk of transmission of CJD via endoscopes and on precautions required when performing endoscopy on patients identified as risk. A subgroup of the JWG was convened to address these issues and present a report to the JWG.

5.3 Ventilators

The Panel was advised on the potential risk from ventilators used on a patient with suspected CJD by the Advisory Committee on Dangerous Pathogens and Spongiform Encephalopathy Advisory Committee Joint Working Group on Transmissible Spongiform Encephalopathies (JWG). The advice was that a single-use filters should

always be used at the patient end of an anaesthetic breathing circuit and that all constituent parts of the patient circuit should be disposable and be discarded at the end of the case.

5.4 Haemodialysis

The Panel considered the issue of possible risks of transmission of CJD from the use of haemodialysis equipment on a patient recipient of potentially contaminated blood products or a patient with suspected CJD. The Panel sought additional guidance from the Advisory Committee on Dangerous Pathogens and Spongiform Encephalopathy Advisory Committee Joint Working Group on Transmissible Spongiform Encephalopathies (JWG).

The JWG advised advice was that, provided the equipment was suitably monitored and there were no failures, such as leakages in the system, and that single-use components such as the dialyser and extracorporeal lines, were not re-used, there was little risk of transmission of CJD from dialysis machines (haemofilters and diafilters). The advice was valid for equipment in which there were filters between the machine and the blood, so the machine itself does not come into contact with blood or other body fluids, and pressure gauges were also barrier-protected. It was noted however that, if older machinery, which may not include such single-use disposable components, has been used, the JWG would be far less likely to conclude that the risks are acceptably low.

5.5 Plasma derivatives

The Panel has requested a full evaluation of the potential infectivity in plasma derivatives before including a final evaluation of the potential risks from receipt of these products. In the interim, the Panel is advising that special precautions should be taken in the treatment of recipients who might eventually be included in the contactable group.

5.6 Decontamination Review

The Panel considered whether any information in the report 'A review of the decontamination of surgical instruments in the NHS in England' published in 2001 changed the decisions as set out in the draft framework document. It was agreed that no revisions were necessary since the proposals had been based on the previously published Scottish review, which had obtained similar results.

The Review had assessed NHS performance with a 'traffic light' system, looking at: i) environment; ii) equipment; iii) training and iv) services. Members were assured that a significant amount of time, manpower and resources had been dedicated to rapidly improving any sites identified to be in urgent need of improvement. This work would be ongoing, and each NHS Trust now had an appointed person responsible for ensuring that standards continue to be met. £200 million had been dedicated to the improvement of decontamination and state-of-the-art Central Sterile Service Departments would be installed over the next three years in each region to maintain standards. £75 million had already been spent. There was also stated to be a commitment across the NHS to ensure that improvements are made and maintained.

It was noted that the decontamination improvement exercise would include some work in primary care and dentistry.

5.7 Potential secondary transmission

The Panel agreed that the surgical history of all patients in the 'contactable' group (including blood product recipients) should be examined individually to determine whether any further risk of onward transmission may have occurred.

5.8 Incidents involving possible or probable sporadic CJD

The Panel agreed that it was possible to give advice in incidents where the diagnosis is possible or probable sporadic CJD in advance of, or in the absence of, a postmortem confirmation of the diagnosis. This decision was based on information from the NCJDSU that of the referrals of 42 possible and 7 probable sporadic CJD cases to the NCJDSU in 2000 no cases were later diagnosed as vCJD.

The Panel has agreed that, although transmission from tissues other than the CNS and eye of sporadic CJD patients cannot be excluded with certainty for all possible individual cases of this form of the disease, the balance of evidence indicates that the risk of this occurring is extremely low. Given that all UK inhabitants must be considered to be at some risk of variant CJD as a result of exposure to BSE before strict enforcement of controls, the Panel concluded that no special actions were justified in incidents involving sporadic CJD and tissues other than the CNS or eye.

5.9 Revision of Panel Advice on matters of principle

The Secretariat agreed that, should the Panel significantly revise its advice on any matter of principle, the Secretariat would write to those people who had reported any relevant incident in the past explaining the reasons for the change of opinion.

5.10 Surgical Instruments

The speedy introduction of traceability of instruments will assist the Panel in providing appropriate and effective advice in the years to come.

Although the Panel is charged with advising on the management of incidents arising from procedures it considers it appropriate to stress the importance of reducing the risk of future incidents occurring by the appropriate introduction of single use instruments where possible. It also strongly supports the effective implementation of the Departments' policies for improvements in decontamination.

The Panel highlighted a particular problem with instruments used for taking brain biopsy samples and will draw this to the attention of the relevant professional bodies.

6 Future Work

- The Framework Document and the sections of the Framework Document relating to blood components and plasma derivatives will be developed as a high priority.
- The framework document will be extended to include dental procedures.
- The framework document will be extended to include organs and tissues donated by patients who subsequently develop CJD.

- The Panel feel that it is crucial that the establishment of a database and the identification of a contactable group be accompanied by an effective communications strategy regarding CJD and its management, including the proper provision and funding of appropriate counselling services. The Panel is concerned that an appropriate system of expert support should be available to support those charged with providing information and counselling to patients involved in look-back and notification exercises. A communication strategy is currently being developed by the Communicable Diseases Surveillance Centre.
- The Panel requests the Department of Health to keep the Panel informed on their plans to mount an exercise to increase public understanding of the nature of CJD, the ethical issues surrounding individual patient interests and public health and the purpose of the proposed database of potentially exposed individuals.
- The Panel is considering asking the Department of Health to reconsider the retention period of health records in the light of the potential long incubation period for CJD and the possible need to trace records over decades.
- The Panel will continue to report to the JWG in the follow ways:-
    - provide the JWG Chairman with Panel meeting agendas in advance of each meeting
    - provide a public summary of each meeting of the Panel for release on the agreement of the JWG Chairman
    - provide an annual report to the JWG for public release
    - append a confidential annex to the annual report containing the minutes of the Panel meetings.

7.References

1. The National CJD Surveillance Unit. 2001Tenth Annual Report 2001. Creutzfeldt-Jakob Disease Surveillance in the UK (www.cjd.ed.ac.uk).
2. Department of Health. Monthly CJD statistics at *www.doh.gov.uk/cjd/cjd_stat.htm*
3. Advisory Committee on Dangerous Pathogens Spongiform Encephalopathy Advisory Committee. Transmissible Spongiform Encephalopathy Agents: Safe Working and the Prevention of Infection. 1998. The Stationery Office.
4. Department of Health. Public Summaries of CJD Incidents Panel Meetings at *www.doh.gov.uk/cjd/incidentspanelmeetings.htm.*
5. Department of Health. CJD Incidents Panel. Management of possible exposure to CJD through medical procedures. A consultation paper. October 2001 (and responses to the consultation) at *www.doh.gov.uk/cjd/consultation*).
6. Det Norske Veritas (DNV) Assessment of the risk of exposure to variant CJD infectivity in blood and blood products. Final report for the Spongiform Encephalopathy Advisory Committee and Department of Health February 1999.
7. Department of Health. Health Service Circular HSC 2000/032. Decontamination of medical devices.

APPENDIX 1

EXTRACT FROM CMO'S UPDATE 27AUGUST 2000

Expert panel on the management of incidents involving Creutzfeldt-Jakob Disease (CJD) and surgery

- An expert panel has been set up to provide advice to clinicians on what action to take if a patient is diagnosed as having, or develops symptoms suggestive of, Creutzfeldt-Jakob Disease (CJD) some time after having undergone invasive surgery.

- The panel will advise on what action, if any, needs to be taken with the instruments involved and on the likely level of risk to other patients on whom the instruments may have been used. The level of risk will depend on a number of factors and the panel will consider each case individually.
  Clinicians with patients in this category should contact the secretariat who will arrange for details of the case to be put to the panel for advice.

APPENDIX 2 Membership of CJD Incidents Panel

Name	Expertise
Chairman	
Professor Michael Banner	Ethics
Vice Chairman	
Professor Don Jeffries	Virology
Members	
Mr John Barker	Sterile Service Management
Professor Mike Bramble	Gastroenterology
Dr Geoff Craig	Dental Surgery
Professor Ian Cooke	Obstetrics and Gynaecology
Professor Len Doyal	Ethics
Ms Jean Gaffin	Lay Representative
Dr Noel Gill	Epidemiology
Mr Luke Gormally	Ethics
Dr Pat Hewitt	Blood Safety
Professor Peter Hutton	Anaesthesia
Professor James Ironside	TSE and Neuropathology
Ms Diana Kloss	Law
Professor John Lumley	General Surgery
Ms Susan MacQueen	Infection Control
Mr Henry Marsh	Neurosurgery
Professor John O'Neill	Ethics
Dr Mike Painter	Microbiology
Dr Geoff Ridgway	Microbiology
Dr Roland Salmon	Epidemiology
Professor Graham Smith	Anaesthesia
Professor Dame Lesley Southgate	General Practice
Dr David Taylor	TSE and Decontamination
Mr Andrew Tullo	Ophthalmology
Ms Gillian Turner	Lay Representative
Dr Hester Ward	Epidemiology
Ms Kate Woodhead	Theatre Nursing
Dr Tim Wyatt	Microbiology

Observers

Name	Affiliation
Dr Martin Donaghy	Scottish Executive Health Directorate
Dr Glenda Mock	Department of Health, Social Services and Public Safety, Northern Ireland
Dr Mike Simmons	National Assembly of Wales

Secretariat Name	Affiliation
Dr Nicky Connor (until May 02)	CJD/ BSE Policy Unit, DH
Dr Pip Edwards	CJD/ BSE Policy Unit, DH
Miss Claire Mills (until June 02)	CJD/ BSE Policy Unit, DH

APPENDIX 3: CODE OF PRACTICE FOR MEMBERS OF THE CJD INCIDENTS PANEL

The Code of Practice for CJD Incidents Panel members is based on a Cabinet Office model, which contains guidance on matters such as required standards in public life, the role of the Panel, declarations of interest and the handling of Panel papers. The code has been agreed with the Panel.

INTRODUCTION

1. The CJD Incidents Panel operates as a subgroup of the ACDP/SEAC Joint TSE Working Group. Its terms of reference are given in Annex A.

2. In line with Government policy on standards in public life, openness and accountability, the CJD Incidents Panel Secretariat has drawn up the following Code of Practice which members have agreed to follow in carrying out duties associated with the Panel.

STANDARDS IN PUBLIC LIFE

3. Members of the CJD Incidents Panel are expected to:

- follow the Seven Principles of Public Life as set out by the Committee on Standards in Public Life (see Annex B), as they apply to their service on the Panel;

- comply with this Code, and ensure that they understand their duties, rights and responsibilities, and that they are familiar with the function and role of the Panel and relevant Government policy;

- not misuse information gained in the course of their Panel duties for personal gain or for political purpose, not seek to use the opportunity of Panel service to promote their private interests or those of connected persons, firms, businesses or other organisations; and;

- not hold any paid or high profile unpaid posts in a political party, and not engage in specific political activities on matters directly affecting the work of the Panel. When engaging in other political activities, members should be conscious of their public role and exercise proper discretion.

ROLE OF MEMBERS

4. The terms of appointment of CJD Incidents Panel members are set out in Annex C.

5. Members of the CJD Incidents Panel have collective responsibility for the operation of the Panel. They should engage fully in the collective consideration of issues, taking account of the full range of relevant factors, including any guidance issued by the Spongiform Encephalopathy Advisory Committee/Advisory Committee on Dangerous Pathogens Joint TSE Working Group. The members are expected to:

- agree the advice, recommendations and reports as set out in the Panel terms of reference;
- ensure that the Panel does not exceed its remit.

ROLE OF THE CHAIRMAN

6. The Chairman has particular responsibility for providing effective leadership on the issues above. In addition, he/she is responsible for:

- ensuring that the advice and recommendations, produced by the Secretariat, and any reports to the Spongiform Encephalopathy Advisory Committee/Advisory Committee on Dangerous Pathogens Joint TSE Working Group accurately record the decisions taken and, where appropriate, the views of individual Panel members have been taken into account. The Chairman will indicate that the advice, recommendations and reports accurately reflect the Panel's views by "signing-off" once they have been agreed by the Panel;
- representing the views of the Panel to the general public as appropriate; and
- briefing new members on appointment, as appropriate; and providing an assessment of their performance, on request, when they are being considered for re-appointment to the Panel.

ROLE OF THE DEPUTY CHAIRMAN

7. The Deputy Chairman has all the responsibilities of the Panel members. In addition, he/she:

- provides advice and support to the Chairman in the exercise of his/her duties as described in paragraph 9 above and
- takes over the Chairman's duties in the event that the Chairman is for any reason unable to fulfil them.

ROLE OF THE SECRETARIAT

8. The Secretariat is provided by Department of Health officials. Communications between the Panel and the clinicians, Regional Health Authorities or Health Boards and the SEAC/ACDP TSE Working Group will generally be through the Secretariat, except where it has been agreed that an individual member should act on the Panel's behalf. Nevertheless, any Panel member has the right of access to the Joint TSE Working Group on any matter, which he or she believes raises important issues relating to his or her duties as a Panel member. In such cases, the agreement of the rest of the Panel should normally be sought.

9. The Secretariat is also responsible for:

- maintaining an up-to-date record of Panel Members' interests;
- ensuring that the Panel does not exceed its powers or functions;
- ensuring that the Code of Practice is adhered to, and any complaints are dealt with appropriately.

DECLARATIONS OF INTERESTS

10. It is important to avoid any danger of members of the CJD Incidents Panel being influenced, or appearing to be influenced, by their private interests in the exercise of their public duties. All members should, therefore, declare any personal or business interests which may, or may be perceived (by a reasonable member of the public) to influence their judgement. This should include, as a minimum, payments to members personally and payments to the relevant part of the organisation for which a member works. Financial or clinical involvement in any particular establishment or individual cases under consideration, and financial interests in businesses supplying medical equipment are examples of interests that should be declared. Members should be aware of their responsibility not to be seen to allow their judgement to be influenced in considering receipt of any gifts or hospitality offered in the exercise of their public duties.

11. If members feel that there are interests, outside the scope of this Code, which could be perceived as influencing their work in relation to the CJD Incidents Panel, for example the personal or business interests of close family members (personal partners, parents, children, brothers and sisters and the personal partners of any of these) they should declare those or approach the Secretariat for advice.

Declarations of interests at meetings

12. A declaration of any interest should be made at any Panel meeting where it relates specifically to a particular issue under discussion. The Secretariat will

record this declaration in the minutes (whether or not a member also withdraws from the meeting). Members should not participate in the discussion or determination of matters in which they have an interest, as defined above, and may be asked by the Chair to withdraw from the meeting.

Register of interests

13. The Secretariat will maintain a Register of Members Interests. This will be kept up to date, will be included in the reports to the SEAC/ACDP Joint TSE Working Party, and will be publicly available. Members should notify the Secretariat, immediately, of any changes in interests of relevance to the work of the Panel.

OPENNESS

14. The majority of papers considered by the Panel will relate to specific clinical cases, and therefore must be considered as confidential and are excluded from the requirement for public disclosure (see Annex D).

15. The minutes of meetings will include details of individual cases and must therefore also remain confidential.

16. The underlying basis on which the Panel reaches conclusions will be publicly available through the SEAC/ACDP Joint TSE Working Group.

17. Advice given to individual Health Authorities or Health Boards and clinicians involving individual cases will be given in confidence, but the Health Authorities or Health Boards and clinicians may choose to make the advice publicly available if they consider this appropriate.

18. Annual reports to the SEAC/ACDP Joint TSE Working Group will be publicly available following acceptance by the Working Group.

RELATIONS WITH THE MEDIA

19. The Secretariat (via the DH Press Offices or Regional Health Authorities or Health Boards, as appropriate) will usually be responsible for handling media enquiries about the CJD Incidents Panel and its work. However, members may need to deal with direct enquiries from the media, and should do so with circumspection. Unless the Panel has agreed that an individual member should speak on their behalf, members should make it clear that they speak as individuals, not on behalf of the Panel. Members may prefer to refer any such media enquiries to the Secretariat in the first place, or to seek advice on how to handle particular enquiries.

20. Members may, in the course of their work, address conferences and seminars, or have other speaking arrangements at which the media are present. In these

circumstances, members should take care to make it clear that they are speaking in a personal capacity and not as a member of the CJD Incidents Panel. **ANNEX A**

CJD Incidents Panel
Terms of Reference

"To assist individual Health Authorities or Health Boards and clinicians to decide on the most appropriate action to take to handle incidents involving potential transmission of Creutzfeldt-Jakob Disease (CJD) and variant CJD (vCJD) between patients through clinical interventions, including via surgical instruments, tissues, organs and blood and to keep the relevant devolved administrations informed.

To consider what information should be collected on patients who may have been exposed; advise on what studies or follow-up may be needed; advise Directors of Public Health on patient tracing and notification exercises where these are indicated; and advise on whether any other measures are needed to protect the wider public health.

To make regular reports to the Spongiform Encephalopathy Advisory Committee and Advisory Committee on Dangerous Pathogens Transmissible Spongiform Encephalopathy Joint Working Group (JWG).

To keep the expert guidance under review and make recommendations to JWG for further guidelines as necessary, in the light of experience of incidents and research in progress."

ANNEX B

THE SEVEN PRINCIPLES OF PUBLIC LIFE

Selflessness

Holders of public office should take decisions solely in terms of the public interest. They should not do so in order to gain financial or other material benefits for themselves, their family, or their friends.

Integrity

Holders of public office should not place themselves under any financial or other obligation to outside individuals or organisations that might influence them in the performance of their official duties.

Objectivity

In carrying out public business, including making public appointments, awarding contracts, or recommending individuals for awards and benefits, holders of public office should make choices on merit.

Accountability

Holders of public office are accountable for their decisions and actions to the public and must submit themselves to whatever scrutiny is appropriate to their office.

Openness

Holders of public office should be as open as possible about all the decisions and actions that they take. They should give reasons for their decisions and restrict information only when the wider public interests clearly demands.

Honesty

Holders of public office have a duty to declare any private interests relating to their public duties and to take steps to resolve any conflicts arising in a way that protects the public interests.

Leadership

Holders of public office should promote and support these principles by leadership and example.

ANNEX C

TERMS OF APPOINTMENT OF CJD INCIDENTS PANEL MEMBERS

Appointments to the Panel are made by the Chief Medical Officer. Terms of appointment usually range from 1-3 years. Appointments may be terminated at members' request; Panel members can normally be removed from office by the Chief Medical Officer if they fail to perform the duties required of them in line with the standards expected in public office, or at the Chief Medical Officers' discretion.

Members may claim travel and subsistence allowances at standard DH rates.

ANNEX D

EXEMPTIONS FROM PUBLIC DISCLOSURE

1. The **Code of Practice on Access to Government Information** allows exemption from disclosure of:

- information which would harm national security, defence or international relations;
- information that would harm the frankness and candour of internal discussion;
- information which would prejudice law enforcement and legal proceedings or would harm public order or public security;
- vexatious requests and requests which are manifestly unreasonable or formulated in too general a manner;
- information about to be published;
- incomplete analysis, research or statistics or information held only for the purpose of research and statistics, where the individual record will not be identified;
- information which would cause an unwarranted invasion of personal privacy;
- commercially confidential information;
- information given in confidence;
- information whose disclosure is prohibited by law.

APPENDIX 4 DECLARATIONS OF MEMBERS INTERESTS

Name	Name of Organisation	Nature of Interest
Rev. Prof. Michael Banner	1. Animal procedures Committee, Home Office 2. Agriculture and Environment Biotechnology Commission 3. King's College, University of London 4. Shell Advisory Panel on Animal Testing	1. Chairman 2. Member 3. Professor of Moral and Social Theology 4. Chair
Mr John Barker	1. Nuffield Hospital 2. Institute of Sterile Service Management	1. Decontamination Manager 2. Fellow
Prof. Mike Bramble	1. Astrazeneca 2. Roche. Wyeth 3. Wyeth	1. Member of advisory board 2. Ad hoc advice 3. Research Grant Holder
Prof. Ian Cooke	1. Denfleet International (pharmaceutical company) 2. M L Laboratories	1. Consultant 2. Consultant on adhesion reduction strategies at operation
Dr Geoff Craig	British Dental Association	Member
Prof. Len Doyal		
Mrs Jean Gaffin OBE	1. Brent Primary Care Trust	1. Chair
Dr Noel Gill	PHLS	Expects to be in receipt of funding to assist in the management of CJD incidents.
Mr Luke Gormally		

Dr Pat Hewitt	None	
Prof. Peter Hutton	1. Birmingham University 2. Anaesthetists Academic Foundation 3. Academy of Medical Royal Colleges	1. Professor of Anaesthesia 2. Trustee 3. Chair
Prof. James Ironside	1. Baxter Healthcare USA	1. Research investigator on a Baxter funded project on the transmission of CJD (principle investigator Dr Paul brown USA)
	2. Department of Health	2. Research grant holder: Surveillance of CJD (neuropathology); DoH 1216469 – National retrospective review of CJD and respective disorders; DoH 1216982 – Immunocytochemical testing for disease-associated prion protein in lymphoid tissues; Advisor:- Decontamination of surgical instruments; Assessment of risk of exposure to vCJD: infectivity in blood and blood products.
	3. Medical Research Council	3. Grant Holder:- G9708080 – Edinburgh HIV brain and tissue resource; G9627376 – Phenotypic variation in CJD, a clinical pathological and molecular study
	4. BBSRC	4. Grant Holder:- 15/BS204814 – Neuronal pathology in CJD: an

	5. European Union 6. Committee on Safety of Medicines 7. World Health Organisation 8. UK Xenotransplantation Interim Regulatory Body	immunocytochemical study with quantitative and microscopic analysis; 20L/BS410537 – The relationship between neuron damage and clinical disease: relating murine and ovine scrapie to BSE Advisor: BSEP 5. Grant Holder:- ECBI04-98-6046 – Diagnosis of TSE using PrP^{sc}/PrP^{c}; EC CT98-6015 – European centralised facility for human transmissible spongiform encephalopathies (prion disease); EC PL97-6003 – Transgenic mice expressing human prion protein. Use for characterisation of human encephalopathies and sensitivity for detection of infectivity; EU CT98-6048 – Quantitative analysis of MR scans in CJD (QAMRIC) Advisor 6. Advisor 7. Advisor 8. Advisor
Prof. Don Jeffries	1. Glaxo Smith Kline Stevenage 2. Head of Department of Microbiology and Virology St Bartholomews, Royal London School of Medicine & Dentistry	Non personal, non specific honorarium to department to provide out of hours HIV consultant services

Ms Diana Kloss	1. Hon. Senior Lecturer, School of Law 2. Barrister, 28 St John Street Manchester	Retiring from the University on 31.07.02 but will still be a barrister in private practice, a part-time Chairman of Employment Tribunals, and an honorary Senior Lecturer in the University
Prof. John Lumley	None	
Ms Susan Macqueen	1. Infection Control Nurses Association	1. Past Chair
Mr Henry Marsh	1. Society of British Neurological Surgeons	1. Member
Prof. John O'Neill	1. Lancaster University	
Dr Mike Painter	1. Consultant Public Health Physician, Greater Manchester Health Protection Unit	
Dr Geoff Ridgway	1. UCLH NHS Trust (includes Eastman Dental & NHNN) 2. Royal College of Pathologists 3. Infection Control Services Ltd 4. Abbott Diagnostic Laboratories 5. Lykos, Becton Dickinson, Biev-Merieus-Abbott 6. Pharmaceutical and Device Manufactury Industry	1. Consultant Microbiologist Infection Control Doctor 2. Council Member 3. Director. Infection control service provider to private sector 4. Paid consultancy, renewable annually 5. Hospitality and travel grants in last year 6. Consultant
Dr Roland Salmon	1. Public Health Laboratory Service, Wales	1. Consultant Epidemiologist
Prof. Graham Smith	1. European Academy of Anaesthesiology 2. British Journal of Anaesthesia 3. Royal College of Anaesthetists	1. senator 2. Chairman 3. Member of Counsel
Prof. Dame Lesley Southgate	1. General Medical Council	1. Leader assessments for poorly performing doctors (throughout the

	2. University College London 3. GMC Revalidation Technical Group 4. Royal College of General Practitioners 5. Academy of Medical Royal Colleges	profession) 2. Professor 3. Member 4. President 5. Vice Chair
Dr David Taylor	1. Waste Reduction Europe 2. Johnson & Johnson 3. Abbott Laboratories 4. Scottish Centre for Infection and Environmental Health 5. Joint Advisory Committee on Dangerous Pathogens/Spongiform Encephalopathy Advisory Committee 6. USA National Academy of Sciences Institute of Medicine Committee on Transmissible Spongiform Encephalopathies	1. Scientific Advisor 2. Scientific Advisor 3. Paid Lecturer 4. Inspector 5. Member 6. Member
Mr Andrew Tullo	1. Royal College of Ophthalmologists	1. Member
Ms Gillian Turner	1. CJD Support Network	1. Co-ordinator
Dr Hester Ward	1. National CJD Surveillance Unit 2. Scottish Centre for Infection & Environmental Health	
Ms Kate Woodhead	1. International Federation of Perioperative Nurses	1. Vice President
Dr Tim Wyatt	1. Consultant Microbiologist, Belfast	

APPENDIX 5 Meetings of CJD Incidents Panel November 2001-November 2002

Date	Meeting title	Timing	Attendees
30/11/2001	Blood/ Tissues	½ day	Secretariat & Organ Donation body representative
12/12/2001	Consultation Report Discussion	½ day	Secretariat & Shamrock Marketing Rep.
14/12/2001	PI 69	½ day	Panel Sub-group
09/01/2002	Open meeting planning	½ day	Secretariat and conference organisers
11/01/2002	Draft consultation report discussion	½ day	Secretariat & Shamrock Marketing Rep.
25/01/2002	Progress meeting with Chair	½ day	Secretariat and Chair of Panel
07/02/2002	Consultation report discussion	½ day	Secretariat & Shamrock Marketing Rep.
14/02/2002	Database issues	½ day	Secretariat and CDSC rep.
15/03/2002	Open meeting planning	½ day	Secretariat and conference organisers
18/03/2002	Communication strategy planning	½ day	Secretariat and CDSC rep.
10/04/02	Open meeting briefing	½ day	Chairman and Secretariat
11/04/2002	Open meeting facilitator briefing	½ day	Secretariat, Chair & Vice-Chair of Panel, conference organisers and Michael Buerk
12/04/02	Closed meeting briefing	½ day	Chairman and Secretariat
16/04/2002	Briefing for panel open meeting	½ day	Secretariat and members responding to questions at open meeting
17/04/2002	**Full Panel meeting**	**½ day**	**Members and observers and Secretariat**
17/04/2002	Open Meeting to discuss consultation document	½ day	Members, Secretariat and the public
07/05/02	Chairman's meeting	½ day	Chairman and Secretariat
08/05/2002	Communications strategy planning	½ day	Secretariat and CDSC reps.
14/05/2002	Discussion BMA of concerns about framework document	½ day	Panel sub-group
17/05/2002	PI 117	½ d0ay	Panel sub-group
29/05/2002	BMA concerns about framework document	½ day	Secretariat, Panel sub group and BMA reps.

20/06/2002	**Full panel meeting**	**½ day**	**Panel members, observers and Secretariat**
26/06/2002	Future support for the Panel	½ day	Chairman, Secretariat, Deputy Chief Medical Officer

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Management of possible exposure to CJD through medical procedures

CJD INCIDENTS PANEL

Management of possible exposure to CJD through medical procedures

A consultation paper

October 2001

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Foreword

This document sets out proposals for managing incidents involving possible exposure to CJD in healthcare settings. Incidents arise when patients who are diagnosed or suspected of having CJD are found to have undergone a medical procedure at some time in the past. Other patients could be put at risk if CJD is transmitted through contaminated instruments and/or devices, blood or other tissues or organs donated by patients with CJD.

The CJD Incidents Panel is the expert committee set up by the Department of Health to advise Health Authorities and Trusts on how to manage these incidents. This document explains the basis on which the panel provides advice.

The risk of transmitting CJD through medical interventions is not fully understood, and this document has been prepared in the face of great scientific uncertainty. While there are many areas of doubt, this guidance has been able to draw on the work of the Spongiform Encephalopathy Advisory Committee (SEAC), the government's expert scientific committee on CJD and BSE.

The guidance particularly draws on two reports: 'Risk Assessment for Transmission of variant CJD via Surgical Instruments: A modelling approach and numerical scenarios (referred to in this guidance as the surgical risk assessment), and 'Assessment of the risk of exposure to variant CJD infectivity in blood and blood products' (referred to in this guidance as the blood risk assessment). The guidance also builds on the conclusions of an expert Peer Review Group that was set up by SEAC to assess the available data in this area. The risk assessment for blood and plasma derivatives requires further work and the framework document provides provisional guidance, based on the assessment currently available.

This is a working document and will be updated as new scientific evidence becomes available.
It currently covers incidents involving surgery and blood donations. Future versions will also address tissue and organ donations and transplantation, as well as dental procedures carried out on patients who subsequently develop CJD.

This document sets out the reasoning behind the Incidents Panel's advice, and is intended to support health care professionals and trust managers involved in incidents.

The document is also being made available to others in the medical and allied professions and to anyone else with an interest. It is being published on the Department of Health's website at:
http://www.doh.gov.uk/cjd/consultation

Executive summary

It is possible that variant and sporadic CJD may be transmitted on surgical instruments used on patients incubating the disease, or in blood, other tissues or organs donated by individuals incubating the disease. These risks are unknown, but current procedures for decontaminating surgical instruments between uses cannot be guaranteed to eliminate the abnormal prion proteins that are thought to be responsible for the transmission of CJD. In addition, while there is evidence that sporadic CJD is not transmitted in blood, less is known about variant CJD. Therefore transmission of variant CJD in blood cannot be ruled out.

The Department of Health has set up an expert advisory group to advise health authorities and trusts on managing incidents in which an invasive medical procedure has been carried out on someone who later develops CJD.

The panel includes bioethicists, lay members, and relevant experts, under the chair of a moral theologian. This document sets out a proposed framework for the Panel's advice, and will also inform health professionals and managers involved in these incidents.

Public health actions are needed as contaminated surgical instruments may transmit CJD to other patients. Public health actions are also needed in case blood transmits variant CJD.

There is a great deal of scientific uncertainty about the infectivity of different tissues (including blood) in people incubating CJD, and about the effects of decontaminating surgical instruments and of processing blood. This document sets out what is known about these factors, and shows how the Panel assesses the risk for different medical procedures.

The document also advises on identifying, investigating and managing these incidents. The Panel proposes four main courses of action:

1 Removing the instruments/blood products from use

This protects public health while the risks are being assessed. The Panel may advise that instruments are destroyed or that they are unlikely to pose a risk to the public and may be returned to use. The Panel will also advise on the removal from use of blood or plasma products donated by people who later develop CJD.

2 Setting up a confidential database of all possibly exposed people

The database would be used for the long-term follow up of individuals who could have been exposed to CJD through medical procedures. This database would be used to find out whether any exposed individuals go on to develop CJD themselves, so increasing our knowledge of these risks.

It is proposed that most people would not be informed about their possible exposure. This is because the average incubation period for CJD transmitted between people is unknown but could be well over 10 years; there is currently no reliable diagnostic test for people incubating the disease; there is no cure for this fatal disease; and the risks of transmitting CJD through medical procedures are very uncertain. Moreover, CJD is not thought to spread between people through normal social contact. Therefore, learning about one's exposure would be of doubtful benefit to individuals and could inflict psychological harm.

There is a strong argument that people should be able to choose whether or not they are told about their possible exposure. Therefore it is proposed that possibly exposed people are not asked for their informed consent before being recorded on this register. This is because such action would remove the choice of not being told about their exposure. Instead it is proposed that individuals who wish to know if they are on the database, and the details and significance of their exposure, should be able, after appropriate counselling, to obtain the information through their doctor.

3 Informing some individuals about their exposure to CJD

The exception to this would be a small sub group of possibly exposed people who the Panel considers to be at sufficient risk to warrant public health action. It is proposed that these people are contacted and informed about their exposure so that they can be advised not to donate blood or organs, and to contact their doctor if they required surgery in the future.

4 Providing publicity

The Panel proposes that publicity is provided to alert the public to the existence of the database and that information is provided on how someone could find out whether they are on the database, and how they can have their details removed if so desired.

Section 1: Introduction

Background

Creutzfeldt-Jakob disease

1.1 Creutzfeldt-Jakob disease (CJD) is a rare and fatal neurological condition that affects the nervous system. It is one of a group of transmissible disease known as the prion diseases or transmissible spongiform encephalopthies (TSEs). All types of CJD are associated with a conformational change in a protein called the 'prion protein'. The abnormal form of this protein accumulates in the brain in these disorders and results in the death of nerve cells.

1.2 The commonest form of CJD is sporadic CJD, which affects approximately one per million of the population per annum across the world, and accounts for around 85% of all cases of CJD. Around 60 cases of sporadic CJD are reported annually in the UK. The underlying cause of sporadic CJD is not known. Around 10% of cases occur as familial diseases (Familial CJD, Gerstmann-Sträussler-Scheinker syndrome and Fatal Familial Insomnia). These disorders are associated with mutations in the prion protein gene and are inherited as autosomal dominant conditions. Rarer forms of TSEs include acquired diseases such as Kuru (confined to the Fore tribe in Papua New Guinea), and iatrogenic CJD transmitted between people by medical and surgical procedures including injections with human pituitary hormones, dura mater (membrane covering the brain) grafts, and very rarely by neurosurgical instruments.

1.3 Variant CJD (variant CJD) is a novel form of human TSE which was first recognised in 1996. This new disease is associated with the same transmissible agent that is responsible for Bovine Spongiform Encephalopathy (BSE). Experimental studies have shown that the BSE agent is not related to sporadic CJD. There have been over 100 confirmed or probable cases of variant CJD in the UK[a]. Variant CJD is thought to have resulted from the consumption of contaminated bovine food products. Most of the population of the UK has probably been exposed to BSE, and we do not know how many people have been infected but currently show no signs of neurological disease. Estimates range from a few hundred to many thousands. Variant CHD also differs from other human TSEs in that the transmissible agent accumulates outside the central nervous system in the lymphoid tissues throughout the body and in parts of the peripheral nervous system (see section 2).

Transmission of CJD

1.4 While there is no evidence that any type of CJD can spread between people through normal social contact, sporadic CJD has been transmitted between patients undergoing certain medical treatments. Transmission has followed neurosurgical procedures, corneal graft operations and treatment with hormones prepared from human pituitary glands. One of the reasons that transmission may occur is that prion proteins are resistant to normal methods of decontaminating surgical instruments.

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[a] On 3rd August 2001, 106 definite and probable cases of variant CJD had been reported to the CJD Surveillance Unit

1.5 Variant CJD has not yet been shown to be transmitted through surgical operations, or blood or tissue donations. However, it is a new disease, and there is no practical screening test to detect it during its (probably) long incubation period. This means that it may be too early to detect any cases that may have been transmitted between individuals.

Action to prevent transmission of CJD through healthcare

1.6 Guidance has been issued on what action should be taken to prevent CJD being transmitted from patients who have symptoms of CJD or who have a specific risk of developing CJD **(Annex 1)**. Actions include destroying surgical instruments used on these patients[3] and not donating their blood, tissues or organs to other patients[4].

1.7 However, it is more difficult to prevent transmission of CJD from patients who are incubating the disease. This is relevant when patients diagnosed or suspected of having CJD are found to have undergone surgical procedures or donated blood, tissues or organs in the past.

1.8 For procedures performed some years ago, most of the risk from instruments contaminated with prion agents is likely to have already occurred. However, as prion agents resist standard decontamination procedures, it is possible that such instruments could continue to pose a risk to future patients.

1.9 This situation is difficult to manage as it may not be possible to identify which instruments were used in a particular operation carried out some time ago. To remove all possibly remaining risk one would need to destroy any instrument that might have been used on a patient with CJD. In practice this could leave surgical units unable to function.

1.10 Some people with CJD may have donated blood, tissues or organs before they developed symptoms. The long incubation period of CJD makes it likely that such donated tissues will have been used by the time the donors are diagnosed with CJD.

1.11 Action has been taken to reduce the risk of transmitting variant CJD through plasma derivatives such as clotting factors and immunoglobulins. Since 1998 the plasma used to make these products has been imported from countries with little or no BSE. Donors in these countries are highly unlikely to be incubating variant CJD.

1.12 Much remains to be discovered about the infectivity of different tissues and the effect of decontamination processes on prion proteins. As the risk of transmitting CJD in healthcare settings is unknown, a precautionary approach to the management of the possible risk is advisable. However, the unknown risk of acquiring CJD from medical procedures needs to be considered alongside the background risk to the UK population following exposure to BSE. The known risks and benefits inherent to surgery and other medical procedures must also be considered.

1.13 There are ethical and practical issues around informing people that they might have been put at risk. Some of these people may have a relatively high chance of being infected with CJD. They will need to be informed so that they do not themselves transmit the infection to other patients. Other people will have a smaller risk of acquiring the disease. For this group, information about possible exposure risks should be made available to those who want it. However, this information potentially brings with it a great burden, as CJD is a fatal disease for which there is as yet no diagnostic test and no cure.

Aims

1.14 This document provides a framework for managing incidents which arise when individuals have undergone medical procedures or have donated blood, tissues or organs and are subsequently diagnosed or suspected of having CJD. This framework has four main aims:

- To protect patients from the risk of acquiring CJD in healthcare settings.
- To ensure that those who might have been exposed are informed in a manner appropriate to their level of risk.
- To ensure that those who might have been exposed to lower levels of risk, while not being actively informed, are able to find out about their exposure if they so wish.
- To increase our knowledge about the risk of transmitting CJD in healthcare settings, to be better able to manage any risk.
- To ensure that the public is informed about possible risks of acquiring CJD through healthcare.

Purpose of document

1.15 The CJD Incidents Panel is an expert group set up by the Department of Health on behalf of all UK Health Authorities to advise Health Authorities (Health Boards in Scotland) and Trusts on how to manage possible exposures to CJD in healthcare settings. The Panel advises on incidents throughout the UK.

1.16 All incidents should be referred to the CJD Incidents Panel at the start of any investigation.

1.17 This document sets out the basis for decision making by the CJD Incidents Panel, and should be used by public health doctors, infection control teams, clinicians, trust managers and other professionals responding to local incidents.

1.18 This framework sets out what is known about the risk of transmitting CJD through invasive medical procedures including blood donation. It then describes how incidents should be identified and investigated, and the public health actions to be taken. The final section describes how public communication should be carried out.

1.19 Current scientific uncertainties mean that this framework will evolve, being revised as scientific research proceeds.

1.20 This guidance should be seen in the context of other policy and advice on preventing the spread of CJD in healthcare **(Annex 1)**.

Principles

1.21 Incidents should be managed according to the following principles:

- To protect patients from the risk of acquiring CJD in healthcare settings.
- To provide consistently high quality advice and information to people who may have been put at risk.
- To provide information to people who may have been put at risk while respecting where possible the wishes of those who do not want to be informed.
- To be open about the risk of acquiring CJD in healthcare settings and the scientific uncertainties surrounding this risk.
- To increase our knowledge about the risk of spreading CJD through medical procedures.
- To protect the confidentiality of infected patients and those at risk of acquiring CJD.
- To ensure that actions taken to protect the public health do not prejudice individual patient care.

Section 2: Supporting Evidence

Introduction

2.1 This section describes what is currently known about the risk of transmitting variant Creutzfeldt-Jakob Disease (CJD) or sporadic CJD through medical interventions. While some of our understanding is based on direct evidence on variant CJD or sporadic CJD in humans, more is known about how other Transmissible Spongiform Encephalopathies (TSEs) behave in animal models.

2.2 Little work has been carried out into tissue infectivity in familial or iatrogenic CJD. This guidance assumes that infectivity in these diseases resembles that found in sporadic CJD. Similarly, in the absence of any data to the contrary, other human TSEs are assumed to have the same infectivity pattern as sporadic CJD.

2.3 Broadly, four inter-relating factors determine whether the use of a surgical instrument is likely to transmit CJD infection between patients. These are:

- The infectivity of the tissues in the patient with CJD that come into contact with instruments.
- The amount of infectivity remaining on the instruments following decontamination.
- Which tissues in subsequent patients come into contact with the instruments.
- The susceptibility of subsequently exposed patients.

2.4 In a similar way, the likelihood of transmitting CJD through blood or tissue donation depends on the infectivity in the donated blood and other tissues; the amount of infectivity remaining after processing, the amount of blood or tissue that is transferred to the recipient patients; and the susceptibility of recipient patients.

2.5 A key element affecting the transmission of an infection is the relationship between the dose received and the 'response' to it – i.e. the chance of becoming infected. This guidance is based on a linear dose-response relationship, i.e. the chance of infection is proportional to the dosage received, with no lower threshold. This assumption has been endorsed by SEAC as a provisional working model and has been used for the basis of risk calculations.

Infectivity of tissues in variant CJD

2.6 There is a growing body of experimental evidence on which tissues contain PrP^{Sc} and which may transmit CJD. There is also epidemiological evidence on the transmission of CJD through medical procedures involving different tissues.

2.7 Most of the experimental research has been carried out using animal models and TSEs other than CJD. Only a small number of studies have examined the behaviour of CJD in humans. Because of this, the available evidence has been categorised according to its likely relevance to transmission of CJD in healthcare. Studies considered to be most relevant are those that have demonstrated infectivity in the tissues of patients with CJD. Studies considered to be least relevant include those that have detected infectivity in tissues of animals infected with TSEs such as scrapie (Table 1). This classification does not reflect the quality of the studies considered.

Table 1 Relevance of experimental evidence

Experimental evidence	Relevance of evidence
CJD in human tissue: infectivity demonstrated	A
CJD in humans: epidemiological evidence	B
CJD in human tissue, PrP^{Sc} detected	C
TSE in animal model, infectivity demonstrated	D

Infectivity in the brain and spinal cord

2.8 Brain tissue of patients who have died of variant CJD has the highest level of infectivity of all the tissues studied[5]. **A**

2.9 The brain and spinal cord tissue have also been found to have the highest levels of infectivity in studies conducted on scrapie-infected mice,[6]. The dura mater of scrapie-infected hamsters[7] has also been shown to transmit infection. **D**

2.10 Experiments performed on scrapie-infected mice indicate that abnormal prion protein in the brain and spinal cord appears later in the incubation period than in lymphoreticular tissue[8]. **D**

Infectivity in the eye

2.11 Recent research has detected PrP^{Sc} in the optic nerve and retina of a single patient with variant CJD . The amount of PrP^{Sc} in these tissues was equivalent to 2.5% and 25% respectively of the levels found in the brain. PrP^{Sc} was not detected in the sclera, vitreous humour, lens, aqueous humour, iris or cornea. The limitations of the detection methods used in this study mean that if PrP^{Sc} was present in these tissues, it was at levels less than 1/400 of that found in the brain. It is not known how levels of PrP^{Sc} relate to tissue infectivity. **C**

2.12 Studies on scrapie-infected hamsters indicate that infectivity levels in the optic nerve and retina are comparable with levels in the brain[10]. Lower levels of infectivity are present in the cornea, pigment epithelium/choroid and lens. This animal model experiment also suggested that infectivity is present in the brain and eye before the signs of disease. **D**

2.13 Experiments on hamsters infected with transmissible mink encephalopathy also indicate that the cornea is less infective than brain tissues[11]. This study did not demonstrate infectivity in the aqueous humour. **D**

2.14 PrP^{Sc} has been detected in eye tissues in experimental scrapie at a similar point in the incubation period as it is found in the brain[12]. **D**

Infectivity in the lymphoreticular system (LRS)

2.15 Recent research has found that the spleen and tonsil have similar levels of infectivity in variant CJD, and that these levels are 100 to 1,000 times lower than infectivity levels in the brain[5]. **A**

2.16 Other research has indicated that levels of PrP^{Sc} are higher in the tonsils than in other parts of the LRS[9]. **C** The relationship between the amount of PrP^{Sc} in tissues and infectivity is not clear.

2.17 The LRS is involved in the incubation period of variant CJD infection. PrP^{Sc} has been detected in the appendix of a patient eight months before symptoms of variant CJD developed[13]. **C**

2.18 The LRS continues to be involved during clinical disease, and PrP^{Sc} has been detected in the tonsil, spleen and lymph nodes of people who have died of variant CJD and in tonsilar biopsies of patients with symptomatic disease[14] . **C**

2.19 Infectivity has been detected in the LRS of scrapie-infected mice and sheep early in the incubation period[8 15]. Infectivity levels in the LRS of scrapie-infected mice have been found to be lower than in brain and spinal cord tissue.[6] **D**

Infectivity in other tissues

2.20 Studies on peripheral nerve tissue from four patients with variant CJD did not detect PrP^{Sc}. PrP^{Sc} has been detected in dorsal root ganglia and trigeminal ganglia in variant CJD[16]. **C**

2.21 Research on other peripheral tissues has detected low levels of PrP^{Sc} in the rectum, adrenal gland and thymus of a single patient with variant CJD. Levels of PrP^{Sc} in these tissues were about 1/50,000 of that found in brain tissue[9]. **C**

2.22 Infectivity has been demonstrated in the dental tissue of scrapie-infected hamsters that were in the clinical stage of the disease[17]. This experiment indicated that infectivity levels in the gingival and pulp tissues were lower than in the trigeminal ganglia. **D**

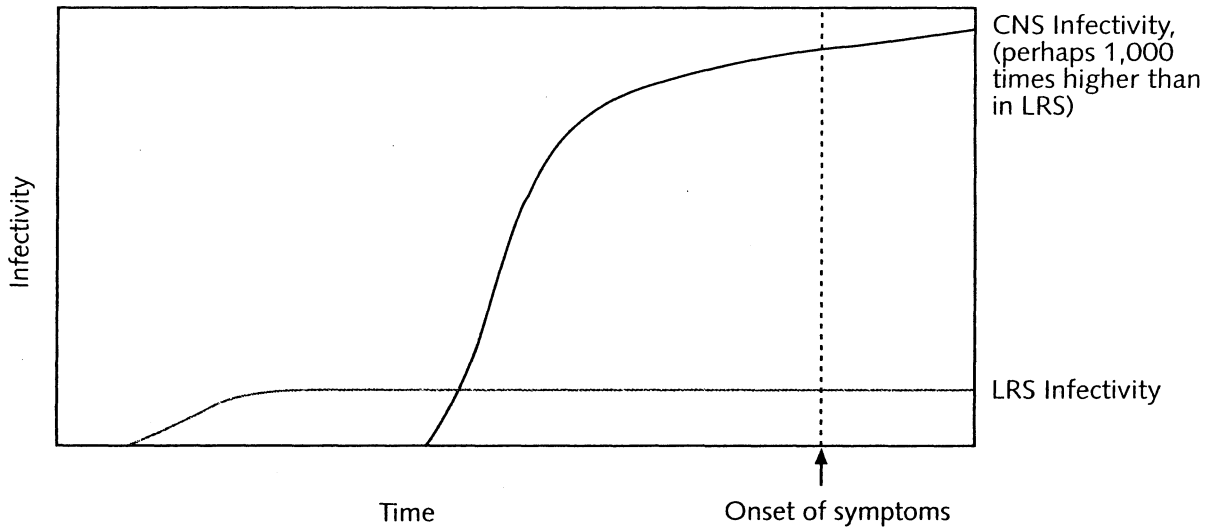
2.23 Other studies on scrapie-infected mice indicate that gingival tissues are infective, although experimental transmission was only achieved with difficulty.[18 19] **D**

Disease progression

2.24 The incubation period for variant CJD is not known, but the median incubation period could be between 10 and 30 years. For practical purposes, this is taken to be any time since BSE could have started in 1980. Extrapolating from animal models, the distribution of PrP^{Sc} and infectivity in variant CJD is expected to change as the infection progresses.

2.25 The expected time course for the changes in infectivity in different tissues in variant CJD is shown schematically in Figure 1.

Figure 1 Probable pattern of tissue infectivity in variant CJD, based on scrapie models



Route of transmission

2.26 Disease transmission depends not only how much infectivity is present in the tissue, but also on where in the recipient the tissue is deposited. Animal experiments indicate that the most efficient transmission route is directly into the brain (intracerebral inoculation)[20 21 22]. **D**

2.27 This guidance follows the assumptions made in the surgical risk assessment[1], that transmission of variant CJD via material deposited into brain, spinal cord or posterior eye is at least ten times more efficient than if similar material is deposited into any other site. The same assumption is made for sporadic CJD.

Conclusions on tissue infectivity in variant CJD

2.28 The infectivity levels in different tissues in variant CJD are uncertain. However, assumptions may be based on the limited amount of evidence that is available. This guidance builds on the infectivity assumptions used in the surgical risk assessment[1] endorsed by SEAC. These conclusions are described in Table 2. **[Dental tissues will be added at a later date].**

Table 2 Infectivity estimates in variant CJD

CNS

Infectivity within the CNS is low in the early incubation stage, but increases as disease develops[b]. Infectivity levels of 10^8 i/c ID_{50}/g may occur in the last 40% of the incubation period and increase to 10^9 i/c ID_{50}/g, or even 10^{10} i/c ID_{50}/g during clinical disease.

Eye

The retina and optic nerve are thought to have infectivity levels that could be as great as that found in brain tissue. Other parts of the eye (cornea, lens, conjunctiva) are thought to contain 10 to 10^2 times less infectivity than brain tissue.

Infectivity in the eye is believed to increase as disease develops, with the levels cited appearing in the last 40% of the incubation period. A further 10-fold increase may also occur in the final year before the onset of symptoms.

Lymphoreticular System (LRS)

From early in the incubation period until death, infectivity levels of 10^6 – 10^7 i/c ID_{50}/g may be widely dispersed in the LRS.

Other Tissues

Other tissues may have some infectivity, but at much lower levels than CNS, eye or LRS tissues

2.29 These infectivity estimates have been combined with possible transmission routes to give infectivity estimates for exposed tissues in subsequent patients. These estimates in Table 3 assume that instruments come into contact with similar tissues in the CJD patient and subsequent patients.

Table 3 Potential infectivity in variant CJD, by source tissue and site of exposure

Source tissues and tissues exposed during surgery	Disease stage	Infectivity (ID_{50}/g)
CNS to CNS (or retina or optic nerve)	First 60% of incubation period	0 – 10^4
	Last 40% of incubation period and during clinical disease	10^8 (this could increase to 10^9 in the final year and to 10^{10} after the onset of symptoms)
Other parts of eye to other parts of eye	First 60% of incubation period	0 – 10^4
	Last 40% of incubation period and during clinical disease	10^5 – 10^6
LRS to LRS	All of the incubation period and during clinical disease	10^5 – 10^6
Remaining tissues, including blood	All of the incubation period and during clinical disease	0 – 10^4

[b] Infectivity is expressed as an ID_{50}. This is the dose that is expected to cause disease in 50% of the recipients to whom it is administered. A pre-script, indicates the route of administration. Thus for a tissue that contains 1 i/c ID_{50}/g, one gram of tissue contains a dose which, when given by intracerebral inoculation, is expected to infect 50% of recipients.

Infectivity of tissues in sporadic CJD

Infectivity in the brain, spinal cord and eye

2.30 PrP^{Sc} has been detected in the brain and spinal cord and eye (personal communication, Professor James Ironside) of patients with sporadic CJD. High levels of infectivity have also been found in the brain and eye tissue of patients who have died of sporadic CJD[24]. **A, C**

2.31 There have been 267 reports of transmission of sporadic CJD by medical procedures throughout the world[25]. These have followed treatment with growth hormone, dura mater grafts, neurosurgery, treatment with gonadotropin, corneal transplants and stereotactic EEG. These data are summarised in Table 4. **B**

Table 4 Global cases of iatrogenic transmission of CJD (up to July 2000)[25]

Mode of infection	Number of patients infected
Tissues/Organs	
Growth Hormone	139
Dura mater graft	114*
Gonadotropin	4
Surgery/invasive procedures	
Neurosurgery	5†
Corneal transplant	3#
Stereotactic EEG	2

*In two cases, dura was used to embolise vessels of non-CNS tissues, rather than as intracranial grafts.
†Contaminated neurosurgical instruments
#One definite, one probable and one possible case.

2.32 The level of PrP^{Sc} in the brain, spinal cord, retina and optic nerve in sporadic CJD is thought to be similar to levels in variant CJD.

2.33 Experiments in which corneas from humans and guinea pigs infected with CJD have been transplanted into animals indicate that corneas can transmit CJD[26 27]. **A, D**

2.34 Transmission of sporadic CJD has been reported after corneal graft operations[28 29]. It is not known whether other parts of the anterior eye are infective. **B**

Infectivity in other tissues

2.35 Most evidence indicates that in sporadic CJD tissues outside the nervous system, including the LRS, do not contain significant levels of infectivity[14] **C.**

2.36 However, one report suggested that low levels of infectivity are present in the kidney, liver and lung tissues of patients with sporadic CJD[24]. This report did not demonstrate infectivity in several other peripheral tissues including peripheral nerve, intestine and blood. **A**

2.37 Interpretation of the positive findings is uncertain, and further work is needed to confirm or refute these observations. This guidance assumes that if any tissues outside the nervous system are infective in sporadic CJD, then it is only with low levels of infectivity.

2.38 A recent experiment on dental tissues from patients with sporadic CJD did not detect PrP^{Sc}, but further work is needed in this area. C

2.39 The incubation period for sporadic CJD is not known. For practical purposes, this guidance assumes that the incubation period is 20 years. This assumption is used to estimate the duration of infectivity of tissues such as the brain and eye.

Conclusions on tissue infectivity

2.40 The likely infectivity of tissues from patients with sporadic and variant CJD are summarised in Table 5. These relative infectivity levels are based on current knowledge and advice from SEAC. Dental tissues will be added at a later date.

Table 5 Tissue infectivity in sporadic and variant CJD

Tissue	Sporadic CJD	Variant CJD
Brain, spinal cord, cranial and spinal ganglia, dura mater	High	High
Optic nerve and retina	High	High
Other eye tissues	Medium	Medium
Appendix	Low	Medium
Tonsil	Low	Medium
Spleen	Low	Medium
Other lymphoreticular tissues	Low	Medium
Blood[1]	Low	Low
Other tissues	Low	Low

High: >=10^7 ID_{50}/g[c]; Medium 10^4-10^7 ID_{50}/g; Low <$10^4ID_{50}/g$

[1] See section on infectivity in blood.

Infectivity transmitted via instruments

2.41 Instruments may be contaminated with prion agents during contact with infective tissue in surgery. There is concern that prion agents can resist normal decontamination processes, and that infectivity may remain on instruments when they are used on other patients.

2.42 Little evidence is available in this area, which is the subject of a research programme. Until further evidence becomes available, this guidance builds on the assumptions made in the surgical risk assessment1 endorsed by SEAC.

2.43 The amount of infective material contaminating an instrument following surgery depends on the type of instrument and the tissues with which it is contaminated. This guidance follows the assumptions used in the surgical risk assessment[1] that an average of 10 mg of material could remain on an instrument. This is derived from an estimate that 5mg may adhere to an instrument with plane surfaces, such as a blade[31]. This is an area of considerable uncertainty, but the amount of material contaminating an instrument directly after surgery is less important than the amount that remains after decontamination.

c 10^7 is a mathematical expression for 10×10×10×10×10×10×10 = 10,000,000

2.44 A *decontamination cycle* for a surgical instrument involves two stages; physical cleaning, typically using a mechanical washer/drier; followed by inactivation of any remaining infectious material, e.g by autoclaving.

Cleaning

2.45 Instruments undergo a large number of decontamination cycles during their working lives. Studies on instruments with flat surfaces indicate that the first cycle of cleaning may reduce the amount of protein on an instrument by 10^3 [32]. However, instruments with serrated edges and hinges, and others, and others with narrow lumens such as flexible endoscopes, are much more difficult to clean. This guidance follows the assumptions made in the Risk Assessment[1] that cleaning is likely to reduce the infectivity remaining on an instrument by a factor of 10^2 to 10^3.

2.46 Subsequent cleaning rounds are likely to be much less effective as any material that has survived the first cleaning cycle may have been baked on during further processing. There is little experimental evidence on how much would remain. This guidance follows the assumptions made in the surgical risk assessment[1] that subsequent cleaning cycles could reduce the amount of infectivity remaining on an instrument by as much as a factor of 10^2.

2.47 This guidance uses the assumption of the ACDP/SEAC Joint Working Group on TSEs, that cross-contamination of instruments during cleaning was unlikely to occur. This was because in a wet environment, and in the presence of detergents, proteins are unlikely to migrate from one surface and stick on another.

Inactivation

2.48 Inactivation is generally carried out by high pressure steam autoclaving of instruments. Different autoclaving processes vary in their effectiveness in inactivating prion agents[33]. The effectiveness may be altered by small differences in temperature[34]. This guidance uses the assumptions made in the Risk Assessment[1], that the first autoclaving cycle would achieve a 10^3 to 10^6-fold reduction in infectivity. C

2.49 Subsequent autoclaving cycles may have less additional effect. This guidance follows the assumptions made in the surgical risk assessment[1] that these could achieve up to 10^3-fold reduction in infectivity.

2.50 It is possible that even following a great many cycles of use and decontamination, some infectivity remains on instruments. This guidance assumes that any infectivity that has resisted removal and remained on instruments, would be firmly attached and unlikely to transfer to subsequent patients during normal surgical procedures. This guidance follows the provisional assumptions made in the surgical risk assessment[1], that infective material must be transferred from an instrument into a subsequent patient for disease transmission to take place.

Combined effect of cleaning and inactivation

2.51 This guidance follows the assumptions made in the surgical risk assessment[1] that the first washing and autoclaving cycles combined would achieve at least a 10^5-fold reduction in infectivity. Subsequent cycles may have much less effect. In ideal conditions decontamination processes are likely to be even more effective but these cautious estimates allow for less than optimal working practices.

2.52 A major research programme into instrument decontamination is underway and the results of these studies may provide some of the basic information that is currently lacking in this area. This guidance will be revised as new evidence becomes available.

2.53 The guidance assumes that infectious and non-infectious material is removed from instruments in similar proportions. There is as yet no data to suggest otherwise.

2.54 The likely effectiveness of instrument decontamination is summarised in Table 6. This summarises the assumptions made in the surgical risk assessment[1] endorsed by SEAC.

Table 6 Effectiveness of instrument decontamination

Variable	Value/range
Initial amount of material on instruments (mean, per instrument)	10 milligrams
Cleaning (washing/disinfecting)	
Reduction in amount of material after first cleaning	10^2 – 10^3 fold reduction
Reduction in amount of material after subsequent cleanings	0 – 10^2 fold reduction
Deactivation (sterilising/autoclaving)	
Reduction in infectivity after first autoclaving	10^3 – 10^6 fold reduction
Reduction in infectivity after subsequent autoclaving	0 – 10^3 fold reduction

Type of instruments used

2.55 Decontamination is affected by an instrument's material and construction – whether it has joints, lumens, serrated jaws, ratchets etc. (**Annex 2** categorises types of instrument by their ease of decontamination).

2.56 In some cases, only parts of instruments may come into contact with infective tissues (for example drill bits or the probe in a stereotactic frame). These may cross-contaminate the rest of the instrument.

2.57 Some instruments cannot be autoclaved. These include flexible endoscopes and other optical equipment. Glutaraldehyde is sometimes used to decontaminate rigid endoscopes. However, this is likely to stabilise any proteins present on the instruments.

2.58 Endoscopes are more difficult to decontaminate effectively than normal stainless steel instruments, and this problem is increased if biopsies are carried out using endoscopes. Endoscopes that come into contact with LRS and other infective tissue may continue to pose a risk to subsequent patients despite going through many cycles of use and decontamination. Certain CNS procedures also use devices that are very difficult to decontaminate – e.g. ventricular endoscopes and these may be considered separately.

Modelling scenarios

2.59 Scenarios modelling the infection risk for subsequent patients following surgery on a 'index' patient with CJD are illustrated in Figures 2–5. These scenarios use different tissue infectivity levels in the 'index' patient and different proportions of contaminating prion protein transferred from the instruments to subsequent patients. In each scenario the risk of transmitting infection drops dramatically for subsequent patients and is close to zero before the 10th reuse of an instrument.

2.60 These scenarios have been prepared by the Economics and Operational Research Division of the Department of Health, and are based on the following assumptions:

- 20 instruments are used per operation.
- Each instrument used is initially contaminated with 10 mg of tissue.
- The first decontamination cycle reduces contamination by a factor of 10^5
- Subsequent decontamination cycles reduce contamination by a factor of 10.
- The instruments contact the same type of tissue in the CJD and subsequent patients.

Figure 2 Scenario modelling probability of infecting subsequent patients. Tissue Infectivity 10^{10} ID_{50}/g (e.g. CNS in patient with symptoms of CJD)

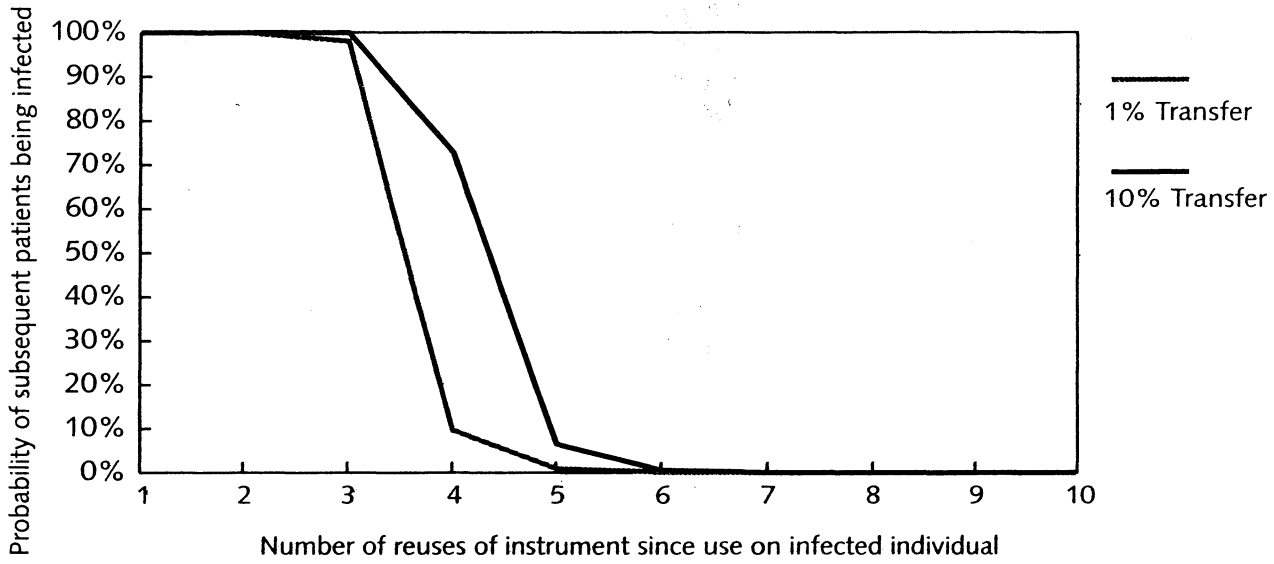


Figure 3 Scenario modelling probability of infecting subsequent patients. Tissue Infectivity 10^8 ID_{50}/g (e.g. CNS in patient in the later stages of incubation period)

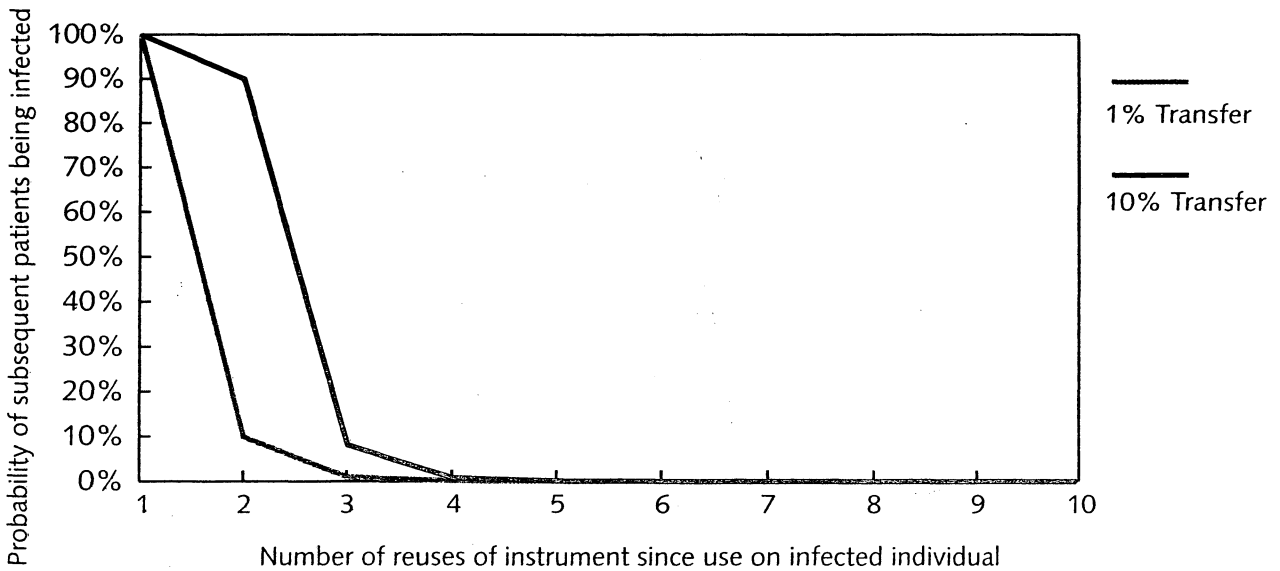


Figure 4 Scenario modelling probability of infecting subsequent patients. Tissue Infectivity 10^6 ID_{50}/g (LRS or anterior eye in patient at any stage of CJD infection, more pessimistic assumption)

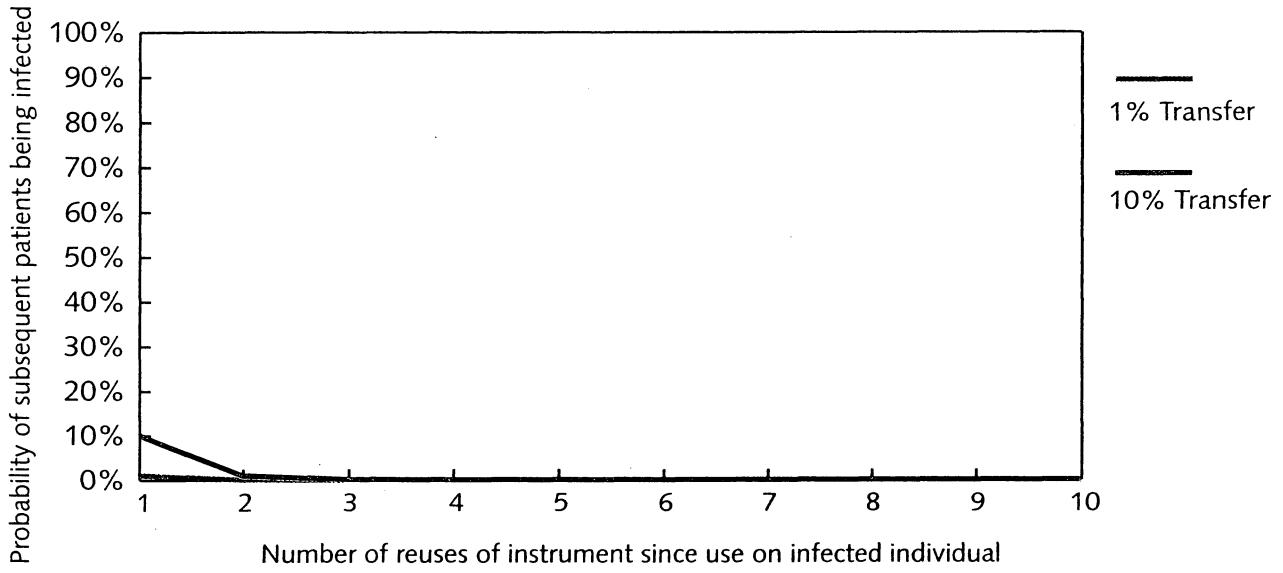
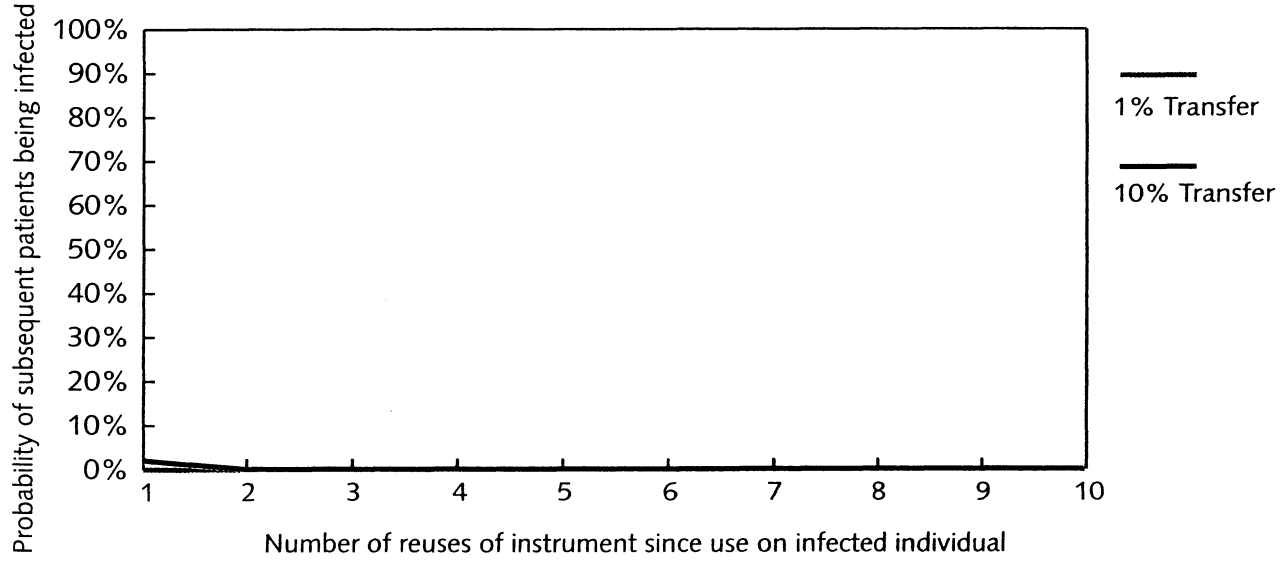


Figure 5 Scenario modelling probability of infecting subsequent patients. Tissue Infectivity 10^5 ID_{50}/g (LRS or anterior eye of patient in any stage of CJD infection, less pessimistic assumption)



Conclusions

2.61 On the basis of the preceding evidence and reasoning, most instruments that have gone through ten cycles of use and decontamination are unlikely to pose a significant risk. However, this is an area of active research, and the CJD Incidents Panel should consider the type of instrument used in each incident as some are particularly difficult to decontaminate.

Infectivity of Blood Components and Plasma derivatives

Definitions

2.62 This section deals with the potential infectivity of blood components and plasma derivatives produced from blood donated from people who go on to develop CJD.

2.63 Blood components are derived from a single blood or plasma donation or in the case of platelets, a small pool usually of about four donations. These are labile products with a short shelf life. Blood components include whole blood, red cell concentrates; platelets (cell fragments involved in blood clotting), granulocytes (a form of white blood cell), fresh frozen plasma, and cryoprecipitate (made by freezing and thawing plasma).

2.64 Plasma derivatives are prepared from human plasma pooled from a large number of donations. These products have a long shelf life and, unlike blood components, are licensed medicinal products. Plasma derivatives include clotting factors, immunoglobulins, albumin, and anti-thrombin.

Background

2.65 This document builds on the information summarised in the blood risk assessment[2], which has been accepted by SEAC. This risk assessment will be reviewed to reflect new research on plasma derivatives and the effects of purification processes. This section will be revised when the new assessment becomes available.

2.66 There is no epidemiological evidence that any form of CJD (familial, sporadic or variant CJD) has ever been transmitted as a result of treatment with blood components or plasma derivatives. Studies of recipients of blood donated by people who go on to develop sporadic CJD, and studies of sporadic CJD prevalence among haemophiliacs, have not demonstrated an increased risk of developing CJD[2 35]. **B**

Variant CJD

2.67 In variant CJD the disease process involves many tissues, including the LRS. There is however, no evidence that variant CJD can be transmitted by blood components or plasma derivatives. However, variant CJD is a new disease with a long incubation period, and it may be too soon for cases transmitted by this route to be detected.

2.68 Evidence on the possible infectivity of blood in variant CJD is limited. One study has investigated whether blood from people with variant CJD can transmit the disease to mice[5]. This study did not detect infectivity in plasma or in buffy coat (a blood fraction rich in white cells and platelets). However, the methods used had a detection limit of about 200 human i/v ID_{50}s per ml, and therefore would not have detected levels of infectivity that could result in transmission of variant CJD in humans. **A**

2.69 Even low infectivity levels could be important because large quantities of blood and plasma derivatives are used to treat individual patients. These quantities greatly exceed the trace amount of protein remaining on surgical instruments after decontamination.

2.70 Another research study failed to detect any PrP^{Sc} in the buffy coat of blood of a patient with variant CJD[9]. The detection limits of the techniques used meant that if any PrP^{Sc} was present, it must have been at a concentration 300,000-fold lower than that found in the patient's brain. **C**

2.71 Research is also being carried out on whether BSE can be transmitted between sheep by whole blood transfusion[36]. BSE has been transmitted to one transfused animal. This study is ongoing, and it is not yet possible to estimate the infectivity levels. **D**

Whole blood

2.72 The infectivity of whole blood is estimated as most likely to be 1 i/v ID_{50} per ml. This estimate is drawn from the blood risk assessment, and is based on infectivity levels reported in the blood of hamsters infected with scrapie, and in mice infected with a familial form of human CJD. The relevance of this model to estimates of infectivity in the blood of variant CJD in humans is uncertain. However, the data from studies of people with variant CJD are consistent with infectivity values ranging from zero to 200 i/v ID_{50}s per ml[5].

2.73 Infectivity in blood is assumed to be constant throughout the incubation period for variant CJD. For practical purposes, the earliest time that patients could start to incubate the disease is taken to be the onset of the BSE epidemic in 1980.

2.74 The route of administration affects the transmission of TSEs in animal models. The intravenous and intramuscular routes used for blood components and plasma derivatives are less efficient than direct inoculation into the brain. This document follows the assumption made in the blood risk assessment[2] report, that the intravenous route is 10 times less efficient than the intra-cerebral route. Recent studies by Brown *et al* suggest a comparable value[37].

Leucodepletion

2.75 The LRS is involved in variant CJD and this raises the possibility that white blood cells could contain infectivity. While this has not been demonstrated, leucodepletion (removal of white blood cells) has been carried out on all UK-sourced blood since 1999 as a precautionary measure. In the absence of convincing evidence, this guidance has not made any assumptions about the effect of leucodepletion on infectivity.

Blood components

2.76 Most modern treatments use blood components rather than whole blood. The literature on infectivity of different components of blood was reviewed as part of the blood risk assessment. This concluded that studies carried out on familial CJD in mice provide the best available model for the distribution of infectivity in variant CJD in human blood[38]. However, this model may not be directly relevant to infectivity in the blood of humans with variant CJD. One recent study has reported experimental transmission of BSE in a sheep model following experimental infection. It may be that data emerging from this model will be more relevant to variant CJD in humans. **D**

2.77 Other studies have examined infectivity in blood that has been 'spiked' with brain material from hamsters infected with scrapie. This model has also been used to investigate the effects of different processing steps on infectivity. However, these experiments may not give a true impression of the distribution of infectivity in blood in people with variant CJD. This guidance and the blood risk assessment have only drawn on data from these experiments when no other information is available.

2.78 Estimates for infectivity used in the blood risk assessment are reproduced in Table 7.

2.79 These results should be interpreted with some caution as the distribution of infectivity within blood in people with variant CJD may well differ from that found in mice infected with a familial human prion disease. Also, the fractionating procedures used in the mice experiments may not be directly comparable with those used for human blood.

Table 7 Possible infectivity levels of blood components in variant CJD

Component	Infectivity per ml (iv ID_{50}/ml)	Infectivity per unit (iv ID_{50}/unit)
whole blood	1	450
plasma	1	200
White cells + platelets	7	100
red cells	0.005-1*	1-200*
cryo-precipitate	8	20

*This depends on the purification processes used

2.80 Preparations of red cells and plasma with varying degrees of purity are transfused into patients. Given the uncertainties over the infectivity values in general, and over how infectivity is distributed between white cells and platelets, this guidance assumes that the infectivity of platelet preparations is the same as the mixed white cell plus platelets fraction.

2.81 The figures in Table 7 are based on very uncertain estimates from the blood risk assessment[2] that are derived from the data from Brown *et al* 1998[38]. However studies using the same model that have been published since the blood risk assessment[37 39] give similar estimates for infectivity.

2.82 Patients usually receive more than one unit in a transfusion, and may be transfused several times. Even so a patient is unlikely to receive more than one unit of a blood component from a particular donor with variant CJD.

Estimates of infectivity in plasma derivatives

2.83 Plasma is estimated to have approximately the same infectivity as whole blood, i.e. 1 ID_{50}/ml (see Table 7). The infectivity in plasma derivatives depends on the size of the pool of donations used to manufacture the derivative, the effect of processing, and the amount administered.

Size of donor pool

2.84 Tens of thousands of donations of plasma may be combined to prepare plasma derivatives, so greatly diluting any single infected donation. For example, if plasma derivatives are derived from a pool of 20,000 donations, then the infectivity in the starting product is estimated to be 0.5×10^{-4} iv ID_{50}/ml.

2.85 Specific immunoglobulins (e.g. anti-D, hepatitis B, tetanus, rabies, Varicella zoster) are produced from much smaller pools of donations. The number of donations used depends on the type of immunoglobulin and the producer, and ranges from less than 50 to 4,000.

2.86 In specific incidents, the size of the pool used should be used to calculate the potential infectivity of plasma derivatives.

Effect of processing

2.87 Plasma derivatives undergo various processing stages including cryoprecipitation, extraction with ethanol, precipitation, filtration, partitioning, virus inactivation and heat treatment.

2.88 Discussions on the effect the different processing steps for various products have been based on the known characteristics of infectivity isolated from brain. Studies on the effects of processing on infectivity have also been carried out on hamster blood 'spiked' with brain material infected with scrapie. However the characteristics of any infectivity that might be present in blood could be quite different from that found in the brain.

Dose

2.89 A 'dose' of a plasma derivative may contain high concentrations of proteins. Some clinical conditions require repeated doses, so that large amounts may be given over a period of time. This is important as patients could receive multiple doses from the same possibly contaminated batch of plasma derivative. This document assumes that the risks from such repeated doses of variant CJD would be additive.

Infectivity

2.90 The risk from plasma derivatives is even more uncertain than from blood components. Further risk assessment work is being carried out on the infectivity of different fractions and the effects of processing. In the meantime, this guidance provides an interim assessment of the risk, based on the blood risk assessment.

2.91 The blood risk assessment based its infectivity calculations on a combination of the low dose and spiking experiments of Brown et al 1998. It assumed that the infectivity (per gram of protein) in the end-product plasma derivatives was the same as in the plasma fraction from which it was derived. The calculations ignore any possible dilution effects arising from the pooling of plasma donations. The infectivity values in Table 8 are derived from the blood risk assessment.

Table 8 Estimates of the infectivity of plasma derivatives in variant CJD

Derivative	Infectivity[a]
Factor 8 (Crude)	24 ID_{50} per standard dose of 2000 iu
Factor 8 (Highly purified)	4 * 10^{-2} ID_{50} per standard dose of 2000 iu
Factor 9	4 * 10^{-1} ID_{50} per standard dose of 1250 iu
Normal Immunoglobulin	660 ID_{50} per 90g intravenous dose
Albumin 20%	2 * 10^{-3} ID_{50} per standard dose of 100ml

a These values ignore any possible dilution effect arising from the pooling of plasma donations.

2.92 The blood risk assessment did not provide estimates of infectivity values for any other plasma derivatives.

Conclusions

2.93 While the pool size and processing details will need to be assessed for each incident, it seems clear that albumin, Factor IX, and high purity Factor VIII are all likely to have low infectivity levels.

2.94 Crude factor VIII and immunoglobulin may, however, be of concern. The management of incidents involving these, and other plasma derivatives is discussed in section 6.

2.95 These risks will be reassessed once a revised estimate of infectivity has been completed.

Sporadic CJD

2.96 There is no epidemiological evidence that sporadic CJD has ever been transmitted as a result of treatment with blood components or plasma derivatives[2]. **B**

2.97 There is a general consensus that blood components and fractionated plasma derivatives prepared from donors who go on to develop sporadic CJD, are unlikely to increase the risk of recipients developing the disease. This guidance has not attempted to further characterise this risk.

Susceptibility of subsequent patients

2.98 All patients with variant CJD for whom genetic information is available have the same genotype (methionine homozygous) at codon 129 position on the PrP gene. This does not mean that other genotypes are not susceptible. Indeed, patients with other genotypes have been infected with CJD following treatment with contaminated growth hormone[40].

Conclusions

2.99 The role of genetic susceptibility in the transmission of CJD between people is unclear. Until the role of genetics is better understood, it is prudent to assume that everyone is equally susceptible to transmission from CJD, although the incubation period may vary.

Summary of infectivity of blood components and surgical instruments

2.100 The risks from blood components and plasma derivatives are unknown. However, should blood be infective, the risk from blood components could be on a par with that from surgical instruments. This is because the quantity of a blood component used to treat patients is much larger than the traces of tissue transferred to patients from contaminated surgical instruments. This means that even relatively low infectivity levels may be of concern. Table 9 compares the possible infectivity transmitted to patients following surgery with that following treatment with blood components (variant CJD only).

Table 9 Comparison of possible infectivity of blood components and surgical instruments

Source tissues and tissues exposed during surgery (all CJD)	Possible infectivity transferred to next patient per procedure[2]
CNS to CNS, or optic nerve/retina to optic nerve/retina (last 40% of incubation period)	20 ID_{50}
Other eye tissues to other eye tissues (last 40% of incubation period) or LRS to LRS for whole duration of infection	0.2 ID_{50}
Blood components (Variant CJD Only) – whole duration of infection	**Possible infectivity per unit**
whole blood, plasma, white cells + platelets, red cells, cryoprecipitate	Possibly zero, but estimates for different components range from 20-450 ID_{50}[1]

1 See Table 7

2 Assuming an infectivity of 10^8 ID_{50}/g for CNS and back of the eye to similar tissues; an infectivity of 10^6 ID_{50}/g for other eye tissues and LRS to similar tissues; 10 mg initial load per instrument; 20 instruments per procedure; 10^5-fold decrease in infectivity by decontamination and a 10% transfer of residual infectivity to the subsequent patient.

Clinical procedures categorisation by risk

2.101 This document categorises clinical procedures according to their likely risk of transmission of prion proteins. In sporadic CJD, only CNS and the eye pose a major risk. These categories are summarised in Table 10. **Annex 3** provides a detailed breakdown by type of operations.

Table 10 Clinical procedures – categorisation by possible risk[a]

High risk procedures
All procedures that involve piercing the dura, or contact with cranial ganglia (including the trigeminal and dorsal root ganglia), or the pineal and pituitary glands.
Procedures involving the optic nerve and retina.
Treatment with blood components. **Variant CJD only**
Medium risk procedures
Other procedures involving the eye, including the conjunctiva, cornea, sclera and iris.
Procedures involving contact with lymphoreticular system (LRS). **Variant CJD only**
Anaesthetic procedures that involve contact with LRS during tonsil surgery (for example laryngeal masks). **Variant CJD only**
In certain instances only, to be assessed for each batch of product, treatment with high doses of specific immunoglobulins, normal immunoglobulin and certain clotting factors. **Variant CJD only**
Low risk procedures
All other invasive procedures including other anaesthetic procedures.
Treatment with albumin, Factor IX, and high purity Factor VIII and certain doses of normal immunoglobulins. **Variant CJD**
Treatment with any blood component or product. **Sporadic CJD**

a Applies to both sporadic and variant CJD unless otherwise stated

Section 3: Public Health Investigation of Incidents

3.1 This section describes the role of the local health teams and the Department of Health's CJD Incidents Panel in investigating incidents that involve invasive medical procedures. The investigation of incidents involving blood donations is covered in Section 5. Advice on the investigation of incidents involving tissue and organ donation will be added at a later date.

3.2 Health Authorities are currently responsible for protecting the population from communicable disease. The public health response to an incident involving possible exposure to CJD through an invasive medical procedure will usually be led by the Consultant in Communicable Disease Control (CCDC).

3.3 In all incidents, the CCDC should contact the Department of Health secretariat to the CJD Incidents Panel.

Identifying possible exposures to CJD in healthcare settings

3.4 The National CJD Surveillance Unit (CJDSU) collects, manages and analyses information on all suspect cases of CJD in the UK. Suspect cases are referred to the CJDSU by clinicians. A neurologist from the unit then visits each case and assigns them to a diagnostic category.

3.5 The clinician caring for the patient should inform the Consultant in Communicable Disease Control (CCDC), or equivalent, about all possible, probable and confirmed cases of sporadic and variant CJD. This reporting system is described in recent guidance prepared by the CJDSU, the Public Health Medicine Environmental Group and the UK Health Departments .

3.6 The CCDC is responsible for co-ordinating the initial response to this information including contacting the Department of Health's CJD Incidents Panel.

3.7 Should other local professionals become aware of a possible incident, they should contact the local CCDC who will liase with the CJDSU and the Incidents Panel.

Initial Information Collection

3.8 The CCDC should gather the initial information on the case so that the Incidents Panel can assess the need for immediate action. The CCDC should use the reporting form in **Annex 4** to collect information on the clinical status of the patient with CJD, and the invasive medical procedures carried out on this patient.

3.9 The CCDC or their equivalents from all parts of the UK should swiftly inform the Department of Health secretariat to the CJD Incidents Panel about incidents. Those from Scotland, Wales and Northern Ireland should also send a copy of the notification to the medical officer in their respective Health Department with responsibility for CJD.

3.10 The contact point for the Incidents Panel is Dr Philippa Edwards at the Department of Health.

Telephone: 020 7972 5324; Fax: 020 7972 5092

E-mail: philippa.edwards@doh.gsi.gov.uk

Initial Appraisal and Control Measures

3.11 The CJD Incidents Panel will rapidly appraise the information on the reporting form, and decide:

either

that there is no significant risk to other patients and no further action is required.

or

that there may be a risk to other patients and that the potentially contaminated instruments should be removed from use (quarantined). This should be carried out following the ACDP/SEAC Guidance[3]. The CJD Incidents Panel will advise on what additional information is required to assess the risk to other patients.

Further information to characterise risk

3.12 Where further investigation is required, the CCDC may set up a local incident management team. Epidemiologists from the PHLS Communicable Disease Surveillance Centre (CDSC) may assist with any risk characterisation exercise, particularly when more than one health authority is involved. This arrangement pertains to Scotland, Wales and Northern Ireland.

3.13 The team should collect detailed information about the surgical instruments used on the patient with CJD and the patients who may have been exposed to each instrument (Table 11). This information should be presented to the Incidents Panel so that the potential risks may be assessed and managed.

Table 11 Further information required to characterise risk

Surgical instruments
Description of instruments including name, make, size, function and any identifying number.
Standards of documentation of use and decontamination of instruments.
Details of subsequent use of the instruments.
Number of times the instruments have been reused.
Details of decontamination procedures.
Date of removal if the instruments have been removed from clinical use.
Information on whether the instruments have remained in the same set.
If use and decontamination of instruments are not documented, information will also be required on:
Number of instruments in use at the time of the index patient's procedure.
Number of procedures for which they are used prior to being discarded.
Number and type of procedures for which these instruments are used in a given time period.
Possibly exposed patients
Number of patients definitely and possibly exposed to the instruments.
Details of how they are identified as being definitely or possibly exposed.
Date, location and type of procedures in which instruments were definitely or possibly used.
Tissues to which the instruments would have been exposed during these procedures.

Risk assessment

3.14 The Incidents Panel will assess the risk of exposure to CJD to subsequent patients by reviewing the data collected by the local incident team. In each case the Panel will consider the clinical condition of the patient, the type of instruments used, the decontamination processes in place and whether the instruments can be traced.

Question Box: Investigation of incidents

We have proposed a system to identify and investigate incidents involving surgical procedures carried out on people who later develop CJD. This would build on existing public health systems, both locally and nationally.
Q1 Do you agree with our proposals for investigating and managing surgical incidents?

Section 4: Public Health Management of Surgical Incidents

4.1 While the risk of transmitting CJD through invasive medical procedures is uncertain, precautionary action should be taken to prevent the possible transmission of infection. It is also important to collect information about possible exposures to CJD so that the risk of transmitting CJD can be better understood. It is important to ensure that actions taken to protect the public health do not prejudice individual patient care.

4.2 The Incidents Panel will advise the local Incident Management Team on the action required to manage incidents involving possible exposure to CJD in healthcare settings. These actions have four main aims:

- To prevent transmission of CJD from potentially contaminated instruments.
- To prevent further transmission of CJD through healthcare from exposed patients who are considered to have a significant risk of having contracted CJD.
- To collect information on people who could have been exposed to further our understanding of the risk of transmitting CJD in healthcare settings.
- To inform the public about a local incident.

4.3 The Incidents Panel will use the algorithm in **Annex 5** to help make decisions on managing possibly exposed patients and instruments. The decision points in the algorithm are not automatic, and multiple factors will need to be considered for each case.

Instruments

4.4 In most circumstances, instruments used on the 'index patient' will already have been re-used many times by the time the patient is diagnosed. It follows that most of the risk associated with these instruments will have already occurred.

4.5 Nevertheless, there are grounds for a strongly precautionary approach toward instruments, withdrawing all those that *might* be implicated as soon as possible. Where it is necessary to destroy instruments, this should be done by incineration where possible, as described in the ACDP/SEAC Guidance[3].

4.6 In general, instruments that have undergone **ten or fewer decontamination cycles** since being used on the index patient with CJD should be incinerated. Some of these instruments are of potential research value and the Panel will advise on this.

4.7 The Panel may advise that particular instruments are incinerated even if they have undergone more than 10 decontamination cycles. This may be because they are difficult to clean, or because they can not be mechanically washed or autoclaved.

4.8 This advice should not be interpreted as meaning that possibly contaminated instruments may be repeatedly decontaminated and then returned to use. This is because current scientific knowledge is insufficient to be sure that such instruments would be safe.

4.9 If instrument tracing systems are inadequate, it may not be possible to identify the instruments used on the index patient with CJD. In these cases, **any** instrument that may have been used on the index patient, and is not known to have undergone at least 10 decontamination cycles might have to be incinerated.

Question Box: The surgical instruments

Q2 Do you agree with our proposal that instruments used on infective tissues of patients who later develop CJD, may continue to be used if they are judged to have undergone a sufficient number of cycles of use and decontamination?

Q3. Do you agree with our proposal that instruments that have not undergone a sufficient number of cycles of use and decontamination, should be permanently removed from use (either destroyed or used for research)?

People with a 'contactable risk' of CJD

4.10 While the risk of transmitting CJD through invasive medical procedures is very uncertain, the modelling set out in figures 2–5 in Section 2 shows that some patients are likely to be at a higher risk than others. The modelling indicates that patients who have undergone procedures with instruments that have only undergone a small number of cycles of use and decontamination since being used on tissues infective for CJD, will be at a greater risk of becoming infected than other exposed patients.

4.11 If these patients do acquire CJD, then they too could pose a risk to others. Therefore these people should be contacted and informed about their possible risk. This is in order to protect public health by advising these individuals not to donate blood, organs or tissues. They should also be advised to inform their carers should they require further surgery. Details of patients in this group should also be recorded on the confidential database (see paragraphs 4.19–4.25). These individuals would not have the option of removing their details from this database

4.12 The CJD Incidents Panel will advise the Incident Management Team on how many people should be included in this 'contactable' group **[Annex 5]**. The size of this group will depend on the infectivity of the source tissues in the 'index' patient with CJD [Table 8].

4.13 If instrument tracing systems are inadequate, it may not be possible to identify these patients with certainty. Decisions on the group to be contacted should then be made by the CJD Incidents Panel on a case-by-case basis.

Table 12 Patients to be included in 'contractable' group

Clinical procedure in index patient[d]	'Contactable' group
High risk procedures	
CNS, retina, optic nerve procedures in patient with symptoms or within one year of developing symptoms of any type of CJD	First 6 patients
CNS, retina, optic nerve procedures in patient who subsequently develop any type of CJD (in last 40% of incubation period*).	First 4 patients
Medium risk procedures	
Other eye tissue procedures in patients who have, or subsequently develop any type of CJD (in last 40% of incubation period*).	First 2 patients
LRS procedures in patients who have, or subsequently develop variant CJD (at any stage in incubation period).	First 2 patients

* In sporadic CJD the mean incubation period is assumed to be 20 years. In variant CJD the incubation period is assumed to start in 1980.

4.14 The CCDC should inform the patients' general practitioners and the UK Blood Service.

4.15 Particularly sensitive arrangements will be needed for informing patients that they are included in this group. This information will be burdensome and of little overall benefit to the individuals themselves. It might additionally result in practical difficulties (e.g. insurance).

4.16 We would hope that the task of informing patients would be readily accepted by an appropriate clinician already responsible for the individual's care, in many cases their general practitioner. However a small cadre of individuals should be developed, knowledgeable as to the broader aspects of CJD and experienced in discussing its implications, from whom those clinicians could expect active support up to and including sharing the relevant consultation(s).

4.17 Appointments should be scheduled at such a time and be of sufficient length to allow exploration of issues and concerns. There should be a facility to supplement advice with telephone contact and a further appointment if required. Written material supporting the consultation, to be taken away, will be available, prepared under the auspices of the CJD Incidents Panel.

4.18 In essence, patients will be counselled as to the current incomplete understanding of risk, and requested to collaborate with active follow up by informing whoever manages the database of any changes of address. They will, as stated, be advised against blood or organ donation. They will also be advised of the need to inform their carers if they require further surgery.

Question Box: The 'contactable' group

We propose that public health action may be required for certain patients who have been exposed to CJD. These exposed people should be advised not to donate blood, or organs and to inform their doctors if they require future surgery. We propose that they should be told about their exposure by their doctor, and given appropriate counselling and support.

Q4. Do you agree with our proposals to reduce the risk of further spread of CJD via surgery and donated blood and organs?

Q5 Do you agree with our proposals to contact these exposed patients so that public health actions may be taken to protect others?

d See Box 2 for detailed categorisation of clinical procedures

People with a 'possible' risk of acquiring CJD

4.19 It is unlikely that anyone outside the 'contactable' group would acquire CJD from an incident. Even so Incident Management Teams should collect information on other 'possibly exposed' people so that the risk of transmitting CJD through invasive medical procedures can be better understood.

4.20 To this end, a public health database will be maintained at CDSC. This database will include relevant details of exposed individuals from all countries within the UK. The databse will enable the long term follow up of people possibly exposed in incidents. The database may also be used to contact people should a prophylaxis for sporadic or variant CJD be developed.

4.21 The CJD Incidents Panel will advise the local team which people should be recorded on this confidential public health database.

4.22 It is important that members of the public are aware of the existence of this database, and realise that they are able to a) find out if they are on the database and b) ask for their records to be altered if incorrect, or deleted (see Public Awareness section).

4.23 All patients in the 'contactable' group should be included in this database.

4.24 In general, the Panel will advise that **the first ten patients** operated on with the instruments used on the index patient with CJD should be entered on this database.

4.25 If instrument tracing systems are inadequate, it may not be possible to identify these patients. In this case, anyone who could be one of the first 10 patients should be entered on the database.

Question Box: The 'possibly exposed' group

We propose that a database is set up to enable follow up of all patients who might have been exposed to CJD through medical procedures. While we believe that the risk for most people in this group is low, the database will be used to find out whether any of them develop CJD. This will increase our knowledge and understanding about risks from medical procedures.

We propose that patients (except for those in the contactable group) are not told about their possible exposures and that their details are recorded on the database. We propose that the database is publicised so that individuals are aware of its existence, and can find out about their exposure details and have their names removed from the database if they wish.

Q6. Do you agree with our proposals not to inform possibly exposed people (except for those in the contactable group) of their possible exposure?

Q7. Do you agree with our proposals to set up a database to follow up all possibly exposed people, with the aim of increasing our knowledge of the risk of transmitting CJD through medical interventions?

Q8 Do you agree with our proposal that informed consent should not be sought from individuals before recording their details on the database?

Q9 Do you agree with our proposal that the database should be publicised so that individuals can find out whether they are on it, and about their possible exposures?

Q10 Do you agree with our proposal that individuals (except for those in the contactable group) should be able to remove their names from the database, without having to find out whether they have been put at risk?

Section 5: Interim advice on the investigation and management of incidents involving blood (variant CJD only)

Investigation

5.1 The UK Blood Services (UKBS) work with the CJD Surveillance Unit to identify blood donations from people who later are found to have developed variant CJD[42].

5.2 If blood from donors who later develop variant CJD has been used to produce plasma derivatives, UKBS inform the relevant manufacturer; Bio Products Laboratory for England and Wales, and the Protein Fractionation Centre for Scotland and Northern Ireland.

5.3 The manufacturer can then identify and trace the implicated products. If the products are still within their shelf life, the manufacturer is obliged to notify the incident to the Medicines Control Agency (MCA). The MCA will then advise the manufacturer to recall any implicated products by contacting pharmacy departments, haemophilia centres etc. Where necessary, the MCA facilitates this process by issuing a 'Drug Alert' to health professionals.

5.4 If the products are still within their shelf life the manufacturer is also obliged to inform other companies who have purchased implicated products as ingredients in other medicines.

5.5 If implicated products have been sold overseas, the manufacturer should inform their customers and the regulatory authorities. The MCA will issue a rapid alert to regulatory authorities in other EC member states, and will contact other countries via the WHO.

5.6 If the products are time expired (as is likely to be the case in a variant CJD Incident), recall is not an option, and the manufacturer is not obliged to take any action.

Proposals

5.7 When the UKBS become aware of implicated blood donations, they should inform the local CCDC for the trust(s) where the blood components were used. The CCDC should inform the CJD Incidents Panel about the incident. The CCDC should also inform CDSC who will provide assistance, and help co-ordinate incidents that involve more than one health authority.

5.8 The CCDC, together with the hospital infection control doctor, should then investigate the incident, identifying the recipients of the blood components.

5.9 The UKBS should inform the CJD Incidents Panel if any implicated blood has been used to manufacture plasma derivatives.

5.10 The UKBS should ask the manufacturers to provide the CJD Incidents Panel with the information required to assess the risks from the plasma derivatives. This should include details of the products issued, their manufacture and the number of plasma donations pooled.

Management

Removal of blood from use

5.11 The UKBS are responsible for ensuring that any implicated blood components that are in date are withdrawn from use.

5.12 The relevant manufacturer is responsible for ensuring that implicated plasma derivatives are withdrawn from use.

Blood Components

5.13 While blood has not yet been found to be infective in variant CJD, as a precautionary step, recipients of blood components (red cells, platelets, plasma, white cells, cryoprecipitate) donated by someone who goes on to develop variant CJD should be included in the contactable group.

5.14 The CCDC should ensure that these individuals are informed about their exposure, and receive public health advice. This may be carried out by the patients' GP or other suitable health professional (see Section 4).

5.15 The CCDC should also pass information about these individuals to the CJD Incident database at CDSC.

Plasma Derivatives

5.16 The risk from plasma derivatives is less clear and the CJD Incidents Panel will need to assess each case individually, using the information supplied by the manufacturer.

5.17 As an interim measure (see Section 2), the CJD Incidents Panel may advise contacting recipients of some implicated plasma products where assessment indicates a medium level of risk. In this interim period, advice on the precautions required should these patients undergo surgery may be less stringent than those recommended for the contactable group in surgical incidents.

5.18 As an interim measure the CJD Incidents Panel may advise that recipients of albumin, Factor IX, and high purity Factor VIII need not be contacted, but where possible, they should be recorded on the CJD incidents database.

5.19 The CJD Incidents Panel will ask the manufacturers to inform organisations in their distribution chain, including pharmacy departments and haemophilia centres, about the implicated product.

5.20 The CJD Incidents Panel will provide information to the manufacturer for distribution to these organisations. This will explain which doses of products are unlikely to pose a risk to recipients, and will direct the organisation to contact the local CCDC(s).

5.21 The CCDC will then work with the hospitals and other organisations to identify recipients and collect details of the doses of derivatives that have been given. The CCDC will then pass this data on to CDSC for entry onto the database.

5.22 It may not be possible to identify all recipients. For example, albumin is used in a wide variety of medicinal products, and there may be no way of identifying who has received products made from an implicated batch.

5.23 When the Panel advises that recipients should be contacted, the CCDC should ensure that these individuals are informed about their status, and that public health advice is given. This may be carried out by the patients' GP or other suitable health professional (see Section 4).

Question Box: People who receive implicated blood components and plasma derivatives

Q12. Do you agree with our proposal to include people who have received blood components donated by people who later develop CJD, in the contactable group?

Q13 Do you agree with our proposals to manage people who have received plasma products derived from blood donated by people who later develop CJD?

Section 6: Public awareness

Principles

6.1 Principles of public openness underlie this guidance:-

6.2 Information about CJD should be widely available. This should include information on the current knowledge of the risk of contracting CJD through medical procedures and the actions being taken to improve our knowledge and minimise these risks.

6.3 Members of the public have a right to know about specific incidents and if they could have been exposed to a potential risk. Concerned individuals who wish to find out about possible exposure should be advised that there is currently no test to find out whether someone is incubating CJD and no cure for the disease.

6.4 Health teams should try to avoid informing people about possible risk-exposure against their will. The only exception to this is where there is a need to take action to protect the public health. In these cases patients would always be informed.

6.5 A database of possibly exposed patients will be set up to help to determine the risk of transmitting CJD through invasive medical procedures. Patients have a right to decide whether their personal information is kept on this database. Systems should be set up to allow patients to exercise this right without necessarily having to find out about their own exposure status.

Objectives

6.6 Following on from this, the public communication has five main objectives:-

- To provide general information on CJD, the current knowledge of the risk of contracting CJD through medical procedures and actions being taken to improve our knowledge and minimise these risks.
- To provide general information about particular incidents.
- To provide an opportunity for individuals to discuss, clarify and obtain reassurance about any of this.
- To provide a mechanism for individuals who remain concerned to find out if they were possibly exposed and to receive appropriate local care and support.
- To provide information to concerned individuals about the current lack of a diagnostic test and cure for CJD.
- To provide a mechanism for individuals to remove themselves from the database of exposed individuals without needing to find out if they were actually exposed.

National Information

6.7 The public should have access to information about CJD, what is known about the risk of transmitting CJD through invasive medical procedures, how we are reacting to this situation, and the need for further research.

6.8 The public may be informed through publicity material including leaflets and posters that are made widely available in healthcare settings. A media campaign would also be effective in informing members of the public.

6.9 Additional information should be available on recognised health websites.

6.10 Further information and support may be provided by **NHS Direct**. Equivalent arrangements for Scotland have yet to be established. Until such time information on local incidents should be the subject of local arrangement following the principles described in this document.

Local information in an incident

6.11 The public should have access to information on particular incidents. This should:

- Reiterate the general information outlined above.
- Provide specific information about the incident.
- Provide reassurance where possible.
- Explain the purpose, value and mechanism of the database of exposed people.
- Advertise a means for individuals who remain especially concerned to discuss or clarify any issues.
- Enable individuals who still remain especially concerned to be removed from the database and/or to find out whether they were exposed.

6.12 This would be done in the following ways:

- A press release which refers to the general information leaflet and websites as sources of information (points a to d above).
- These information sources also advertise that individuals who remain concerned can ring **NHS Direct** to discuss the issues involved.

Information for Concerned Individuals

6.13 Individuals who ring NHS Direct speak initially to a Health Information Adviser who notes the caller's demographic details and that this call is related to clinical exposure to CJD. There are then two possible options.

6.14 The concerns are addressed by this Health Information adviser using the attached flowchart **(Annex 6)** and question and answer sheets.

6.15 The call is passed to one of a smaller group of Health Information Advisers who are experienced in this field. They would also use the flow chart and question and answer sheets to address the caller's concerns.

Question Box 2: Public awareness

Q14. Do you agree with our proposals for a national publicity campaign to raise public knowledge and awareness about these risks?

Q15. Do you agree with our proposals for local publicity campaigns for each incident?

Q16. Do you agree with our proposals for enabling concerned individuals to find out about their possible exposures and whether they are on the database?

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Annex 1: Advice and policy on reducing the risk of CJD though medical procedures

Rigorous implementation of washing, decontamination and general hygiene procedures is key in minimising the risk of transmitting CJD on surgical instruments. This is the advice from SEAC which has been incorporated into several sets of advice from the Department of Health to the NHS.

Health service Circular (HSC) 1999/179 emphasises the importance of implementing existing guidance on the cleaning & sterilisation of medical devices[1]. It is complemented by a CD-ROM titled *Decontamination Guidance*, which draws together existing guidance on decontamination of medical equipment.

Health Service Circular HSC 2000/032 requires NHS organisations to review their management arrangements urgently and to carry out a health and safety audit of their decontamination procedures[2].

Systems that can track instrument sets through decontamination and use on patients are vital in identifying which instruments are used on a particular patient. Health Service Circular HSC 2000/032 also instructs trusts to set up such systems.

In addition to advising on the importance of effective decontamination, SEAC also advised that the use of single use instruments should be considered where practicable, provided patient safety is not compromised.

This advice is reiterated in HSC 1999/178. This describes the actions that health organisations and clinicians should take to reduce the risk of transmission[3].

Following the advice from SEAC, the Department of Health has introduced single-use instruments for tonsil surgery[4].

The Advisory Committee on Dangerous Pathogens (ACDP) advises government on health and safety risks from infectious diseases. A SEAC/ACDP Joint Working Group has been set up to advise on health and safety risks arising from CJD. This committee has issued advice on the measures to be taken when surgical interventions are carried out on patients with known or suspected CJD, or in one of the 'at risk' categories (3). This includes advice on the use and disposal of surgical instruments.

The Joint Working Group guidance considers the following groups to be potentially 'at risk ' of developing CJD: recipients of hormone derived from human pituitary glands e.g. growth hormone, gonadotrophin; recipients of dura mater grafts; people with a family history of CJD, i.e. close blood line relatives (parents, brothers, sisters, children, grandpartents and grandchildren).

1 Health service Circular (HSC) 1999/179 "*Controls Assurance in Infection Control: Decontamination of Medical Devices*"

2 Health Service Circular HSC 2000/032 "*Decontamination of medical devices*"

3 HSC 1999/178 "*Variant Creutzfeldt-Jakob Disease (vCJD): Minimising The Risk Of Transmission*"

4 Department of Health Announcement 04 January 2001

Three precautionary measures have been taken to reduce any potential risk of transmitting CJD through blood. First, people at risk of developing CJD are excluded from donating blood. Second, since April 1999, all major blood products (e.g. Factor VIII, immunoglobulins and anti-D for Rhesus negative pregnant women) have been manufactured from plasma donated outside the UK. Third, since October 1999 blood donated in the UK has been processed to remove its white blood cells (leucodepletion).

Annex 2: Instrument construction

The large majority of surgical instruments are manufactured from stainless steel. This can vary in quality (there are over 60 types of steel). Major European and USA manufacturers usually use high quality steel, but instruments of other origin may be made from lower grade steel which is difficult clean effectively.

The finish on an instrument can be polished or matt, and matt finished devices are more difficult to clean. Other materials such as aluminium, titanium and plastics can be part or the whole of an instrument structure. Aluminium and plastic are more difficult to clean than high grade stainless steel. Titanium devices should clean easily. Construction of devices varies from simple "single surface" to complex, multi-jointed or multi-part construction.

The following categorisation of instruments may help in considering how easily cleanable a particular instrument might be. Expert advice should be sought on instruments where category is not clear.

Instrument category	Examples of instruments
Category A: Can be decontaminated[5]	
Single-surface, no working parts	Macdonalds dissector, Deaver retractor
Jointed smooth jaws and no ratchet	Sinus forceps/scissors
Jointed with serrated jaws and ratchet	Spencer-Wells artery forceps
Multi-part instrument that can be dismantled into component parts	Balfour retractor
Category B: Varying degree of decontamination possible	
Multi-part/jointed instrument that cannot be fully dismantled	Compound action bone rongeur
Instruments with lumen	Minimal invasive surgery kit
Category C: Impossible to guarantee safe decontamination[6]	
Power tools(air or electric driven), not machine washable	Maxi-driver, Hall saw
Exotic kit with multi-part, multi-material, only partly strippable	Stereotactic neuro set
Fibre optic flexible scopes	
Instruments with lumen	neuro brain canula

5 If made from poor quality steel instruments may not be effectively decontaminated.

6 Some well-constructed kit in this category may be possible to decontaminate

Annex 3: Classification of specific procedures

Following advice from SEAC and various specialist subgroups, the following table classifies specific procedures according to whether they are normally liable to encounter potentially-infective tissues. These are defined as in the annual Hospital Episode Statistics, and shown with the standard "two letter" HES coding. Only procedures that would commonly have involved re-usable instruments are included.

Procedures encountering CNS (including pituitary and pineal glands) or posterior ophthalmic tissue

AA Tissue of brain

AB Ventricle of brain and subarachnoid space

AC Cranial nerves

AD Meninges of brain

AE Spinal cord and other contents of spinal canal
Excluding: Therapeutic epidural injection, Drainage of CSF, Therapeutic/Diagnostic spinal puncture, Spinal nerve root
i.e. **leaving only:** Partial extirpation of, Other open operations on, Other destruction of and Other operations on spinal cord; Repair of spina bifida; Other operations on meninges of spinal cord; Drainage of spinal canal – except of CSF

BA Pituitary and pineal glands

CA Orbit

CE Conjunctiva and cornea
Excluding: Subconjunctival injection

CF Sclera and iris
Excluding: Laser iridotomy

CH Retina and other parts of eye
Excluding: Cauterisation/Cryotherapy of lesion of retina, Laser photocoagulation of retina for detachment, Biopsy of lesion of eye nec, Repair of globe, Suture of eye nec, Removal of foreign body from eye nec, Fluorescein angiography of eye, Examination of eye under anaesthetic, Other

LC Carotid, cerebral and subclavian arteries
Excluding: Reconstruction/Other open/Transluminal operations on carotid artery, Transluminal operations on cerebral artery, Reconstruction/Other open/Transluminal operations on subclavian artery
i.e. **leaving only:** Operations on aneurysm of, and other Open operations on, cerebral artery

LG Veins and other blood vessels
Excluding: Arteriovenous shunt; Embolisation of Arteriovenous abnormality; Connection of vena cava (or branch of vc); Other bypass operations on/Repair of valve of vein; Other operations for venous insufficiency; Ligation of/Injection into varicose vein in leg; Open removal of thrombus from vein; Other vein related operations; Other open operations on vein; Therapeutic/Diagnostic transluminal operations on vein; Other operations on blood vessel
i.e. **leaving only:** Other arteriovenous operations except Embolisation of arteriovenous abnormality

VA Bones of cranium and face
Excluding: Plastic repair, Opening of cranium; 90% of other operations on cranium without elevation of depressed fracture; Excision of bone of face; Reduction of fracture of maxilla/other bone of face; Division/Fixation of other operations on bone of face; Excision of/Reduction of Fracture of (bones); Division of/Fixation of/Other operations on mandible; Reconstruction of/Other operations on temporomandibular joint
i.e. **Leaving only:** Elevation of depressed fracture of cranium, 10% of the remaining other operations on cranium (V05\V053)

Procedures encountering Anterior Eye tissue

CG Anterior chamber of eye and lens
Excluding: Capsulotomy of posterior lens capsule

Procedures encountering Lymphatic and equivalent risk tissue

BC Other endocrine glands

BD Breast

FD1 Excision of tonsil

FE Salivary apparatus

GA Oesophagus including hiatus hernia

GB Stomach pylorus & general upper gastrointestinal tract endoscopy

GC Duodenum

GD Jejunum

GE Ileum

HA Appendix

HB Colon

HC Rectum

JA Liver

JB Gall bladder

JC Bile duct

JD Pancreas

JE Spleen

MC Bladder

TG Lymphatic and other soft tissue

Provisionally excluded from any of the above categories:

A Nervous system

AE Operations on spinal nerve root,
Insertion of/attention to neurostimulator adjacent to spinal cord

AE Therapeutic epidural injection, Drainage of CSF,
Therapeutic/Diagnostic spinal puncture

AF Peripheral nerves

AG Other parts of nervous system

B Endocrine system and breast

BB Thyroid and parathyroid glands

C Eye

CB Eyebrow and eyelid

CC Lacrimal apparatus

CD Muscles of eye

CE Subconjunctival injection (C434)

CF Laser iridotomy (C623)

CG Capsulotomy of posterior lens capsule (C733)

CH Cauterisation/Cryotherapy of lesion of retina, Laser photocoagulation of retina for detachment, Biopsy of lesion of eye nec, Repair of globe, Suture of eye nec, Removal of foreign body from eye nec, Fluorescein angiography of eye, Examination of eye under anaesthetic, Other)

D Ear

DA External ear and external auditory canal

DB Mastoid and middle ear

DC Inner ear and Eustachian canal

E Respiratory tract

EA Nose

EB Nasal sinuses

EC Pharynx

ED Larynx

EE Trachea and bronchus

EF Lung and mediastinum

F Mouth

FA Lip

FB Tooth and gingiva

FC Tongue and palate

FD Tonsil and other parts of mouth **apart from** "FD1 Excision of tonsil"

H Lower digestive tract

HD Anus and perianal region

K Heart

KA Wall septum and chambers of heart

KB Valves of heart and adjacent structures

KC Coronary artery

KD Other parts of heart and pericardium

L **Arteries and veins**

LA Great vessels and pulmonary artery

LB Aorta

LC Reconstruction/Other open/Transluminal operations on carotid artery, Transluminal operations on cerebral artery, Reconstruction/Other open/transluminal operations on subclavian artery

LD Abdominal branches of aorta

LE Iliac and femoral arteries

LF Other arteries

LG Arteriovenous shunt; Embolisation of Arteriovenous abnormality; Connection of vena cava; Other bypass operations on/repair of valve of vein; Other operations for venous insufficiency; Ligation of/injection into varicose vein in leg; Open removal of thrombus from vein; Other vein related operations; Other open operations on vein; Therapeutic/Diagnostic transluminal operations on vein; Other operations on blood

M **Male Urinary**

MA Kidney

MB Ureter

MD Outlet of bladder and prostate

ME Urethra and other parts of urinary tract

N **Male genital organs**

NA Scrotum and testis

NB Spermatic cord and male perineum

NC Penis and other male genital organs

P **Lower female genital tract**

PA Vulva and female perineum

PB Vagina

Q **Upper female genital tract**

QA Uterus

QB Fallopian tube

QC Ovary and broad ligament

R **Female genital tract associated with pregnancy, birth & puerperium**

RA Foetus gravid uterus

RB Induction and delivery

RC Other obstetric

S **Skin**

SA Skin or subcutaneous tissue

SB Nail

T **Soft tissue**

TA Chest wall pleura and diaphragm

TB Abdominal wall

TC Peritoneum

TD Fascia, ganglion and bursa

TE Tendon

TF Muscle

V **Bones and joints of skull and spine**

VA 90% of Other operations on cranium without Elevation of depressed fracture (90% V05\V053)

VA Remaining Bones of cranium and face

VB Jaw and temporomandibular joint

VC Decompression operations on spine

VD Operations on intervertebral disc

VE Other operations on spine

W **Other bones and joints**

WA Complex reconstruction of hand and foot

WB Graft of bone marrow (W34)

WB Other Bone (Excluding Graft of bone marrow)

WC Joint

X **Miscellaneous operations**

XA Operations covering multiple systems

XB Miscellaneous operations

Annex 4: Reporting form for possible exposures to CJD through medical procedures

Please complete this form for all invasive medical procedures.

Please report all possible exposures to Pip Edwards at the Department of Health on 020 7972 5324.
Please send this form to her by fax on 020 7972 5092, or by e-mail at Philippa.edwards@doh.gsi.gov.uk.

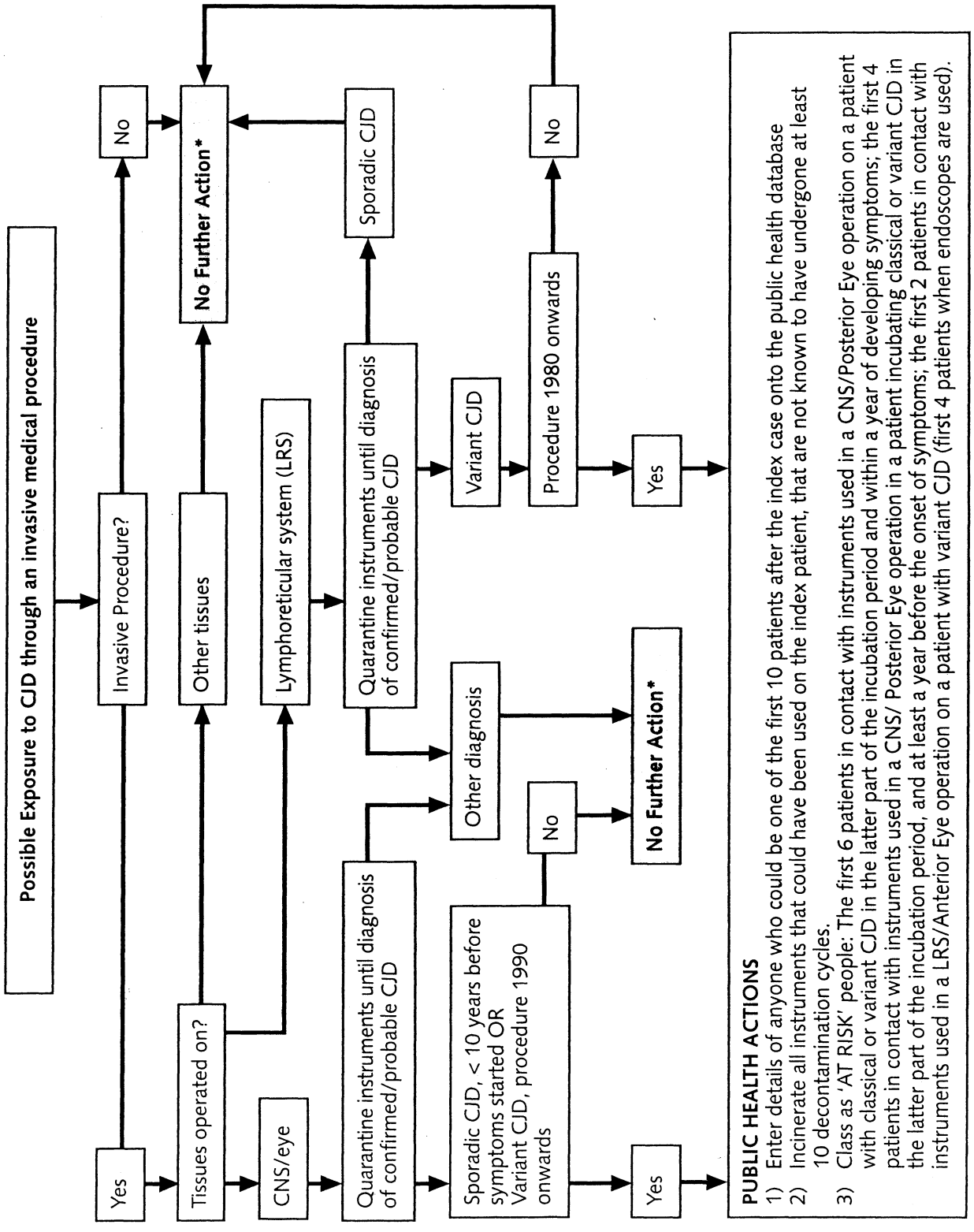
DH team member contacted	Date	PI
Your details (name, position)		
Organisation (address)		
Telephone/fax/email contact details		

Patient's name			
CJD diagnosis (please tick box)	possible	probable	confirmed
sporadic	☐	☐	☐
variant	☐	☐	☐
familial	☐	☐	☐
iatrogenic	☐	☐	☐
If diagnosis has not been confirmed, please give supporting details			
Who made the diagnosis (NCJDSU, local neurologist etc.)			
Date of onset of symptoms of CJD			

Possible exposure (please use a new page for each procedure)

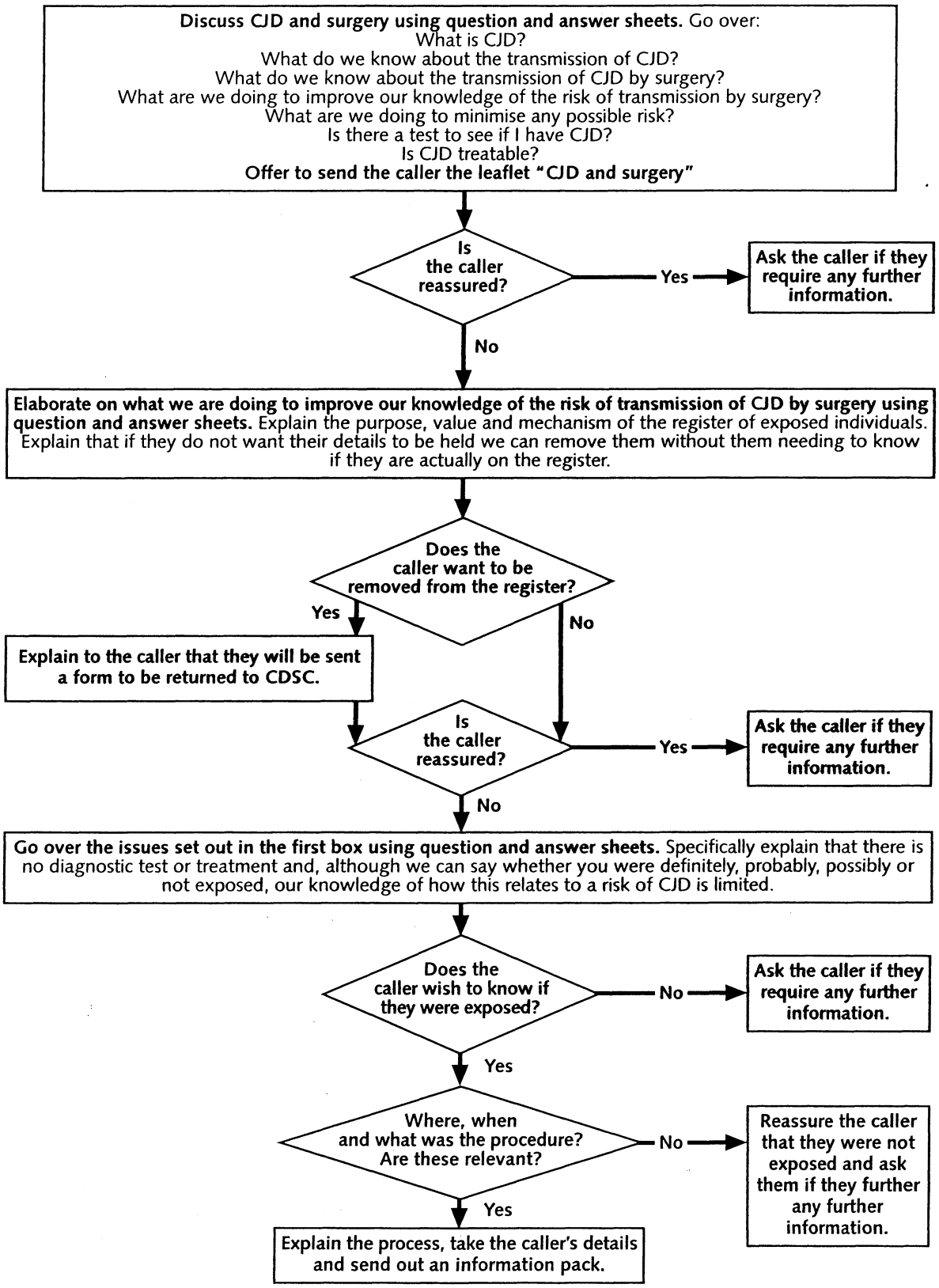
Date of procedure	
Description of procedure	
Tissues involved	
Anaesthetic procedures	
Clinical reason why the procedure was required (for surgical procedures)	
Was an endoscope used? (please tick box)	Yes ☐ No ☐

Annex 5: Possible exposure to CJD through an invasive medical procedure



* Clean and sterilise instruments according to guidance and return to use. No other action required.

Annex 6


Discuss CJD and surgery using question and answer sheets. Go over:
What is CJD?
What do we know about the transmission of CJD?
What do we know about the transmission of CJD by surgery?
What are we doing to improve our knowledge of the risk of transmission by surgery?
What are we doing to minimise any possible risk?
Is there a test to see if I have CJD?
Is CJD treatable?
Offer to send the caller the leaflet "CJD and surgery"
Is the caller reassured?
Yes
Ask the caller if they require any further information.
No
Elaborate on what we are doing to improve our knowledge of the risk of transmission of CJD by surgery using question and answer sheets. Explain the purpose, value and mechanism of the register of exposed individuals. Explain that if they do not want their details to be held we can remove them without them needing to know if they are actually on the register.
Does the caller want to be removed from the register?
Yes
No
Explain to the caller that they will be sent a form to be returned to CDSC.
Is the caller reassured?
Yes
Ask the caller if they require any further information.
No
Go over the issues set out in the first box using question and answer sheets. Specifically explain that there is no diagnostic test or treatment and, although we can say whether you were definitely, probably, possibly or not exposed, our knowledge of how this relates to a risk of CJD is limited.
Does the caller wish to know if they were exposed?
No
Ask the caller if they require any further information.
Yes
Where, when and what was the procedure? Are these relevant?
No
Reassure the caller that they were not exposed and ask them if they further any further information.
Yes
Explain the process, take the caller's details and send out an information pack.

Glossary

ACDP	Advisory Committee on Dangerous Pathogens, established in 1981 to advise the Health and Safety Executive on all aspects of hazards and risks to workers and others from exposure to pathogens.
BSE	Bovine Spongiform Encephalopathy, a slowly progressive and ultimately fatal neurological disorder of adult cattle transmitted by contaminated animal feed.
CDSC	Communicable Disease Surveillance Centre. Responsible for monitoring human infectious diseases.
CJD	Creutzfeldt-Jakob Disease, a human transmissible spongiform encephalopathy that can occur in sporadic, familial and acquired (iatrogenic) forms.
Cleaning	A process which physically removes contamination but does not necessarily destroy micro-organisms.
CNS	Central nervous system. This includes the brain, cranial nerves and spinal cord.
Contactable Patients	People exposed in an incident who are are considered to have a higher risk of acquiring CJD. They should be contacted and informed about their exposure so that action may be taken to prevent any further spread of disease.
CSF	Cerebrospinal fluid, the fluid that bathes the brain and spinal cord.
Decontamination	A process which removes or destroys contamination and thereby prevents micro-organisms or other contaminants reaching a susceptible site in sufficient quantities to initiate infection or any other harmful response.
Definite case of CJD	An international definition used by the CJD Surveillance Unit that refers to the diagnostic status of cases. In definite cases the diagnosis will have been pathologically confirmed, in most cases by post mortem examination of brain tissue (rarely it may be possible to establish a definite diagnosis by brain biopsy while the patient is still alive).
Dose response relationship	This describes how the amount of an infectious agent affects the likelihood that an exposed individual becomes infected.
Dura mater	The outermost and strongest of the three membranes (meninges) which envelop the brain and spinal cord.
Endoscopes	Tube-shaped instruments inserted into a cavity in the body to investigate and treat disorders. There are many types of endoscopes e.g. arthroscopes, laparoscopes, cyctoscopes, gastroscopes, colonoscopes and bronchoscopes.

Membership of CJD Incidents Panel

Chairman	
Professor Michael Banner	Ethicist, Professor of Moral and Social Theology, King's College, University of London
Members	
Professor Don Jeffries	Vice Chairman, Virologist, St Bartholomew's Hospital (JWG)
Professor James Ironside	Neuropathologist, National CJD Surveillance Unit (JWG)
Dr Hester Ward	National CJD Surveillance Unit
Dr Mike Painter	Consultant in Communicable Disease Control, Manchester (JWG)
Dr Tim Wyatt	Consultant Microbiologist, Belfast (JWG)
Dr Geoff Ridgway	Consultant Microbiologist, London (JWG)
Dr Roland Salmon	Public Health Laboratory Services, Wales (JWG)
Dr Noel Gill	Public Health Laboratory Services, London
Ms Susan MacQueen	Chair, Infection Control Nurses Association
Professor Dame Lesley Southgate	Royal College of General Practitioners
Ms Diana Kloss	Law Faculty, University of Manchester
Ms Jean Gaffin	Lay Representative
Ms Gillian Turner	Lay Representative, CJD Support Network
Professor Len Doyal	Ethicist, Bartholomew's & Royal London School of Medicine & Dentistry
Mr Luke Gormally	Ethicist, Linacre Centre for Healthcare Ethics
Professor John O'Neill	Ethicist, Lancaster University
Mr John Barker	Institute of Sterile Service Management, Technical Committee Member
Professor Mike Bramble	British Society of Gastroenterologists
Professor Peter Hutton	President, Royal College of Anaesthetists
Professor Graham Smith	Vice-President, Royal College of Anaesthetists
Mr Andrew Tullo	Royal College of Ophthalmologists
Ms Kate Woodhead	Chair, National Association of Theatre Nurses
Professor John Lumley	Royal College of Surgeons
Professor Ian Cooke	Royal College of Obstetricians and Gynaecologists
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Mr Henry Marsh	Society of British Neurological Surgeons
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Miss Claire Mills	CJD/ BSE Policy Unit, DH
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Dr Mary O'Mahony	Communicable Disease Branch, DH
Mr Alan Harvey	CJD/ BSE Policy Unit, DH
Mr Peter Jones	CJD/ BSE Policy Unit, DH
Observers	
Dr Glenda Mock	Department of Health, Social Services & Public Safety, Northern Ireland
Dr Martin Donaghy	Scottish Executive Health Directorate
Dr Mike Simmons	National Assembly of Wales
Ms Carole Fry	Communicable Diseases Branch, DH

Reporting form for possible exposures to CJD through medical procedures

Please complete this form for all invasive medical procedures.

Please report all possible exposures to Pip Edwards at the Department of Health on 020 7972 5324.
Please send this form to her by fax on 020 7972 5092, or by e-mail at Philippa.edwards@doh.gsi.gov.uk.

DH team member contacted	Date	**PI**
Your details (name, position)		
Organisation (address)		
Telephone/fax/email contact details		

Patient's age			
CJD diagnosis (please tick box)	possible	probable	confirmed
sporadic	☐	☐	☐
variant	☐	☐	☐
familial	☐	☐	☐
iatrogenic	☐	☐	☐
If diagnosis has not been confirmed, please give supporting details			
Who made the diagnosis (NCJDSU, local neurologist etc.)			
Date of onset of symptoms of CJD			

Possible exposure (please use a new page for each procedure)

Date of procedure	
Description of procedure	
Tissues involved	
Anaesthetic procedures	
Clinical reason why the procedure was required (for surgical procedures)	
Was an endoscope used? (please tick box)	Yes ☐ No ☐

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文献８

Update on the ‘transfusion’ vCJD case

SEAC
Spongiform Encephalopathy Advisory Committee

UPDATE ON THE 'TRANSFUSION' vCJD CASE

Issue

1. In December 2003 the Secretary of State for Health informed Parliament of the death of a patient who died of vCJD 6.5 years after receiving a blood transfusion donated by an individual who subsequently developed the disease. SEAC will be updated on this case.

Background

Blood transfusion vCJD case

2. The recipient was transfused blood in 1996 from a donor who was, at the time of donation, free of clinical signs of vCJD. The donor developed vCJD in 1999. The recipient died of vCJD in the autumn of 2003. A case report has recently been published in the Lancet by Llewelyn *et al* 2004 (Annex 1).

3. It is possible that the disease was transmitted from donor to recipient by blood transfusion, in circumstances where the blood of the donor was infectious, three years before the donor himself or herself developed vCJD, and where the recipient developed vCJD after a six and a half year incubation period. This is a possibility not a proven causal connection, as it is also possible that this patient acquired vCJD by eating BSE-infected meat or meat products.

4. This development is not entirely unexpected, and over the last 7 years, SEAC have worked on the assumption that blood may be infective and based on precautionary risk assessments, measures have already been put in place by the Department of Health and the National Blood Service to protect the blood supply. Additionally, experimental research in animals has shown that prion diseases can be transmitted via blood transfusion.

Parliamentary questions on the case

5. The statement made by the Secretary of State and supplementary Parliamentary questions and answers relating to the vCJD transfusion case are presented in Annex 2.

Measures already in place to protect the blood supply

6. In view of the possibility of transmission of CJD from transfused blood, exclusion criteria have been put in place to prevent people "at risk" from CJD donating blood (Annex 3). The precautionary measures that have been put in place in the UK are as follows:

- All blood for transfusion has been leucodepleted (white cells removed by filtration) since 31 October 1999.
- From the end of 1999, plasma for blood products has been sourced from outside the UK.
- Since December 2002, fresh frozen plasma for those born after 1st January 1996 has been sourced from the USA.

7. In June 2003, the Advisory Committee on Dangerous Pathogens (ACDP) published revised guidance on safe working and prevention of infection for transmissible spongiform encephalopathy agents, see web link: http://www.doh.gov.uk/cjd/tseguidance/. The ACDP guidance assumes that blood can be infective but that the level of infectivity in blood from sCJD or vCJD infected humans is low. This guidance is based on previous SEAC advice and advice from a joint ACDP/SEAC working group.

Previous SEAC opinions

8. SEAC considered the possibility that blood may be infective in October 1997 when they initially advised leucodepletion of blood and that assessments be carried out on the risk of transmission of vCJD by blood transfusion, which would help inform decisions on any measures that may be necessary to protect blood transfusion recipients. In 1999 SEAC considered a report on the assessment of the risk of exposure to vCJD infectivity in blood and blood products by Det Norske Veritas (DNV). Following this assessment, SEAC identified several measures that might provide significant reduction in risk of transmission via blood, in particular leucodepletion and elimination of UK plasma products.

9. In June 2002 SEAC were informed of several research projects which were in progress and where results might necessitate revision of the assessment at a later date.

Experimental research evidence for transmission of TSEs by blood transfusion

10. Houston *et al.*, 2000[a] and Hunter *et al.*, 2002 (Annex 4) transfused blood (400-450mL) or buffy coat (1 unit, equivalent to 400-450mL blood) from sheep experimentally infected with BSE or natural scrapie to scrapie-susceptible recipient sheep. Two out of 17 recipients of whole blood showed clinical signs typical of TSE in sheep. Both these recipients were transfused with whole blood taken during the preclinical stage of donor BSE infection. Although still incomplete at the time of publication, this study indicated a frequency of transmission of BSE in at least 8% of the 24 recipients transfused with either whole blood or buffy coat. This would rise to 17% if a further 2 suspected cases transfused with whole blood taken during the clinical stage of donor BSE infection were to be confirmed.

11. One positive transmission occurred in a sheep transfused with buffy coat taken at the clinical end-point from the donor, no other transmissions from the 7 buffy coat donations were seen at the time of reporting.

12. Of the 21 sheep transfused with whole blood taken from natural scrapie-infected animals, 4 animals have shown clinical signs of scrapie at the time of publication, indicating a frequency of transmission of scrapie in at least 21% of the recipients.

13. Hunter *et al* 2002 comment that infectivity may not be confined to the buffy coat fraction and there may also be significant levels of infectivity in the plasma and/or red cell fractions.

14. Previous studies on the infectivity of blood from animals with TSE have been reviewed by Brown *et al* (2001), see Annex 5. In the experimental models it was clear that blood or its components can be infectious during both the incubation and clinical phases of TSE disease. On the weight of the available data the authors considered that transmission of the disease by the intravenous route required 5-7 times more whole blood, buffy coat or plasma than transmission by the intracerebral route.

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[a] Houston F., Foster J.D., Chong A., Hunter N. and Bostock C.J. (2000) Transmission of BSE by blood transfusion in sheep. Lancet 356, 999-1000

15. From the review by Brown *et al* (2001) attempts to detect infectivity in the blood of humans with CJD have centred largely on sporadic CJD, with isolated studies using blood from iatrogenic CJD and familial CJD, with infectivity demonstrated in buffy coat, whole blood or plasma in some studies using rodent bioassays but not in monkey or chimpanzee bioassays. With vCJD, no infectivity was detected in blood from 2 patients using mouse bioassays (Bruce et al 2001)[b] however sensitivity could be limited by the species barrier.

16. Herzog *et al* 2004 (see paper SEAC INF/81/6) reported that, on the basis of primate data, the intravenous route should be considered as efficient as the intracerebral route for the transmission of BSE, indicating that blood can carry infectivity round the body.

SEAC opinion on transmission of prion diseases by blood transfusion

17. In September 2002 SEAC considered the Hunter et al 2002 transfusion study in sheep and concluded that the work did not directly inform about the level of risk but there remained a theoretical risk for human health from the transfusion of blood or blood products. SEAC recommended that more targeted fractionation studies should be performed to determine which fractions contained infectivity and whether this varies according to the stage in the incubation period, and should include testing for infectivity in leucodepleted sheep blood.

EC Scientific Steering Committee (SSC) Opinion

18. The SSC reviewed the studies on transmission of BSE by blood transfusion in sheep by Hunter *et al* 2002 in their Opinion issued in September 2002 (Annex 6). The SSC concluded that "these results support already published SSC, SCMPMD and EMEA opinions and recommendations on blood safety". (These opinions are summarised on pages 7 and 8 of the SSC opinion in Annex 6). The SSC also stated that "although the transmission of infectivity through blood in vCJD urgently needs further study, the data presented in this paper neither justify nor add arguments for the introduction of new methods or approaches to the assessment of blood safety."

[b] Bruce M.E., McConnell I., Will R.G., and Ironside J.W. (2001) Detection of variant Creutzfeld-Jakob disease infectivity in extraneural tissues. Lancet 358, 208-209

List of accompanying material

Annex 1
Llewelyn C.A., Hewitt P.E., Knight R.S.G., Amar K., Cousens S., Mackenzie J and Will R.G. (2004) Possible transmission of variant Creutzfeld-Jakob disease by blood transfusion. *Lancet* **363**; 417-421

Annex 2
The 17 December 2003 Statement by the Secretary of State for Health and related Parliamentary Questions

Annex 3
ACDP/SEAC guidelines on Transmissible Spongiform Encephalopathy Agents: Safe working and the prevention of infection.
Extract from Part 4: Infection control of CJD and related disorders in the healthcare setting
Annex A.1 Distribution of TSE infectivity in human tissues and body fluids

Annex 4
Hunter N., Foster J., Chong A., McCutcheon S., Parnham D., Eaton S., Mackenzie C and Houston F. (2002) Transmission of prion diseases by blood transfusion. *J. Gen. Virol.* **83**; 2897-2905

Annex 5
Brown P., Cervenáková L. and Diringer H. (2001) Blood infectivity and the prospects for a diagnostic screening test in Creutzfeld-Jakob disease. *J. Lab. Clin. Med.* **137**; 5-13

Annex 6
EC Scientific Steering Committee Opinion on: "The implications of the recent papers on transmission of BSE by blood transfusion in sheep (Houston et al, 2000; Hunter et al, 2002)" adopted on 12-13 September 2002

Guidance from the Advisory Committee on Dangerous Pathogens and the Spongiform Encephalopathy Advisory Committee

Extract from: Transmissible Spongiform Encephalopathy Agents: Safe working and the prevention of infection, Infection control of CJD and related disorders in the healthcare setting

Part 4
Infection Control of CJD and Related Disorders in the Healthcare Setting

Blood

4.10 Ongoing epidemiological studies have not revealed any cases of CJD or vCJD being caused by blood or blood products. However, vCJD is a relatively new disease on which there are few data. There is experimental evidence that intracerebral inoculation of some blood components can occasionally transmit the CJD agent. Recent work (Bruce *et al* 2001, Wadsworth *et al* 2001) found no infectivity or PrP-res in buffy coat prepared from blood from vCJD patients. However, the transmission of experimental BSE from sheep-to-sheep *via* whole blood transfusion has been reported from ongoing experimental work (Hunter *et al* 2002).

4.11 In consideration of the possibility of transmission of CJD *via* transfused blood, exclusion criteria were put in place to prevent people "at risk" from CJD – see Table 4a, sections 2 and 3 - donating blood. In addition, in view of the uncertainties surrounding the risk of transmission of vCJD *via* blood or blood products, the following precautionary measures have been put in place in the UK:

- All blood destined for transfusion has been leucodepleted (white cells removed by filtration) since 31 October 1999;
- Plasma for blood products has been sourced from outside the UK since 1998;
- Fresh frozen plasma (FFP) for those born after 1 January 1996 has been sourced from the United States since 2002.

Patient risk groups

4.16 When considering measures to prevent transmission to patients or staff in the healthcare setting, it is useful to make a distinction between *symptomatic* patients, *i.e* . those who fulfil the diagnostic criteria for definite, probable or possible CJD or vCJD, and *asymptomatic* patients *i.e*. those with no clinical symptoms, but who are potentially *at risk* of developing one of these diseases, *i.e*. having a medical or family history which places them in one of the risk groups – see Annex B for diagnostic criteria.

Table 4a below details the classification of the risk status of symptomatic and asymptomatic patients.

Table 4a: Categorisation of patients by risk

4.17 Patients should be categorised as follows, in descending order of risk:

1. Symptomatic patients	1.1 Patients who fulfil the diagnostic criteria for definite, probable or possible CJD or vCJD (see Annex B for diagnostic criteria). 1.2 Patients with neurological disease of unknown aetiology who do not fit the criteria for possible CJD or vCJD, but where the diagnosis of CJD is being actively considered
2. Asymptomatic patients at risk from familial forms of CJD linked to genetic mutations	2.1 Individuals who have or have had two or more blood relatives affected by CJD or other prion disease, or a relative known to have a genetic mutation indicative of familial CJD. 2.2 Individuals who have been shown by specific genetic testing to be at significant risk of developing CJD or other prion disease.
3. Asymptomatic patients potentially at risk from iatrogenic exposure##	3.1 Recipients of hormone derived from human pituitary glands, *e.g.* growth hormone, gonadotrophin. 3.2 Individuals who have received a graft of *dura mater*. (People who underwent neurosurgical procedures or operations for a tumour or cyst of the spine before August 1992 may have received a graft of *dura mater*, and should be treated as *at risk*, unless evidence can be provided that *dura mater* was not used). 3.3 Patients who have been contacted as potentially *at risk* because of exposure to instruments used on, or receipt of blood, plasma derivatives, organs or tissues donated by, a patient who went on to develop CJD or vCJD*.

NB: A decision on the inclusion of corneal graft recipients in the "iatrogenic *at risk*" category is pending completion of a risk assessment.

* The CJD Incidents Panel, which gives advice to the local team on what action needs to be taken when a patient who is diagnosed as having CJD or vCJD underwent surgery or donated blood, organs or tissues before CJD/vCJD was identified, will identify contacts who are potentially at risk.

文献９

Predicting the CJD epidemic in humans

Predicting the CJD epidemic in humans

Fourteen cases of new-variant Creutzfeldt–Jakob disease have so far been confirmed in the United Kingdom. Are they the start of an epidemic? If so, how informative will cases in the next few years be in predicting its course?

S. N. Cousens, E. Vynnycky, M. Zeidler, R. G. Will and P. G. Smith

Since the description of ten cases of a new variant of Creutzfeldt–Jakob disease (vCJD) in the United Kingdom in March 1996 (refs 1, 2), four more UK cases and one French case have been confirmed[3]. It remains unknown whether the 'new form' of CJD is due to human infection with the agent responsible for bovine spongiform encephalopathy (BSE) in cattle[1,2]. But the possibility that many infected cows have entered the human food supply[4] has fuelled fears that there might be many cases of vCJD in the future. Too little is known about prion diseases to make, at this stage, confident predictions about what might happen in humans. But the rate at which a disease appears early in an epidemic can give clues about its future size.

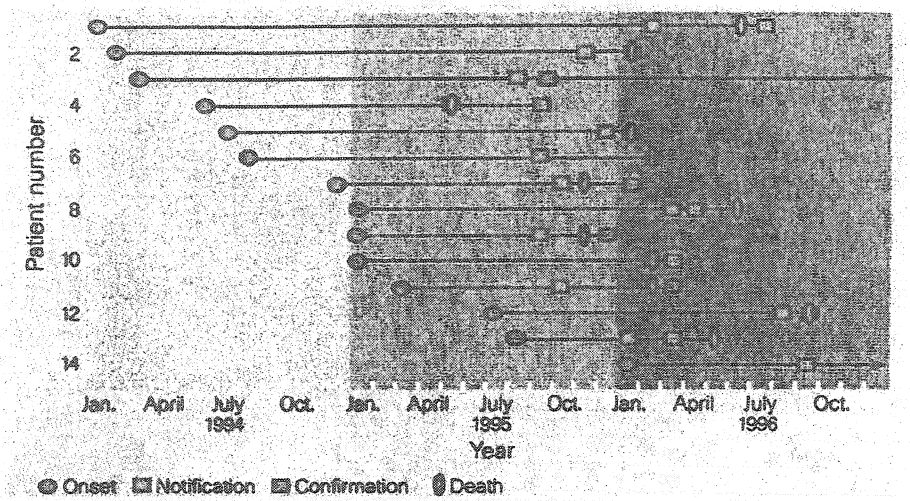
Assuming that vCJD is due to exposure to the BSE agent, we consider two related questions. Given that only 14 UK cases have been confirmed up to the end of 1996, with 13 showing clinical onset in 1994 or 1995, can we rule out the possibility of a large epidemic of vCJD? If not, how informative will cases in the next few years be in predicting the epidemic?

We used mathematical models that make assumptions about the distribution of exposure of the human population to the BSE agent over time and about the time from infection to clinical onset (incubation period) of vCJD. The models estimate, by back calculation[5], how many human infections eventually resulting in disease would have been required to produce 13 cases of vCJD with onset in 1994/95 (see figure) and how many cases might arise in the next three years.

Table 1 Numbers of BSE cases

Year of clinical onset	*No. of confirmed cases* (EPA)	*No. of cases using maximum bounds on under-reporting* (EPB)
1983	0	25
1984	0	50
1985	15	240
1986	63	1,052
1987	662	3,310
1988	3,238	4,760
1989	7,823	7,823
1990	14,693	14,693
1991	26,160	26,160
1992	37,488	37,488
1993	34,089	34,089
1994	22,957	22,957
1995	13,766	13,766
1996*	2,262	2,262

EP, exposure pattern. *Up to 31 March.



Dates of onset, death, referral and confirmation of diagnosis for 14 cases of new-variant CJD in the United Kingdom. For the case with most recent onset, referral and confirmation were almost simultaneous.

We assume that, until 1989, the number of people newly infected with the BSE agent each year was proportional to the number of cases of BSE with onset in that year (Table 1). This assumption is reasonable if bovine material is infectious to humans for only a short period before cattle develop clinical BSE. The order requiring the destruction of cattle clinically suspected of having BSE was not introduced until August 1988, and, until then, clinically affected animals may themselves have entered the human food chain. Two sets of figures for the number of BSE cases are used. The first set, the number of confirmed cases of BSE, assumes that the degree of under-reporting of BSE changed little over time (exposure pattern A). The second set (exposure pattern B) assumes that under-reporting was greatest early in the epidemic (maximum estimates, kindly provided by R. Anderson and N. Ferguson, based on their BSE epidemic model[4]).

In November 1989, UK legislation was introduced that banned specified bovine offals (SBO) from human consumption. We further assume that from 1990 the number of people newly infected each year, while remaining proportional to annual numbers of BSE cases, decreased by 90 or 100 per cent.

We assume that individuals infected with the BSE agent develop vCJD after a long and variable incubation period. Just how long and variable, we do not at present know. For many infectious diseases, the distribution of incubation periods is roughly lognormal[6]. Other distributions used to model incubation periods include the gamma and the Weibull[4,7]. We used all three, unlagged, in our calculations.

The estimated number of infections is extremely sensitive to the shape of the incubation period distribution, its mean and its variability; the number ranges from less than a hundred to many thousands (Table 2). The largest estimates arise with a long mean incubation period and little variation about the mean. Some important differences in the distribution curves greatly affect estimates of the epidemic size based on cases appearing early on. The lognormal distribution generally produces larger estimates than the gamma. The Weibull distribution produces an earlier rise in cases than the lognormal and gamma distributions and so implies a smaller total number of infections. Using the Weibull, the estimated number exceeds 1,000 in only a few situations, the largest being around 3,000.

Few data are available to guide our choice of incubation period for vCJD. But no cases of vCJD with onset before 1994 have been identified. If our model is to predict fewer than, say, five cases with onset before 1994, then the unlagged Weibull would not be a good approximation to the incubation period distribution and the mean incubation period of vCJD would be unlikely to be as short as five years. Several scenarios based on longer mean incubation periods would also be judged incompatible with no cases before 1994 (Table 2). But this restriction alone does not greatly reduce the range of possible outcomes.

For kuru, incubation periods of up to 30 years have been recorded[8]. The mean incubation period for CJD caused by contaminated human pituitary hormone is currently about 13 years[9], although this may be an underestimate as cases with longer incubation periods may yet appear. The range of 'spreads' that we consider (90% of individuals developing disease within 1.5–2 times the mean incubation

Table 2 Predicted numbers of new-variant CJD cases under various possible scenarios

Mean incubation period (yr)	Ninetieth centile of incubation period distribution (yr)	Effectiveness of ban on specifed bovine offals (%)	Lognormal incubation period distribution										Gamma incubation period distribution					
			Exposure pattern A					Exposure pattern B					Exposure pattern A					Exposure pattern B
			Predicted cases with onset				Total no. of human infections	Predicted cases with onset				Total no. of human infections	Predicted cases with onset				Total no. of human infections	Total no. of human infections
			pre-1994	in 1996	in 1997	in 1998		pre-1994	in 1996	in 1997	in 1998		pre-1994	in 1996	in 1997	in 1998		
10	15.0	90	3	12	15	18	213	5	10	12	13	151	4	11	14	17	211	156
		100	3	11	12	12	99	5	9	10	9	83	4	10	11	11	103	88
	20.0	90	13	8	8	7	104	17	7	7	7	101	15	7	8	7	117	114
		100	19	6	5	4	75	23	5	5	4	79	22	6	6	5	92	94
15	22.5	90	1	19	32	48	1,595	3	15	22	30	801	3	14	22	30	1,001	620
		100	1	18	29	40	714	3	14	21	27	430	3	13	19	24	469	342
	30.0	90	10	8	9	10	174	13	8	8	9	158	13	8	8	9	188	177
		100	13	7	6	6	107	16	6	6	6	107	19	7	7	6	137	137
20	30.0	90	1	26	54	97	12,000	2	19	34	54	5,000	2	16	27	41	4,000	2,179
		100	1	25	51	89	5,000	2	19	33	51	2,421	2	15	24	35	1,800	1,189
	40.0	90	8	9	10	11	284	11	8	9	10	244	13	8	9	9	276	255
		100	10	7	8	8	162	13	7	7	7	156	18	7	7	7	195	191
25	37.5	90	1	32	79	166	80,000	2	22	45	83	24,000	2	18	31	50	13,000	7,000
		100	1	31	76	156	35,000	2	22	45	80	13,000	2	17	28	44	6,000	4,000
	50.0	90	7	10	11	13	450	9	9	10	11	370	12	8	9	10	380	346
		100	8	8	9	9	245	11	8	8	8	228	17	7	7	8	263	256

Numbers greater than 2,500 have been rounded to the nearest 1,000. Numbers greater than 25,000 have been rounded to the nearest 5,000.

period) corresponds closely with the range of 'dispersion factors' reported for a variety of acute infectious diseases[6] and is consistent with that used to model the BSE epidemic[4]. A mean incubation period for vCJD of around 15 years points to an epidemic of between several hundred and several thousand cases. But a longer mean incubation period or a 'narrower' incubation period distribution allows for a much larger epidemic.

If under-reporting of BSE cases was common at the start of the epidemic and then declined (exposure pattern B), then we would be further into any BSE-related vCJD 'epidemic' than if under-reporting remained constant over time (exposure pattern A). Exposure pattern B therefore generally leads to lower estimates of the total number of infections. If, say, the distribution of vCJD incubation periods is lognormal, with a mean of 10 years and 90 per cent of infected individuals developing the disease within 15 years, and the SBO ban was 90% effective, exposure pattern B would indicate a total epidemic of about 151 infections (Table 2). Exposure pattern A would indicate a total epidemic of about 213 infections.

If bovine material becomes infectious to humans well before clinical onset of BSE, humans would have been exposed to the BSE agent earlier, relatively, than we have assumed. This would put us further into the vCJD 'epidemic' and so would generally lead to lower estimates of human infections. Although we assume that the SBO ban was either 90% or 100% effective, our results do not critically depend on this assumption. If, say, the SBO ban was only 50% effective, the estimated number of infections in the lognormal model is two to three times greater in the scenarios examined in Table 2. This difference is small compared with the effect of varying the assumptions about incubation period.

If we allow for variability in onset times or the identification of further cases with onset in 1994/95, an even wider range of outcomes is possible. The 13 cases identified are compatible with an underlying expected number of cases with onset in 1994/95 of anything from 6 to 20 (95% confidence interval), resulting in a proportional decrease or increase in the numbers in Table 2. Given the typically long delay between onset and confirmation (see figure), further cases with onset in 1994/95 are likely. If cases continue to accrue at the present rate, the final number with onset in 1994/95 might be about 23 (C. P. Farrington and D. De Angelis, personal communication).

We hesitate to draw sweeping conclusions from calculations based on few data and several currently unverifiable assumptions. Enormous uncertainty inevitably surrounds any modelling when only 14 cases of the disease have been confirmed and without good information about the incubation period distribution. Still, if cases of vCJD are due to exposure to the BSE agent, as recent evidence suggests[10], two tentative conclusions may be drawn. First, it would be premature to conclude that because only 14 UK cases have been confirmed so far, any subsequent epidemic will necessarily be small. Second, although the numbers of cases over the next few years may provide a better indication of how large any epidemic might eventually be, much uncertainty may remain even in four years' time.

If, for example, the number of vCJD cases with onset in each of the next three years is roughly constant and less than 20 a year, the final size of the epidemic may well be a few hundred cases or less. Alternatively, if there are 25 or more cases with onset in 1996, with a doubling or tripling in each of the following years, this would be compatible with a long mean incubation period and an epidemic of many thousand cases. On the other hand, 20 or so cases in 1996, 30–35 in 1997 and about 50 in 1998 would be compatible with both a lognormally distributed incubation period with a mean of 15 years and a ninetieth centile at 22.5 years (around 1,600 infections) and a gamma-distributed incubation period with a mean of 25 years and a ninetieth centile at 37.5 years (around 13,000 infections) (exposure pattern A; SBO ban, 90% effective).

If it is shown that vCJD is due to exposure to the BSE agent, then improved estimates of the incubation period distributions of the two closest analogies we have to vCJD – kuru and CJD in recipients of pituitary hormones – will become a high priority. So too will estimates of the routes and the amount of infectious material entering the human food supply. □

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文献 10

Incidence of variant Creutzfeldt-Jakob disease onsets and deaths in the UK, January 1994-December 2003

Incidence of variant Creutzfeldt-Jakob disease onsets and deaths in the UK

January 1994 – December 2003

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16th January 2004

Summary

Two new cases of vCJD were diagnosed from October to December 2003, bringing the total to 145. Two cases died in the last quarter to bring the total number of deaths to 139 with six diagnosed cases alive.

There is statistically significant evidence (p=0.001 for death, p=0.0003 for disease onset) that the epidemic is no longer increasing exponentially. Furthermore estimates from quadratic models fitted to the incidence suggest that the epidemic may have reached a peak. Estimates for the time of this peak are September 1999 (95% CI: December 1998-June 2001) for disease onset and December 2000 (95% CI: March 2000-August 2002) for deaths. Although these models suggest a peak may have been reached, for the deaths data an alternative model with an increase to a plateau of 19 deaths per year rather than a peak was also fitted and was consistent with the data. The fact that the epidemic may have reached a peak does not exclude the possibility of further peaks in the future.

For the purposes of short-term predictions the model used is important; predictions are best made based on the quadratic model or plateau model rather than the exponential model which has a poor fit. The quadratic models estimate the current incidence of onsets to be 2.5 per quarter and deaths to be 3.5 per quarter with 11 deaths predicted in the next 12 months (95% prediction interval 4 to 19). The plateau model estimates the current incidence of deaths to be 4.9 per quarter with 19 deaths predicted in the next 12 months (95% prediction interval 10 to 29). A plateau model has not as yet been fitted to the onsets data.

An analysis that looks at deaths by birth cohort (pre 1970, 1970s, 1980s) showed that the shape of the epidemic differs between cohorts, mainly due to the fact that deaths of individuals born in the 1980s were only seen from 1999 onwards.

1. Introduction

Each quarter data on diagnosed cases of variant Creutzfeldt-Jakob disease (vCJD) in the UK are reviewed in order to investigate trends in the underlying rate at which disease onsets and deaths are occurring. The present report reviews the data for all individuals who had been classified as definite or probable cases by the end of December 2003. Since the previous report, which covered the period to the end of September 2003 two further cases of vCJD have been diagnosed giving a total of 145 cases. There have now been a total of 139 deaths reported with two in the most recent quarter.

2. Background information

Definite cases are those confirmed neuropathologically. To date all probable cases for which neuropathological data have become available have subsequently been confirmed as definite. The date of diagnosis is taken as the date when diagnosed as probable or, when this is not available, the date of confirmation of a definite case.

For these analyses we have included all cases notified to the National CJD Surveillance Unit and classified as definite or probable by the end of December 2003 (Table 1).

Table 1. Cases of vCJD classified as definite or probable by end of December 2003.

	Died*	Alive	Total
Male	78	4	82
Female	61	2	63
Total	**139**	**6**	**145**

* Deaths including 103 definite, 35 probable (without neuropathological confirmation), 1 probable (neuropathological confirmation pending).

Although 57% are male this proportion is not significantly different from 50% (p=0.14).

Numbers of cases by onset, notification, diagnosis and death are given below by quarter (Table 2) along with the median age at death by year of death (Table 3). The median number of days from onset to diagnosis is 334 days and from onset to death is 414 days. The overall median age at death is 28 with a range from 14 to 74.

Table 2. Quarterly cases by onset, notification, diagnosis & death.

Quarter	Onset	Notification	Diagnosis	Death
94-1	3	0	0	0
94-2	1	0	0	0
94-3	2	0	0	0
94-4	2	0	0	0
95-1	4	0	1	0
95-2	0	1	0	1
95-3	3	3	2	0
95-4	3	4	4	2
96-1	5	4	4	5
96-2	2	1	1	3
96-3	0	3	2	1
96-4	4	1	1	1
97-1	2	6	5	4
97-2	0	0	1	3
97-3	4	5	4	1
97-4	8	2	2	2
98-1	4	1	2	2
98-2	6	4	5	2
98-3	6	7	2	2
98-4	1	8	8	12
99-1	5	2	5	4
99-2	9	5	5	1
99-3	5	6	4	4
99-4	10	3	3	6
00-1	7	8	6	6
00-2	4	8	8	8
00-3	3	7	10	10
00-4	10	6	3	4
01-1	3	4	9	6
01-2	7	8	5	7
01-3	3	4	5	4
01-4	4	5	6	3
02-1	3	6	4	7
02-2	2	4	7	5
02-3	4	3	4	1
02-4	5	2	1	4
03-1	1	4	5	5
03-2	0	4	2	6
03-3	0	4	7	5
03-4	0	2	2	2
Total	145	145	145	139

Table 3. Annual cases by onset, notification, diagnosis and death (including median age at death by year of death).

Year	Onset	Notification	Diagnosis	Death	Median age at death
1994	8	0	0	0	-
1995	10	8	7	3	-
1996	11	9	8	10	30
1997	14	13	12	10	26
1998	17	20	17	18	25.5
1999	29	16	17	15	29
2000	24	29	27	28	25.5
2001	17	21	25	20	28
2002	14	15	16	17	29
2003	1	14	16	18	28
Total	145	145	145	139	28

3. Methods

3.1 Onsets

The incidence of onsets by quarter was analysed with Poisson models using polynomials (constant, exponential, quadratic exponential). When modelling the incidence of onsets over time, delay to diagnosis, and the fact that this delay may be shortening over time because of new diagnostic methods, must be taken into account. Consequently the data were cross-classified by quarter of onset and number of quarters delay from onset to diagnosis, and the delay from onset to diagnosis modelled using a gamma distribution with a mean that can vary over time.

2.2 Deaths

After grouping deaths by quarter the incidence of deaths were modelled by Poisson regression using polynomials. Most deaths are reported quickly so an adjustment for reporting delay is not necessary. So far the age at death has not increased as may have been expected, assuming that most exposure to BSE ceased in the early 1990's. In order to examine this further the cases were stratified by quarter of death and birth cohort (pre1970, 1970s and 1980s). Trends in deaths over time were compared between these cohorts.

In order to further investigate whether the epidemic has reached a peak an alternative model was also considered using annual data in which incidence rises to a plateau.

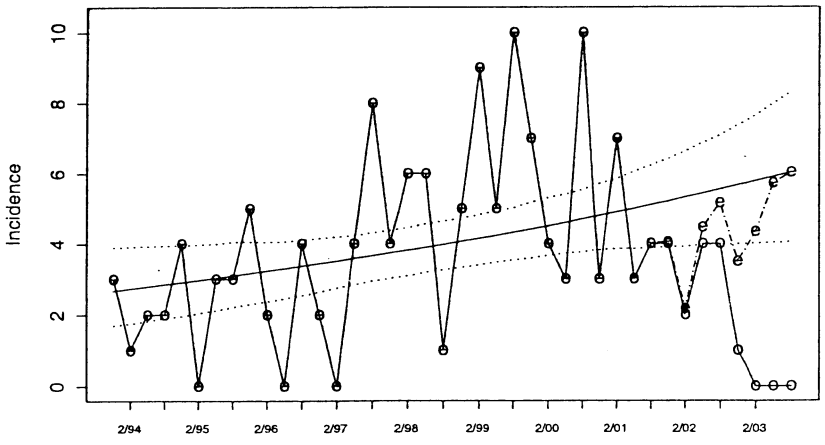
4. Results for Onsets

Since vCJD was first identified, the average interval between the onset of first symptoms and the diagnosis of vCJD has decreased. The mean delay to diagnosis is estimated to have reduced by an average of 5% per year and is currently estimated at 10 months.

Figure1a shows the observed and expected number of onsets and the estimated trend (assuming exponential growth) with 95% confidence intervals (CIs). This model estimates that the number of onsets have increased by 9% per year since 1994 (95%CI 1.3-16). The estimated incidence in the current quarter is 6.1 cases per quarter.

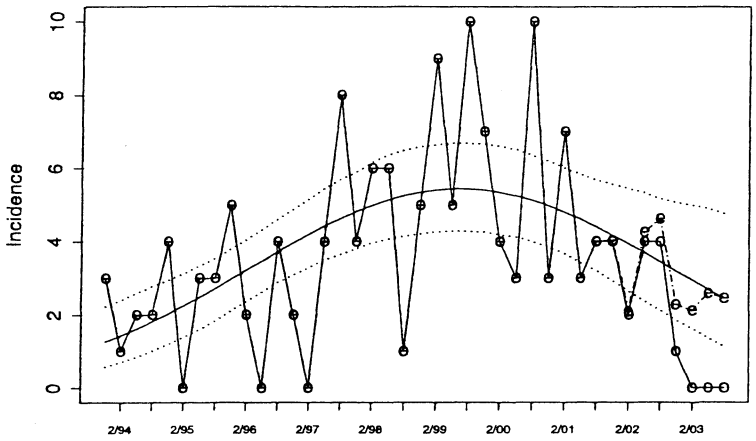
A separate model including a quadratic trend showed significant evidence of a better fit (p=0.001 for quadratic term). Figure 1b shows the quadratic model fitted to the data. The quadratic model is consistent with an epidemic that has reached a peak and this model gives an estimated current incidence of 2.5 onsets per quarter. If the quadratic model is assumed to be correct then the peak is estimated to have occurred in September 1999 with a 95% CI for the time of the peak from December 1998 to June 2001.

Figure1a: Observed (-o-) and expected (-e-) quarterly incidence of vCJD onsets
Fitted exponential trend* (___) is given with its 95% confidence limits (...)



* includes adjustment for delay from onset to diagnosis

Figure1b: Observed (-o-) and expected (-e-) quarterly incidence of vCJD onsets
Fitted quadratic trend* (___) is given with its 95% confidence limits (...)



* includes adjustment for delay from onset to diagnosis

Predicted onsets by the end of December 2003

Based upon the exponential model, the estimated total number of cases with onset by December 2003 is 165 (145 already diagnosed +20 not yet diagnosed) with a 95% prediction interval of 158 to 174. Based on the quadratic model, however, the estimated total number of cases with onset by December 2003 is 155 (145 already diagnosed + 10 not yet diagnosed) with a 95% prediction interval of 150 to 162.

5. Results for Deaths

5.1 All deaths combined

Figure2a shows the observed numbers of deaths by quarter with the exponential model fitted. The annual number of deaths has increased by an estimated 13% per year, (95% CI, 5-20). Based on this model the estimate of the current quarterly incidence of deaths is 6.2.

The model that included a quadratic term gave a significantly better fit (p=0.0003) indicating a departure from a constant exponential increase. Figure 2b shows the data with the fitted quadratic trend. This model estimates that the current quarterly incidence of deaths is 3.5. If the quadratic model is assumed to be correct then the peak is estimated to have occurred in December 2000 with a 95% CI for the time of the peak from March 2000 to August 2002.

An alternative model in which the incidence of deaths rises to a plateau was also fitted to the annual data (figure 2c). This model, which gave an estimate for the plateau at 19.5 deaths per year (4.9 per quarter), fitted the observed incidence of deaths as well as the quadratic model with neither model showing evidence of lack of fit. Therefore it is not possible to distinguish between a trend that has reached a peak and one that has reached a plateau.

Figure2a: Observed (-o-) quarterly incidence of vCJD deaths
Fitted underlying trend (___) is given with its 95% confidence limits (...)

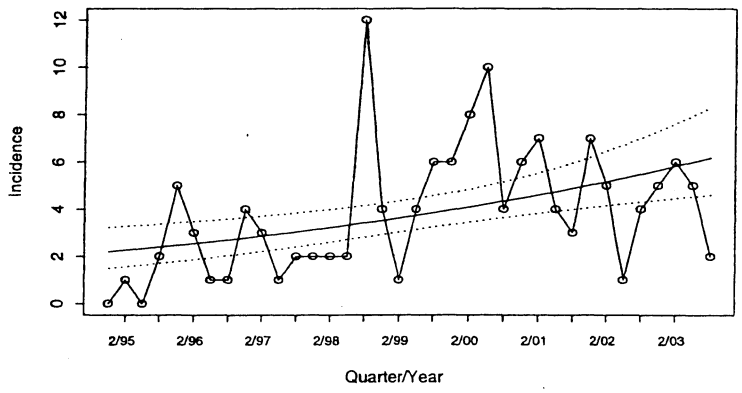


Figure2b: Observed (-o-) quarterly incidence of vCJD deaths
Fitted underlying Quadratic trend (___) is given with its 95% confidence limits (...)

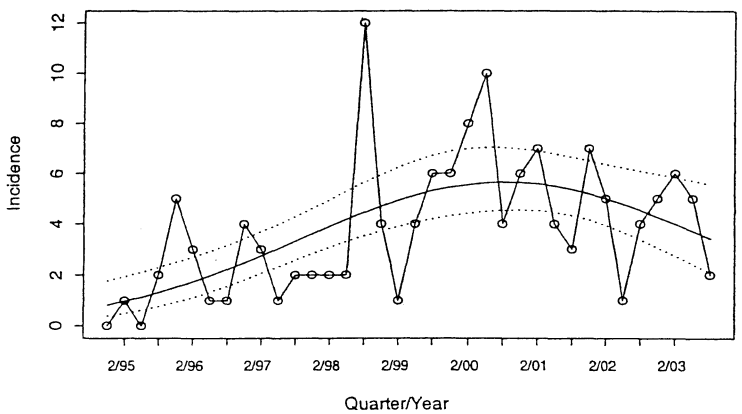
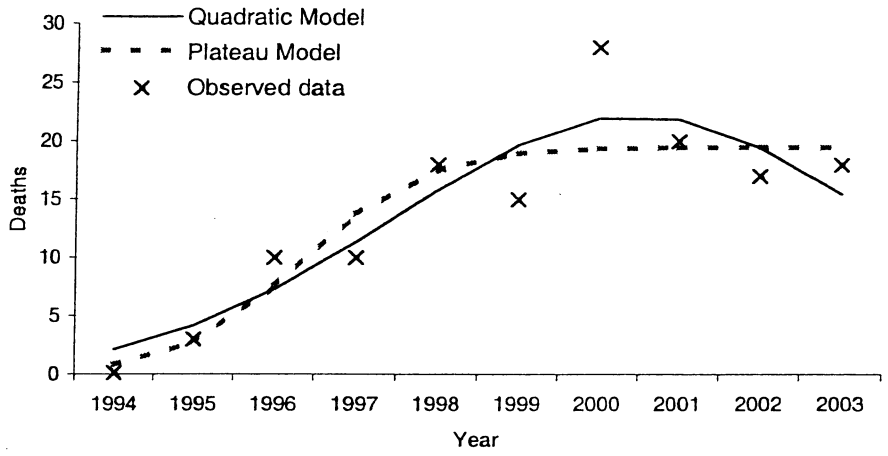


Figure 2c: Quadratic-exponential and plateau models for vCJD deaths incidence trend



Prediction for deaths in the next 12 months

From the model with an increasing exponential trend, the predicted total number of deaths in the next 12 months is 27 with a 95% prediction interval of 16 to 39. However the model with the quadratic term predicts a total of 11 deaths in the next 12 months with a 95% prediction interval of 4 to 19. The plateau model predicts a total of 19 deaths for the next 12 months with a 95% prediction interval of 10 to 29.

Assessment of Predictions made at the end of December 2002

The exponential model gave a prediction of 28 with a 95% prediction interval of 16-40, whereas the quadratic model gave a prediction of 13 with a 95% prediction interval of 5-23. The actual observed number was 18. Although this is within both prediction intervals it is more consistent with the prediction by the quadratic model.

5.2 Deaths by cohort

The age at death has so far remained stable, contrary to what might be expected given that most exposure to BSE is presumed to have ceased in the early 1990s. This finding is consistent, for example, with different age-specific susceptibility or exposure or possibly different incubation periods by age. To examine this in more detail the epidemic curves (quadratic model) are compared in those born before 1970 with those born in the 1970s and the 1980s. This analysis showed significant differences by cohort in the shape of the fitted curves ($p<0.001$). The main difference is due to the fact that in the 1980's cohort no deaths were seen prior to 1999. Figure 3 shows the fitted quadratic epidemic curves for each of the cohorts. The shape of the curve in the pre 1970s cohort does not differ significantly from the 1970s cohort ($p=0.15$). Note that in the

1980s cohort the confidence intervals are very wide due to small numbers and it is unclear in this cohort whether or not the trend is still exponential

Figure3a: Quarterly incidence of vCJD deaths (born pre1970 cohort)
Fitted underlying quadratic trend is given with its 95% confidence limits

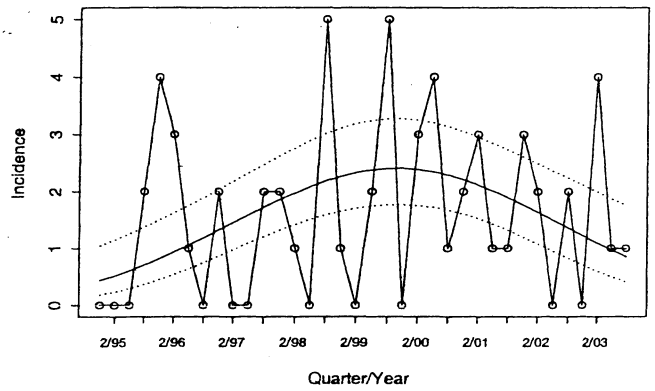


Figure3b: Quarterly incidence of vCJD deaths (born 1970s cohort)
Fitted underlying quadratic trend is given with its 95% confidence limits

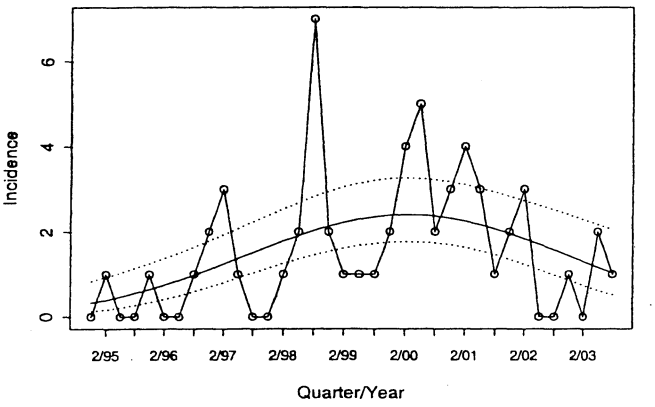
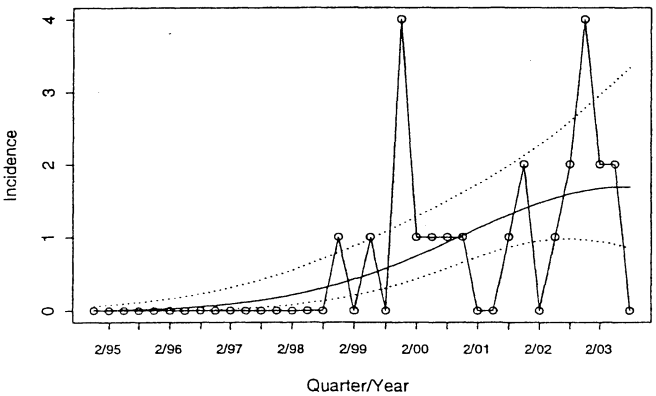


Figure3c: Quarterly incidence of vCJD deaths (born 1980s cohort)
Fitted underlying quadratic trend is given with its 95% confidence limits



Appendix (Extra Details not for the Website)

Appendix 1. Parameter estimates for onsets

The parameters (with parametric percentile bootstrap 95% CI) for the model are given below along with an estimate of the total number of cases which have had onsets by the end of this quarter.

Parameter	Estimate (95% CI) (exponential model)	Estimate (quadratic-exponential model)
α	4.02 (3.29 to 4.67)	5.31 (4.18 to 6.55)
β	0.021 (0.003 to 0.038)	0.017 (0.0001 to 0.037)
Γ		-0.0029 (-0.0048 to -0.0012)
ρ	-0.009 (-0.015 to –0.003)	-0.011 (-0.018 to –0.004)

Models

exponential incidence $\lambda(t) = \alpha \exp(\beta(t-t_m))$

quadratic exponential incidence: $\lambda(t) = \alpha \exp(\beta(t-t_m)+\gamma(t-t_m)^2)$

delay from onset to diagnosis has a gamma distribution with mean (u) = $\exp(\rho t)$

t is the current quarter, t_m is the middle quarter between the first onset and the current quarter

Appendix 2. Parameter estimates for deaths

Parameter	Estimate (95% CI) (exponential model)	Estimate (95% CI) (quadratic-exponential model)
α	0.639	-1.11
β	0.030 (0.012 – 0.046)	0.202
Γ		-0.0036 (-0.0056 to -0.0016)

exponential incidence $\lambda(t) = \alpha \exp(\beta(t))$

quadratic exponential incidence: $\lambda(t) = \alpha \exp(\beta(t)+\gamma(t)^2)$

t is the current quarter

Models are compared by change in deviance. The variance is now NOT re-scaled to allow for over dispersion since it is not significant (p=0.07). The analysis uses all deaths from the first quarter of 1995. The cubic term was also examined and was not significant (p=0.79).

For the plateau model the formula is $y = a/(1+\exp(b - ct))$ where a is the plateau, b effects the location of the rise and c the steepness of the rise. The parameter estimates for a, b and c were 19.5, 4.5 and 1.34 respectively. The residual deviance was for this model was 7.6 on 6 d.f. compared to 8.8 on 6 d.f. for the quadratic exponential model.

Appendix3: Estimated trend of onsets and deaths for this analysis and the analyses in previous quarters

Analysis	Model parameter	Trend for Onsets	Trend for deaths
December 2003	Linear (Linear model) Quadratic term Cubic Term	1.09 (1.01 – 1.16) -0.0029 (-0.0048 to -0.0012) not done	1.13 (1.05-1.20) -0.0036 (-0.0056 to -0.0016) 0.00003 (-0.0002 to 0.0003)
September 2003	Linear (Linear model) Quadratic term Cubic Term	1.10 (1.04 – 1.18) -0.0025 (-0.0045 to -0.0007) not done	1.15 (1.07-1.23) -0.0032 (-0.0054 to -0.0010) 0.000011 (-0.001 to 0.0003)
June 2003	Linear (Linear model) Quadratic term	1.09 (1.03 – 1.19) -0.0032 (-0.0055 to -0.0011)	1.16 (1.07-1.24) -0.0035 (-0.0059 to -0.0011)
March 2003	Linear (Linear model) Quadratic term	1.12 (1.04 – 1.20) -0.0028 (-0.0052 to -0.0008)	1.16 (1.07-1.25) -0.0040 (-0.0066 to -0.0014)
December 2002	Linear (Linear model) Quadratic term	1.13 (1.06 – 1.23) -0.0030 (-0.0057 to -0.0006)	1.15 (1.06-1.25) -0.0040 (-0.0069 to -0.0010)
September 2002	Linear (Linear model) Quadratic term	1.16 (1.07 – 1.25) -0.0021	1.17 (1.05 – 1.30) -0.0040
June 2002	Linear	1.18 (1.08 – 1.29)	1.20 (1.08 – 1.35)
March 2002	Linear	1.18 (1.08 – 1.29)	1.22 (1.08 – 1.38)
Dec 2001	Linear	1.21 (1.09 – 1.34)	1.23 (1.08 – 1.41)
Sep 2001	Linear	1.22 (1.10 – 1.37)	1.27 (1.11 – 1.46)
June 2001	Linear	1.24 (1.10 – 1.38)	1.30 (1.13 – 1.51)
Mar 2001	Linear	1.26 (1.11-1.45)	1.33 (1.13 – 1.56)
Dec 2000	Linear	1.23 (1.07 – 1.41)	1.35 (1.13 – 1.61)
Sept 2000	Linear	1.27 (1.11 – 1.46)	1.38 (1.15 – 1.67)
June 2000	Linear	1.23 (1.07-1.42)	1.33 (1.08 – 1.64)

Appendix 4: Analysis by quarter of diagnosis

Using quarter of diagnosis has the advantage that all cases can be included but the potential disadvantage that changes in diagnostic practice may affect the numbers diagnosed each quarter and unlike onset and death diagnosis is not a disease outcome. However once the criteria for diagnosis as a probable were established previous cases were given retrospective diagnosis dates. This should minimise the effect of changes in diagnostic practice. The analysis by date of onset has shown the time from onset to diagnosis has declined over time, however the change is fairly small and will not effect the overall trends.

The analysis uses all results from the first quarter of 1995.

4.1 Results overall

As with deaths the quadratic term is significant (p=0.0005).

Parameter	Estimate (95% CI) (exponential model)	Estimate (95% CI) (quadratic-exponential model)
α	0.823	-0.743
β	0.024 (0.008 – 0.040)	0.182
Γ		-0.0033 (-0.0053 to -0.0013)

exponential incidence $\lambda(t) = \alpha \exp(\beta(t))$

quadratic exponential incidence: $\lambda(t) = \alpha \exp(\beta(t)+\gamma(t)^2)$

t is the current quarter

The quadratic model predicts 11 diagnoses in the next year with 95% PI (4-19). The exponential model predicts 25 cases (15-37). Note that a cubic term was also fitted but was not significant (p=0.42, term= - 0.00009).

The current quarterly incidence estimated from the quadratic model is 3.5 compared to 5.9 from the exponential model. The data along with the exponential and quadratic models are shown in Figures 4a and 4b. Assuming the exponential model is correct, the estimated time of the peak for diagnoses is August 2000 with a bootstrap 95% CI from September 1999 to January 2002. As with deaths a model using the annual data was also fitted in which incidence rose to a plateau. The residual deviance for this model was 10.0 on 6 d.f compared to 7.4 on 6 d.f. for the exponential model, indicating that neither model shows a lack of fit.

Figure4a: Observed (-o-) quarterly incidence of vCJD diagnoses
Fitted underlying trend (___) is given with its 95% confidence limits (...)

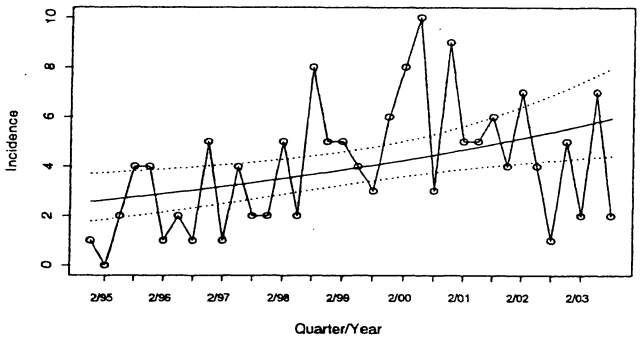


Figure4b: Observed (-o-) quarterly incidence of vCJD diagnoses
Fitted underlying Quadratic trend (___) is given with its 95% confidence limits (...)

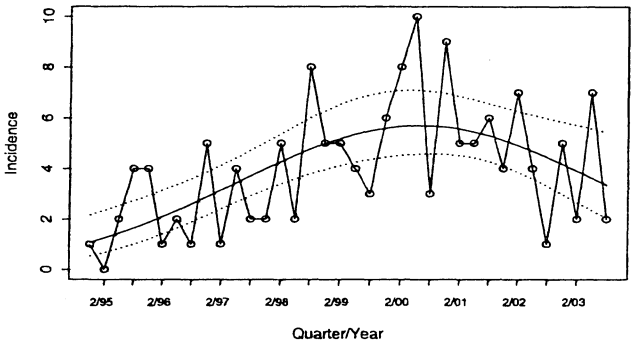
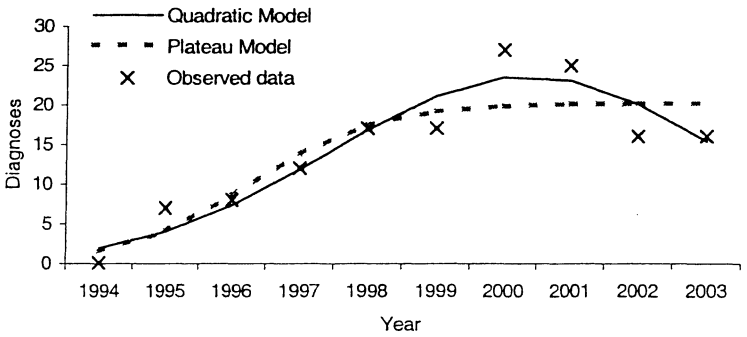


Figure 4c: Quadratic-exponential and plateau models for vCJD diagnoses incidence trend



4.2 Diagnosis results by Cohort

The results show highly significant differences in the shapes of the underlying incidence trends by birth cohort ($p<0.001$). This is mainly due to the recent increase in those born in 1980s. The pattern seen in the 1970s and pre-1970s is fairly similar. The fitted curves can be seen in Figures 5a, 5b and 5c. They appear to show that whilst the pre 1970s and 1970s cohort may be at a peak the 1980s cohort may still be increasing, note however that numbers are small in this cohort.

Figure5a: Quarterly incidence of vCJD diagnoses (born pre1970 cohort)
Fitted underlying quadratic trend is given with its 95% confidence limits

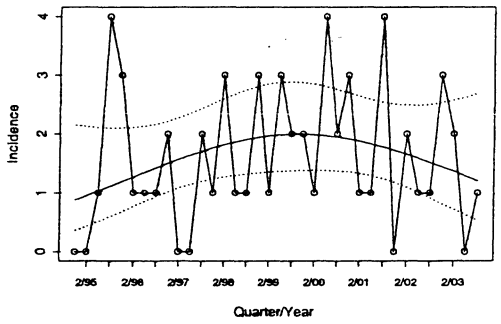


Figure5b: Quarterly incidence of vCJD diagnoses (born 1970s cohort)
Fitted underlying quadratic trend is given with its 95% confidence limits

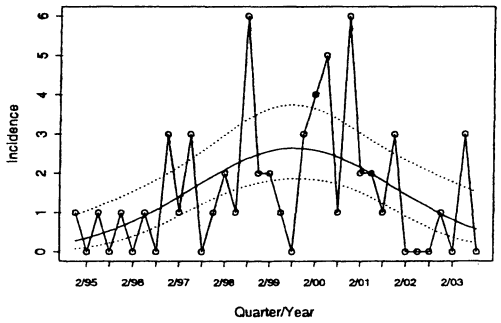
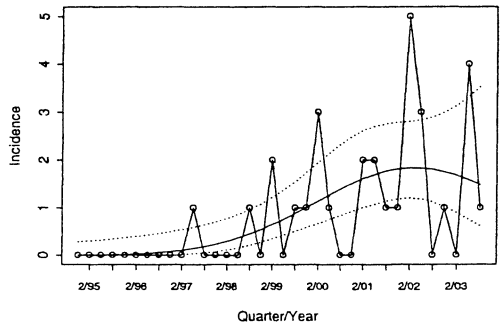


Figure5c: Quarterly incidence of vCJD diagnoses (born 1980s cohort)
Fitted underlying quadratic trend is given with its 95% confidence limits



文献 11

The predictability of the epidemic of variant Creutzfeldt-Jakob disease by back-calculation methods

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The predictability of the epidemic of variant Creutzfeldt–Jakob disease by back-calculation methods

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We present a back-calculation analysis of the variant Creutzfeldt–Jakob (vCJD) epidemic in the UK to estimate the number of infected individuals and to explore the likely future incidence of the disease. The main features of the model are that the hazard of infection was assumed proportional to the incidence of BSE in the UK with allowance for precautionary control measures taken in 1988 and in 1996, and that the incubation period distribution of vCJD follows an offset generalized *F* distribution. Our results indicate that current the numbers of cases with onset up to 31 December 2000 data are broadly compatible with numbers of primary infections ranging from a few hundred to several million. However, if a very large number of persons were infected, the model suggests that the mean incubation period is likely to be well beyond the human lifespan, resulting in a disease epidemic of much smaller size (maximum several thousand). A sensitivity analysis indicates that our results are sensitive to the underreporting of vCJD cases before 1996. Finally, we show that, in the absence of a reliable test for asymptomatic infection, uncertainty in estimates of the total number of infections is likely to remain for at least several years, even if the number of clinical cases remains low.

1 Introduction

Variant Creutzfeldt–Jakob disease (vCJD) is caused by an agent that is currently indistinguishable from that responsible for bovine spongiform encephalopathy (BSE) in cattle.[1–3] However, seven years after the identification of vCJD great uncertainty remains over how many individuals have been infected with the agent and how many of these individuals will go on to develop clinical disease.

In the absence of a test for asymptomatic infection, one approach to estimating the number of infected individuals is provided by back-calculation, a statistical technique developed in the context of the HIV/AIDS epidemic.[4,5] This approach utilizes the number of observed cases, and requires assumptions about the distribution of infection (exposure) over time and the incubation period distribution, to estimate how many individuals must have been infected to account for the number of observed cases. The estimate of the number of infected individuals is then used to make projections about the future incidence of the disease. Previous work has shown that the estimated number of infections/cases produced by this approach is very sensitive to

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the assumptions made about the incubation period distribution[6-8] and about the exposure pattern, *vide infra*.

In making predictions of the AIDS epidemic, it was possible to utilize information on incubation periods with respect to cases of AIDS with known dates of infection.[9] There are few such data to guide the choice of the form of the incubation period for vCJD. Without information about the incubation period distribution derived from other sources, it is unclear at what point during the epidemic it might be possible to make reasonably reliable estimates of the number of individuals infected and, consequently, future cases. This paper presents a back-calculation model developed to estimate the number of individuals incubating vCJD in the UK and discusses the epidemic's predictability within this framework.

2 Methods

2.1 Basic principle of back-calculation

The back-calculation method uses the fact that the number (and timing) of cases of disease that occur (which we can observe) depends on how many people were infected, when they were infected, and when the disease becomes apparent following infection – the incubation period.

Under certain assumptions we can formulate mathematically the relationship between these different components in terms of a number of parameters. Statistical techniques can be used to estimate these parameters and to make predictions within the framework of the model.

To apply this approach to the vCJD epidemic, we use data on when cases occur and make assumptions about when people were exposed to infection and the form of the incubation period distribution.

2.2 A back-calculation model for vCJD

The basic back-calculation equation can be written as:

$$n(t|\rho, \theta) = \int_a^b i(s|\rho) f(t - s|\theta)\, ds \qquad (1)$$

where $n(t|\rho, \theta)$ is the number of cases with disease onset at time t, $i(s|\rho)$ represents the number of individuals newly infected at time s, and $f(t - s|\theta)$ represents the incubation period distribution, ρ and θ being the unknown parameters of these two distributions (the distributions of infections and incubation periods). The times a and b are the lower and upper limits of the calendar time period on which it is assumed there was a non-zero risk of infection. The integration adds together individuals infected at different times but experiencing disease onset at the same time. When fitted to data on the number of cases with onset of disease at different times, the modelling process needs to take account of delays between disease onset and when the disease is diagnosed and reported as vCJD in national statistics. One way of doing this is to allow for such delays explicitly in the model, but this increases the number of parameters to be estimated.

To avoid this (and also at the request of the editor to ensure comparability between studies), we have chosen instead to model only data on onsets up to the end of 2000 on the basis that the current median delay between onset and diagnosis is around 10 months, so ascertainment of cases occurring up to the end of 2000 should be complete or almost complete. Of cases diagnosed since the start of 2001, only one (out of 41) had a delay of 18 months or more between onset and diagnosis.

2.3 Assumptions about the exposure pattern

In the context of vCJD, a plausible assumption regarding the hazard of infection over time is that it was approximately proportional to the incidence of cases of BSE (with some correction for different rates of underreporting of BSE at different times), with the 'constant' of proportionality varying over time as measures were implemented to prevent highly infectious material entering the human food supply. Figure 1 shows the number of cases of BSE reported annually. The data for the period 1982–98 have been adjusted for under-reporting as estimated by Donnelly *et al.*[10] In our model, we assume that the constant of proportionality (a component of ρ in Equation 1) is a step function with a partial step down at the end of 1989, when the specified bovine offals (SBO) ban was introduced (banning bovine brain and spinal cord, among other tissues, from human consumption), and a further step down to zero in 1996, following the identification of variant CJD and the introduction of the over 30 months scheme

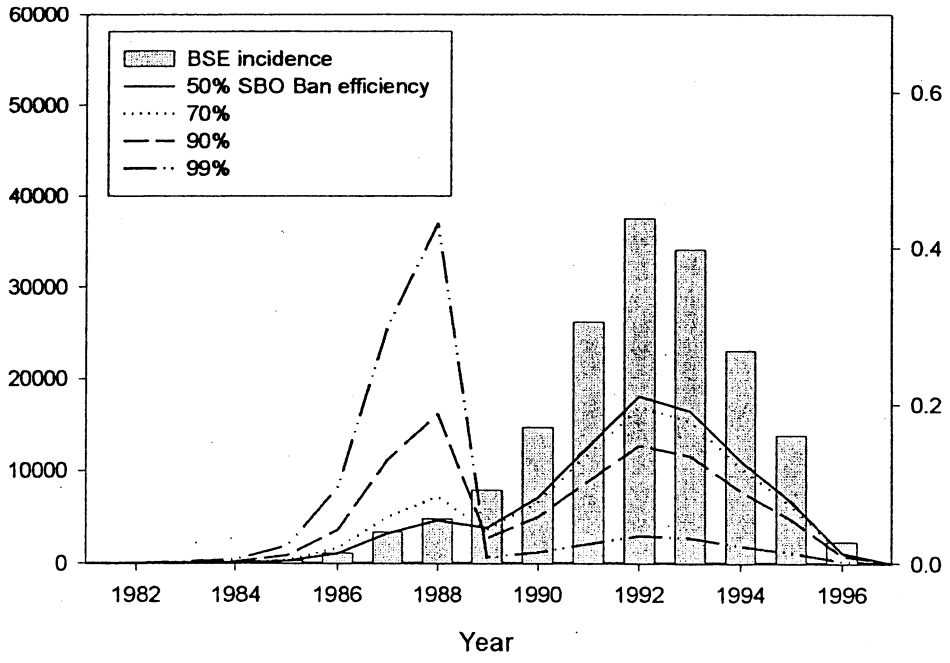

Figure 1 BSE incidence and hazard density of infection of the vCJD back-calculation mode for various values of specified bovine offal (SBO) ban efficiencies. BSE incidence is plotted on the left scale. The hazard densities are normalized and are plotted on the right scale.

(OTMS) preventing cattle over the age of 30 months entering the human food supply. It was assumed that the decision in August 1988 to remove reported clinical cases from human food chain had a significant effect only from 1989. There are no reliable data on the rigour with which the SBO ban was enforced and for some sources of infectivity (e.g., mechanically recovered meat, MRM) it may have had little impact on human exposure to BSE.[11] In the model, we assume that the SBO ban reduced the baseline hazard function by 90%. This percentage can be interpreted as the effectiveness of the 1989 SBO ban. In sensitivity analyses, we allow this proportion to vary between 50 and 100%. The corresponding hazard density functions for human exposure over time are shown in Figure 1 (showing 50, 70, 90 and 99% effectiveness). Clearly, changes in assumptions about the effectiveness of the SBO ban can have a significant impact on the shape of the hazard function.

The expected number of new infections at time s (in one time unit) can be written as $r(s) \times N_{sus}(s)$, where $N_{sus}(s)$ represents the susceptible population at time s, and $r(s)$ is the hazard of infection at time s [assumed to be proportional to the number of BSE cases–$I_{BSE}(s)$, i.e. $r(s) = \rho(s) I_{BSE}(s)$]. If a substantial proportion of the population becomes infected over the course of the exposure period then $N_{sus}(s)$ will decline over time. It can be shown that for a fixed cohort of individuals

$$N_{sus}(s) = \exp[-R(s)] \times N_{sus}(0)$$

where $R(s)$ is the cumulative hazard of infection up to time s. Then, we can express the number of infections occurring at time s as

$$i(s|\rho) = r(s) \times \exp[-R(s)] \times N_{sus}(0)$$

This equation assumes that the total population in the cohort (infected + susceptible) remains constant over the period of exposure (i.e., that changes in the cohort through death or migration are negligible in the period during which infection may have occurred).

2.4 Taking account of age

Any back-calculation model for vCJD will need to take age into account for two reasons. First, vCJD incidence is strongly related to age with roughly half of all cases having disease onset between the ages of 20 and 30 years. This suggests that either exposure or susceptibility or both are strongly age related. The possibility that this age distribution is explained entirely by variations in incubation period with age appears increasingly unlikely as the age distribution of the cases has remained largely unchanged throughout the epidemic so far. Secondly, for a disease such as vCJD with a long incubation period, some infected individuals will die of other unrelated causes before they develop symptoms of vCJD and the probability of this happening will vary with age. To address these issues we incorporate the age structure of the UK population into

the model and include in the equation a term for the probability of surviving from infection to disease onset. We can rewrite Equation (1) for a particular birth cohort c as:

$$n(t, c|\rho, \theta) = \int_a^b i(s, c|\rho)u(s, t, c)f(t - s|\theta)\,\mathrm{d}s \qquad (2)$$

Here $n(t, c)$ represents the expected number of cases from birth cohort c with disease onset at time t, $i(s, c|\rho)$ represents the expected number of individuals from birth cohort c newly infected at time s and $u(s, t, c)$ represents the proportion of individuals from birth cohort c who will survive to the time t among those who have survived up to time s. These survival probabilities are derived from census data and they are not estimated in the fitting of the back-calculation model itself.

To take into account variation in exposure/susceptibility to infection between birth cohorts, the hazard of infection must be allowed to vary with birth cohort in the above equation (i.e., the function r is allowed to vary with c as well as with s). In order for the parameters of the model to be estimable, we must make some assumptions about the way in which $r(s, c)$ varies with c (birth cohort). One possible approach is to assume that $r(s, c)$ can be rewritten as $\phi(s)\eta(c)$, which assumes that the dependency of the hazard on birth cohort does not vary over time. That is, changes in the risk of infection at different times affect the different age groups proportionally. This yields the following expression for the distribution of infection over time:

$$i(s, c|\rho) = \phi(s|\rho)\eta(c) \times \exp[-\eta(c)\Phi(s|\rho)] \times N(0, c)$$

where $\Phi(s|\rho)$ represents the cumulative value of $\phi(s|\rho)$. In this equation, the time dependence in the proportionality factor is contained in the function $\phi(s)$ and the function $\eta(c)$ represents the relative exposure/susceptibility of the birth cohort c. In the model fitting, $\eta(c)$ was derived from the birth cohort distribution of observed cases, assuming the susceptibility/exposure for a given birth cohort was proportional to the incidence of vCJD in that birth cohort. For birth cohorts 1939 backward, the susceptibility/exposure factor was arbitrarily set to one-third of the one of the cohort 1940–44. This was done to avoid gaps in the susceptibility/exposure function. Hence, by construction, the birth cohort – and therefore the age – distribution of the cases expected from the model closely matches the observed age distribution of cases. The validity of this simplification of the model depends upon the assumption that incubation period does not vary with age at infection, an assumption also encapsulated in the absence of any dependence of $f(t - s|\theta)$ on c (see below).

The unknown components in Equation (2) are the incubation period distribution, $f(t - s|\theta)$, and the absolute level of the hazard of infection over time $r(s, c)$. In back-calculation models developed in the context of AIDS, the distribution of the incubation period, $f(t - s|\theta)$ is often assumed to follow a lognormal, gamma or Weibull distribution. However, it has been argued that these common two-parameter distributions may be poor representations of the true incubation period distribution and that the use of a more flexible distribution is desirable.[12] Some authors have suggested the use of a modified lambda distribution.[7] This probability distribution is defined from its inverse

cumulative density function and there is no closed form for the density function itself, making parameter estimation more difficult. In our analysis, it is assumed, initially, that the incubation period of vCJD follows an offset generalized F distribution, a five-parameter distribution that includes most of the classical two-parameter distributions as special cases and which can take a wide variety of shapes.[13] The offset in the incubation period distribution is used to describe a latent period following infection where onset cannot occur. Such a latent period has been observed during all experimental transmission of all types of TSE agents. We also assume that the incubation period distribution does not vary with age at infection or time of infection.

2.5 Parameter estimation and confidence intervals

We fitted a discrete formulation (annual) of the above model to observed cases with onsets up to the end of 2000. To obtain parameter estimates, we maximized the likelihood of the observed data under the assumption that the observed numbers of cases follow a Poisson distribution with mean equal to the expected number of cases obtained using the back-calculation equation.

An initial sensitivity analysis was performed to evaluate the impact of changing the exposure pattern (the support of the hazard of infection) on the estimates and their uncertainty. The various baseline hazard functions are displayed in Figure 1 with bars showing the number of observed clinical BSE cases. These hazard functions have been normalized so that each has a total area of 1. Hazard functions for scenarios with high SBO ban effectiveness therefore have higher density before the SBO ban than those for scenarios with lower SBO ban effectiveness. Another sensitivity analysis was performed to evaluate the impact of any underreporting of vCJD cases before 1996. The model was fitted again with the number of unidentified vCJD cases occurring before 1996 arbitrarily set to 1, 2, 4 and 6. The birth cohorts of these unidentified cases were assumed to be distributed as in the current observed cases.

The simultaneous estimation of all the model parameters needed care because the likelihood function is very flat. That is, different combinations of the parameter values of the incubation period distribution and the number of infections result in almost the same likelihood value. We had to be careful, therefore, to ensure that we found the global maximum likelihood.

We approached this problem by estimating only the parameters of the incubation period distribution, and repeating this estimation across the full range of possible numbers of infections and for different assumptions concerning the effect of the SBO ban, and by using two optimization algorithms successively. The parameters were first estimated using the direction set or Powell's method (computer program developed specifically for this purpose) and the results were then checked using dual quasi-Newton optimization (available from SAS PROC IML routine), with derivatives approximated by finite differences.[14]

There are different ways to quantify the uncertainty around parameter estimates. In the context of likelihood inference, two approaches can be distinguished: the quadratic approximation to the log-likelihood ratio and the profile likelihood. Because the vCJD data are truncated there is a strong natural correlation between parameter estimates.[15] This means that the use of the quadratic approximation to the log-likelihood ratio will inevitably lead to an underestimate of the width of the confidence interval, and we must

therefore use the profile likelihood approach. Bootstrap techniques can also be used to estimate confidence intervals.[16] In the present situation, however, this approach presents some technical problems. Bootstrapping consists of resampling the incidence data and then refitting the model described. All this has to be repeated many times. As mentioned above, the process of fitting the model requires a lot of attention to ensure that the correct solution is obtained, a process which cannot be automated easily.

For a given expected number of infections, and corresponding estimates of the incubation period distribution parameters, the expected number of clinical cases that will occur in the future can be estimated (taking into account survival). Obtaining a confidence interval for the expected number of future cases is more problematic because this number does not appear explicitly in the model, and is a nonlinear function of the model parameters which do appear explicitly (level of the hazard of infections, incubation period distribution, survival).

In order to explore the upper limit of uncertainty around future expected numbers of cases and to obtain 95% confidence intervals for short-term predictions, we fitted models in which the numbers of clinical cases for the years 2005, 2010 and 2020 were set to values between the point estimate and several hundreds and then calculated the likelihood of the data up to 2000 and compared this with the likelihood for the best-fit model to identify numbers of cases which produced a log-likelihood ratio statistic of 3.84 (1 df).

3 Results

In all models whose results are presented here, the susceptible population was assumed to be individuals who are methionine homozygotes at codon 129 of the PRNP gene since all cases to date have been of this genotype. This genotype is estimated to represent about 40% of the general UK population.[17] This, along with the observed age distribution of cases and the assumption that the incubation period distribution does not vary with age at infection, enables us to put a rough initial upper bound on the number of individuals who could conceivably have been infected of around 12 million. This number is obtained by considering the worst case scenario where the prevalence of infection in the birth cohort born between 1970–75 (the birth cohort with maximum incidence observed so far) reaches 100% and that the relative prevalence of infection in other birth cohorts matches the current birth cohort distribution of observed cases. By definition, the marginal age distribution of predicted cases matches almost exactly that of observed cases. However, our conclusions apply only to the methionine homozygous section of the population.

Allowing a very flexible incubation period distribution, we found that the cases observed to the end of 2000 were compatible with almost any number of infections up to several million, with the profile log likelihood for the number of infections very flat over a wide range (Figure 2). However, for the model to predict a very large number of infections required the average incubation period to be very long and, in most instances, well beyond the normal human lifespan. As a result, the corresponding epidemic sizes (expected numbers of clinical cases) lay within a much narrower range, from a few hundred to a few thousand cases (Table 1).

Our results are particularly sensitive to the assumptions we make about the form of the incubation period distribution. Making stronger assumptions about the incubation

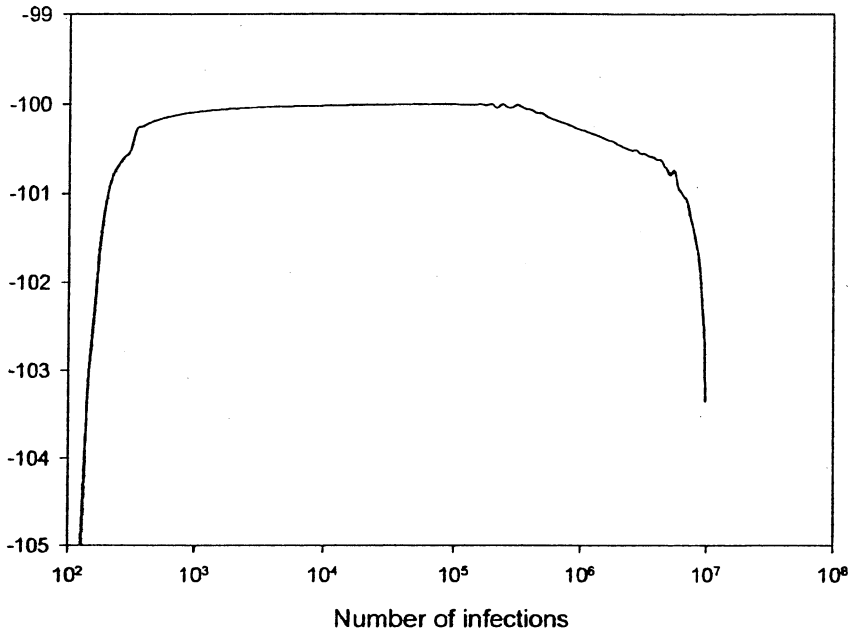

Figure 2 Profile log-likelihood for the back-calculation model assuming that the incubation period distribution follows an offset generalized *F*-distribution.

period distribution (e.g., assuming no offset or constraining the distribution to be log-normal, Weibull or gamma) reduces substantially the upper limits on the expected number of infected individuals (Table 1) but has little impact on point estimates of the expected total number of cases.

Table 2 shows the prediction intervals for the number of cases in the end of the years 2005, 2010 and 2020. For each postulated incubation period distribution, the table gives the central estimate for the number of clinical cases for each year and upper 95 and 99% confidence limits. The last column gives the total epidemic size corresponding to the point estimate and to the 95 and 99% limits. These results indicate that under most assumptions the annual expected number of vCJD death is unlikely to exceed 100 cases per year.

Results with respect to the expected numbers of clinical cases under different assumptions about the incubation period distribution are shown in Figure 3. Three different sets of expected numbers of clinical cases are shown for each different incubation period distribution: expected cases corresponding to the central estimate for the number of infections; expected numbers of cases corresponding to the upper 95 and 99% prediction limits for 2005. Figure 4 shows the corresponding shapes of incubation period distributions, revealing that, in scenarios where the expected number of infection is very large, the mean incubation is very long and, in some instances, the distribution is almost uniform.

The exposure pattern (i.e., the incidence of BSE used as the support for the hazard of infection) used in the model is based on confirmed clinical cases together with some

Table 1 Maximum likelihood estimates of number of infections and corresponding epidemic sizes (clinical cases) assuming an SBO ban effectiveness of 90%

Incubation period distribution	No. of parameters	Log likehood+ constant	Estimated number of infections (expected number of clinical cases)	95% limits for expected number of infection (corresponding range of expected number of clinical cases)	Median incubation period in years (90th percentile)	Median incubation period (years) corresponding to upper 95% confidence limit for expected number of infections
Offset generalized *F*	5	−100.0	Unrestricted[a] (1500)	Unrestricted (170–1500)	10.0 (15.8)	>150
Generalized *F* (no offset)	4	−100.8	250 (240)	143–2700 (142–1600)	10.1 (15.5)	36.2
Offset log-normal	3	−100.1	800 (450)	144–25000 (142–2900)	34.8 (>150)	>150
Offset Weibull	3	−100.1	550 (470)	144–14000 (143–4400)	17.3 (51.1)	67.6
Offset gamma	3	−100.5	310 (300)	108–27000 (107–5000)	11.3 (18.3)	100.3
Log-normal (no offset)	2	−101.2	230 (230)	144–1400 (143–1200)	10.0 (13.2)	22.7

[a]The data were compatible with any number of infections up to 12 million (maximum allowed in the model, cf. text).
The number in brackets is the point estimate of the number of clinical cases for 12 million infections.

Table 2 Upper prediction limits for the expected number of cases in the years 2005, 2010 and 2020 and corresponding total epidemic sizes assuming an SBO ban effectiveness of 90%

Incubation period distribution	Expected number of cases in year (upper 95% and 99% limits[a])			Corresponding total number of clinical cases expected over the whole epidemic[b]		
	2005	2010	2020	2005	2010	2020
Offset generalized *F*	22 (57; 77)	17 (67; 102)	13 (83; 148)	(2800; 4800)	(3100; 5400)	(3400; 6200)
Generalized *F* (no offset)	16 (51; 66)	3 (48; 83)	0 (35; 90)	(770; 1100)	(1200; 2300)	(1400; 3300)
Offset log-normal	21 (51; 71)	8 (48; 103)	1 (61; 291)	(820; 1600)	(1000; 3100)	(2200; 16 000)
Offset Weibull	19 (49; 69)	12 (57; 87)	6 (61; 101)	(1000; 1800)	(1800; 3000)	(2400; 3800)
Offset gamma	21 (51; 76)	14 (64; 124)	7 (112; 137)	(820; 2100)	(1700; 9400)	(5000; 5900)
Log-normal (no offset)	16 (51; 76)	1 (51; 96)	0 (30; 120)	(690; 1400)	(1100; 2400)	(1300; 4000)

[a]Limits of 95 and 99% were obtained by fitting the vCJD model to incidence data where the numbers of cases in 2005, 2010 and 2020 were increase step-by-step. The threshold used to determine the upper bounds was the likelihood ratio test.
[b]Expected number of cases over the whole epidemic when the incidence in a given year is set to its upper 95% (respectively 99%) confidence limit.

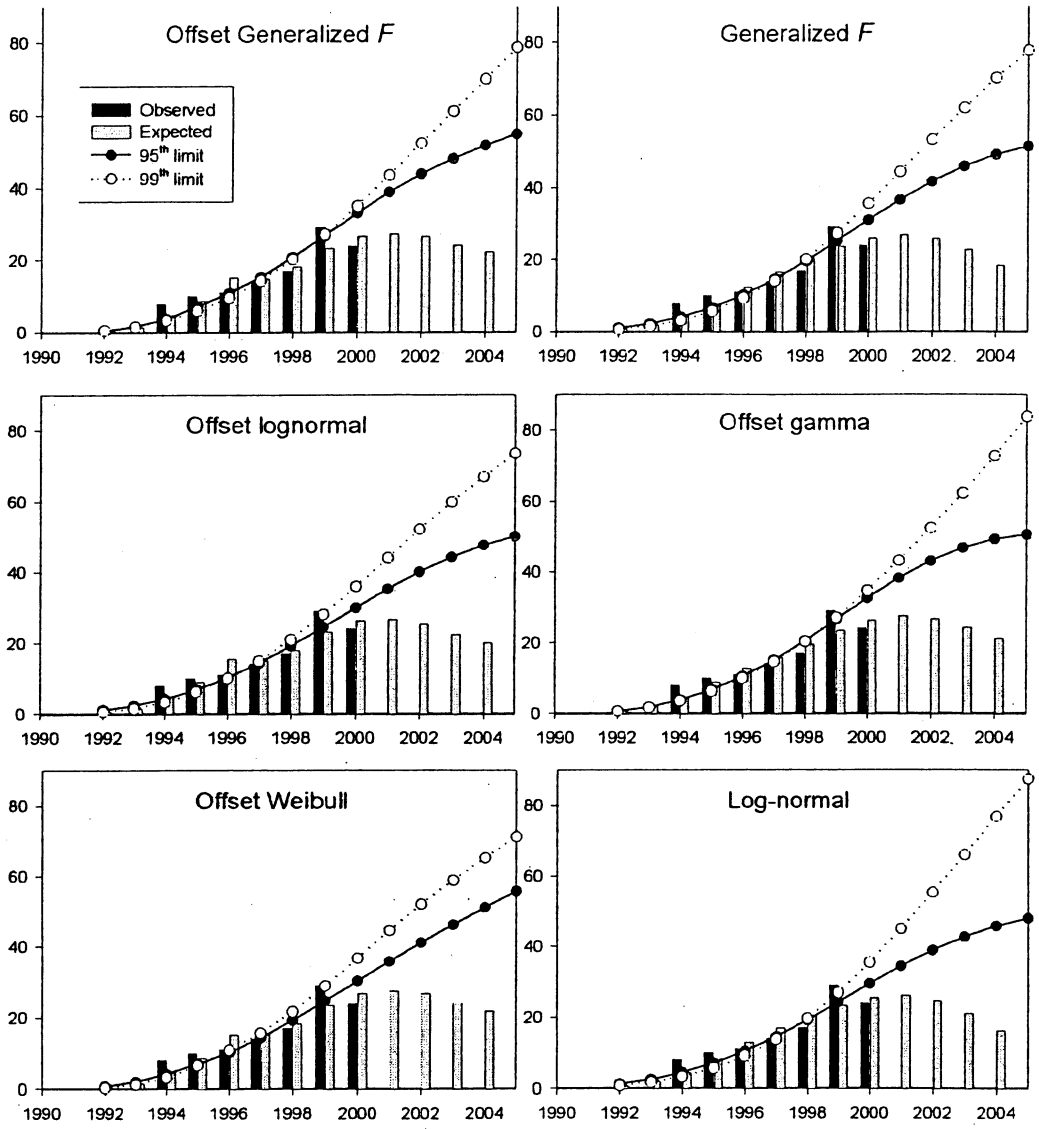

Figure 3 Observed and expected numbers of vCJD cases with upper prediction limits for the expected number of cases (95th and 99th).

adjustment for under-reporting early on in the epidemic based on estimates obtained from a back-calculation model published earlier.[10] This is unlikely to be the exact representation of exposure, in particular, at the beginning of the period, when under-reporting may have been greatest. Two different sensitivity analyses regarding the exposure pattern used in the model were performed. First, we examined the impact of different assumptions about the effectiveness of the SBO ban (Tables 3 and 4).

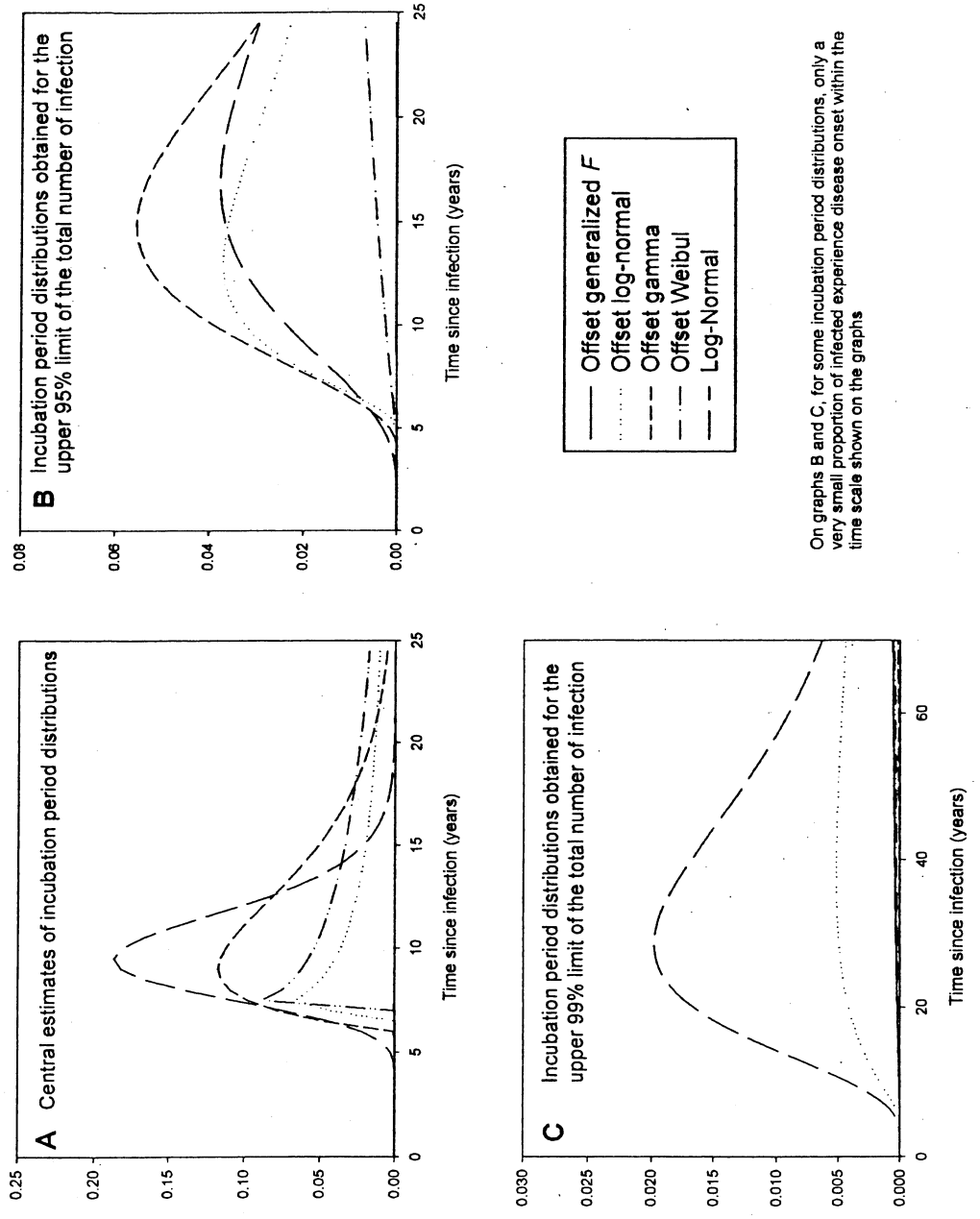

Figure 4 Incubation period distributions.

Table 3 Sensitivity analysis: impact of varying assumptions about the effectiveness of the SBO ban and the extent of under-reporting early in the BSE epidemic

Incubation period distribution	Parameter	100% BSE reporting	50% SBO ban efficiency	70% SBO ban efficiency	90% SBO ban efficiency	99.9% SBO ban efficiency
Offset generalized *F*	Estimated number of infections (expected cases)	Unrestricted (2400)[a]	Unrestricted (1100)	Unrestricted (1700)	Unrestricted (1500)	Unrestricted (960)
	Mean incubation period (90th percentile), in years	10.0 (16.0)	7.7–∞ (8.4–∞)	7.9–∞ (8.8–∞)	8.8–∞ (11.2–∞)	12.7–∞ (18.5–∞)
	95% confidence limits for numbers of infections (expected cases)	Unrestricted (105–2400)	Unrestricted (115–1100)	Unrestricted (127–1700)	Unrestricted (170–1500)	Unrestricted (203–960)
Offset gamma	Estimated number of infections (expected cases)	260 (250)	160 (160)	210 (210)	310 (300)	5400 (2000)
	Mean incubation period (90th percentile), in years	10.1 (15.9)	7.7 (8.7)	9.2 (11.9)	11.3 (18.3)	80.4 (>150)
	95% confidence limits for numbers of infections (expected cases)	140–1 100 000 (140–19 000)	108–260 (107–250)	108–1100 (107–750)	108–27 000 (107–5000)	158–1 200 000 (156–19 000)
Offset log-normal	Estimated number of infections (expected cases)	230 (230)	140 (140)	170 (170)	230 (230)	310 (300)
	Mean incubation period (90th percentile), in years	9.5 (14.3)	7.5 (8.0)	8.3 (9.5)	10.0 (13.2)	14.7 (20.6)
	95% confidence limits for numbers of infections (expected cases)	108–19 000 (107–4400)	108–230 (107–230)	119–280 (118–280)	144–1400 (143–1200)	144–17 000 (142–7300)

[a]The data were compatible with any number of infections up to 12 million (maximum allowed in the model, cf. text). The number in brackets is the point estimate of the number of clinical cases for 12 million infections.

Table 4 Sensitivity analysis: variations with vCJD under-reporting

Distribution	Parameter	One case before 1996	Two cases before 1996	Four cases before 1996	Six cases before 1996
Offset generalized *F*	Estimated number of infections (expected cases)	Unrestricted[a] (1500)	Unrestricted (1500)	Unrestricted (1500)	Unrestricted (1500)
	Mean incubation period (90th percentile), in years	>150 (>150)	>150 (>150)	>150 (>150)	>150 (>150)
	95% limits for number of infections (expected cases)	Unrestricted (153–1500)	Unrestricted (153–1500)	Unrestricted (153–1500)	Unrestricted (140–1500)
Offset gamma	Estimated number of infections (expected cases)	800 (710)	800 (700)	1100 (840)	1100 (830)
	Mean incubation period (90th percentile), in years	24.2 (45.0)	24.6 (46.1)	31.6 (61.5)	32.0 (62.6)
	95% limits for number of infections (expected cases)	108–48 000 (107–6000)	108–110 000 (107–7900)	158–1 800 000 (157–20 000)	108–7 300 000 (107–32 000)
Offset log-normal	Estimated number of infections (expected cases)	230 (230)	260 (250)	280 (280)	410 (400)
	Mean incubation period (90th percentile), in years	10.2 (13.5)	10.7 (14.7)	11.3 (16.3)	14.3 (22.7)
	95% limits for number of infections (expected cases)	144–4100 (143–2700)	144–7900 (143–3900)	144–13 000 (143–4800)	131–7 200 000 (130–18 000)

[a]The data were compatible with any number of infections up to 12 million (maximum allowed in the model, cf text).
The number in brackets is the point estimate of the number of clinical cases for 12 million infections.

A second analysis was performed to evaluate the sensitivity of the results to the degree of under-reporting assumed for clinical BSE in the early 1980s (i.e., no under-reporting of BSE cases). The different corresponding ranges of baseline hazard of infection are displayed in Figure 1. Confidence bounds were sensitive to the assumptions made about the exposure pattern. First, when assuming 100% reporting of BSE incidence, the expected number of cases arising when the number of infections attains its upper bound was increased to about 20 000 (instead of 5000). A similar increase was observed when varying the SBO ban efficiency. However, the impact on point estimates was small (except with the offset gamma distribution for extreme scenarios).

The model was sensitive to under-reporting of vCJD cases before 1996. Point estimates of the predicted number of cases varied slightly (although remaining of the same order of magnitude) but confidence limits were much wider. When allowing for six unseen vCJD cases before 1996, the predicted number of cases corresponding to the upper 95% confidence limit for the number of infections reached 32 000.

4 Discussion

Except for the scenario in which six or more vCJD cases were missed at the beginning of the epidemic, none of our models suggest that the number of primary cases of vCJD in methionine homozygotes is likely to be more than a few thousand, and in most scenarios our best estimates for the number of cases are of the order of a few hundred. However, the number of primary infections underlying the observable clinical cases could be anything from a few hundred to many thousands or even millions. In interpreting these results, and extrapolating them to other codon 129 genotypes, we must bear in mind our model assumptions. Our key finding that, regardless of the number of infections that have occurred, the expected number of clinical cases is unlikely to exceed a few thousand (in any one genotype), is sensitive to a number of assumptions. The principal model assumptions are listed below and discussed.

- The model is restricted to the 40% (approximately) of the UK population assumed to be methionine homozygous at codon 129 of the PrP gene. (All cases of vCJD identified to date have been of this genotype.)
- The incubation period of the disease is assumed to follow an offset generalized *F*-distribution, which is a unimodal five-parameter distribution. As special cases of the generalized *F*-distribution we also investigated the log-normal, Weibull and gamma distributions.
- We assumed that the incubation period of the disease is independent of age at infection.
- The hazard of infection is assumed to have been proportional to the incidence of BSE. We did not consider onward, human-to-human, transmission of the infectious agent.
- Age-specific mortality rates for causes of death other than vCJD were obtained from national census data.

- The models were fitted to the data on cases with onsets prior to 2001 that had been identified by 31 July 2002 and, except in our sensitivity analyses, assume 100% reporting of vCJD cases in this period.

First, we have assumed in codon 129 methionine homozygotes, the incubation period for vCJD has a unimodal distribution. This is a key assumption that is open to question. It has long been known that in mouse models there are genetic factors lying outside the coding region of the PrP gene which have an important influence on the incubation period of TSEs.[18-21] It is possible, therefore, that among human codon 129 methionine homozygotes there are other, presently unknown genetic factors that influence the vCJD incubation period. In our work we have used the generalized *F*-distribution which can take a wide range of unimodal forms. If, across the methionine homozygous population, the mixture of other genetic factors affecting incubation period results in an overall incubation period distribution which is close to unimodal, we would be confident that, broadly, our findings with respect to the numbers of clinical cases hold. If, however, the overall incubation period distribution is strongly multimodal, there might be many more clinical cases of vCJD than our models predict. If the latter is the case, then the development of reliable back-calculation models will only be possible when the relevant genetic factors have been identified and measured in the population. Strong multimodality is most likely to apply if only a small number of other genetic factors are involved and there was little variation between infected individuals in the infecting dose to which they were exposed.

Secondly, we have assumed that the incubation period distribution does not vary greatly with age at infection. There is some experimental evidence in mice that, for a fixed dose, incubation period does vary with age at inoculation. However, this variation is small, with young mice having incubation periods that are seven days longer than older mice, compared with mean incubation periods of several hundred days.[22] An analysis of data on kuru suggests that the infectious dose to which an individual was exposed is more important in determining their incubation period than their age at infection.[23] The variations in mean incubation periods between different subgroups of the population likely to have been exposed to different amounts of infectivity were small relative to the variance of the estimated incubation period distribution. If vCJD infections occurred through diet, infected individuals are likely to have been exposed to varying infectious doses and kuru may provide a good analogy in this regard.

Thirdly, to extrapolate from codon 129 methionine homozygotes to other genotypes, we need to assume that across codon 129 genotypes the relationship between the mean and the variance of the incubation period distribution does not vary greatly. If other genotypes have longer mean incubation periods but with lower variance, then we might observe larger numbers of cases in these genotypes. It is, however, unusual for the variance of a distribution to decrease as the mean increases. If this is not the case, then to extend our results to include all genotypes one could, as a worst case scenario, multiply our predictions by about 2.5 to obtain a figure for the whole population.

A further assumption of the model is that infection was essentially through diet and that the amount of infectivity consumed in food during any given period was proportional to the number of BSE cases occurring up until 1996. In the absence of

ongoing human-to-human transmission of the vCJD agent, our findings are likely to be less sensitive to this assumption than they are to the assumptions about incubation period. Surprisingly, we found that the expected number of vCJD cases increased with the SBO ban effectiveness. The interpretation of this result is unclear. One possibility is that the effect of the increase of the SBO ban effectiveness is to increase the incubation period of the observed cases (by shifting the average time at infection to earlier dates). This could be an indication of a low species barrier and therefore increase the number of infected individuals.

Our models suggest that the number of primary cases of vCJD is unlikely to exceed a few thousand but that considerably greater uncertainty surrounds the number of primary infections with the vCJD agent that have occurred. Although the number of primary infections makes relatively little difference to the number of primary cases that will occur, whether a few hundred or many more people have been infected has important consequences for the potential risk of secondary transmission. Of concern in this regard is the observation in experimental TSE models that the mean incubation period with respect to transmission within species is substantially smaller than that the infection crossing into that species from another species.[24] The impact of secondary transmission on the dynamics of the epidemic could therefore be complex.

The possibility that many individuals might be infected with the vCJD agent but do not develop clinical disease in their lifetime also has important implications for the use and interpretation of any routine test for asymptomatic infection that may become available in the future. First, at the population level, a large number of positive test results would not inevitably imply a large number of clinical cases occurring in the future. Secondly, at the individual level, counselling of individuals testing positive will be challenging. In this context, such testing could also be used to investigate some of the strongest model assumptions, namely the constancy of incubation period with age, and the restriction of the model to individuals who are of the methionine–methionine genotype. This would be possible if age and genotype data on tested individuals are available.

Our work suggests that, in the absence of a reliable test for asymptomatic infection, considerable uncertainty about the number of infected individuals may remain for a number of years.

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文献 12

Department of Health

Annual summary of TSE-related research, April 2002-March 2003

DEPARTMENT OF HEALTH

ANNUAL SUMMARY OF TSE-RELATED RESEARCH
APRIL 2002 – MARCH 2003

SUMMARY OF ACTIVITIES

The Department, through its Research and Development Directorate, commissions research to inform its policy needs concerning human Transmissible Spongiform Encephalopathies (TSE) in the following areas

- Epidemiology and surveillance
- Blood safety
- Tissue infectivity and strain typing
- Diagnosis and detection
- The development and assessment of therapeutic drugs
- Decontamination.

During the period 1/4/02-31/3/03 12 contracts were completed, 55 were still in progress and 5 new contracts were commissioned.

The expenditure for this period was divided among the 6 main research topics as follows

Epidemiology and surveillance	£787,000
Blood safety	£47,000
Tissue infectivity and strain typing	£198,000

Diagnosis and detection	£2,277,000
Development and assessment of therapeutic drugs	£335,000
Decontamination	£1,030,000
Total expenditure for the year	**£4,674,000**

A complete list of projects is attached (Appendix A) and further details can be found on the MRC website, (www.mrc.ac.uk/tse_2c.htm) or in the DH National Research Register (NRR) (www.doh.gov.uk/research/nrr.htm) and DH ReFeR (www.doh.gov.uk/research/rd3/information/findings.htm) databases.

EPIDEMIOLOGY AND SURVEILLANCE

Mathematical analysis of the number of cases of variant Creutzfeldt-Jakob Disease (vCJD) reported each year indicated that the vCJD epidemic may have reached its peak, although all patients analysed so far were homozygous for methionine at ~~codon 129~~codon 129 of the prion protein gene. It may be envisaged that further cases in heterozygotes and valine homozygotes may occur in future years, if these individuals have longer disease incubation periods. Nation-wide surveys of atypical dementia in the elderly and progressive intellectual and neurological deterioration (PIND) in young children continued to fail to provide any evidence that cases were being missed in either the elderly or the very young.

After a fundamental re-assessment, extensive peer review and consideration by the SEAC Epidemiology Sub-Group, the case control study was restarted using a new protocol and initial results suggest that recruitment of controls has improved significantly.

The first PrP^{sc} positive sample of appendix tissue was reported by the Plymouth group and initiated widespread debate about the prevalence of disease. The completion of the prospective study had been delayed due to staff recruitment difficulties. The initiation of the national collection of tonsil tissue was also delayed by a slow passage through the ethics approval process, but ethical approval for this study was eventually granted and the Health Protection Agency (HPA) has agreed to carry out this task.

BLOOD SAFETY

Data continued to flow from the experiments studying transmission of infection through blood transfusion in sheep. Although infection rates appear low (20-25%) they were high enough to begin discussions over designing further experiments to study the ability of leucodepletion and the fractionation of blood products to remove prion infectivity. Support for the Transfusion Medicine Epidemiology Review (TMER) study, to identify possible transfusion-related cases of vCJD, was renewed. Although no prion detection system, suitable for blood screening, has yet been developed, DH convened a subgroup of MSBT to help the blood transfusion services prepare for the rapid introduction of a test, should one become available. The group, chaired by Professor Don Jeffries, met on two occasions and is due to report in the summer of 2003.

TISSUE INFECTIVITY

Newly commissioned research to analyse levels of infectivity in spinal cord, cerebro-spinal fluid, appendix, lymph modes, peripheral nerve, dorsal route ganglia, trigeminal ganglia and bone marrow has begun, but results are not expected before autumn 2003. Further work is intended to be commissioned to study infectivity in tissues and organs which have a major impact on the Department's risk assessments, such as eye, dental pulp, gingiva, distal ileum, skeletal muscle, kidney, adrenal gland, heart, liver and lung.

DIAGNOSIS AND DETECTION

The diagnosis of pre-clinical infection remains a major target of the DH programme of CJD-related research, but no suitable diagnostic assay has yet been announced. However all the research contracts recommended for support through the co-ordinated call for research proposals have now been awarded. In addition, further support was awarded to the MRC Prion Unit for the development of diagnostic monoclonal antibodies, and a contract was awarded to the National CJD Surveillance Unit to validate Magnetic Resonance Imaging as a diagnostic tool for all forms of human TSEs, bringing the total number of DH-funded contracts in this area to 13.

Although it is almost universally recognised that it is important to develop a non-invasive test which can detect individuals who are infected with CJD but not displaying clinical symptoms, opinion on how to use such a test is divided. Consequently the Chief Medical Officer for England has asked the Health Protection Agency to organise a workshop to debate ethical issues related to CJD diagnosis.

THE DEVELOPMENT AND ASSESSMENT OF THERAPEUTIC DRUGS

In addition to the expanded programme of research funded directly by DH, the MRC Prion Unit, in conjunction with the MRC Clinical trials Unit, undertook a substantial amount of work to develop a clinical trial protocol for quinacrine. This protocol was peer reviewed through the MRC, who recommended that the opinions of patient groups should be sought before a final decision is made. To this end a very successful one-day workshop with them was held in July 2002. In addition it was recommended that current clinical experience of quinacrine use in CJD therapy should be reviewed before a trial is started, and this data is being collected.

DECONTAMINATION

This major area of DH-funded research continues to grow, with 2 new contracts issued during this financial year. The work is overseen by the Working Group for Research into the Decontamination of Surgical Instruments, chaired by Professor Don Jeffries, and recent progress is summarised below.

Assessing damage to instruments from alkali autoclaving

This research is being carried out by Robert Somerville and Karen Fernie with their colleagues at the Neuropathogenesis Unit (NPU) at the Institute of Animal Health in Edinburgh. Tokens prepared from various grades of stainless steel have been subjected to typical hospital sterilisation protocols or to alkaline autoclaving. These protocols have been designed to simulate the conditions experienced by the average surgical instrument over 12 months. Surface damage has been assessed by visual inspection, scanning white light interferometry and electron microscopy. In general, apart from some surface discoloration, most stainless steels suffer little surface damage when subjected to these conditions and analysed by these methods. The only

exception being some grades of steel with a low nickel content, used in the manufacture of some of the cheaper imported instruments.

Recently commissioned research is concentrating on the evaluation of a commercial "alkali autoclave" and in determining whether less severe procedures involving alkali and heat treatment will be efficacious in removing prion infectivity.

Tissue loading on instruments from a typical hospital Sterile Services Department (SSD), before and after processing

Examination of instruments coming to a typical hospital SSD (Bart's) revealed that most instruments were contaminated with 60-100 mg of tissue, rather less (~30 mg) for brain tissue. These levels were consistent with the values assumed for the risk assessment calculations performed by EOR. After processing in the SSD, instruments are inspected visually and those that failed (~0.5%), i.e. had visible residues, were reprocessed.

Using novel chemical detection methods, commercial enzymic cleaners used in hospital SSDs removed greater than 99% of protein bound to surgical instruments after a single wash cycle. However further cycles removed little more than 1% of the remaining protein. However, once proteins had been dried onto instruments they were more difficult to remove and some proteins such as fibrinogen corroded steel surfaces during prolonged contact. It was of interest to note that most of the commercial cleaners used in hospital SSDs operate at pH 11 or above. It is possible therefore that the combination of these detergents with an efficient autoclave cycle could provide an acceptable level of prion inactivation.

These studies have now been extended to include dental instruments which show that many small reusable instruments such as root canal reamers become heavily contaminated with biological material which is not readily removed by procedures used in most dental surgeries.

Detection of prions on surfaces

Researchers at the Institute of Biotechnology in Cambridge have developed magnetic acoustic resonance sensors (MARS) for the detection of prions on surfaces. Initially it was not possible to improve the sensitivity of MARS as high acoustic frequencies

were absorbed by the steel. Other studies using Auger electron spectroscopy had demonstrated that the surface of stainless steel was essentially an oxidised layer of chromium. Consequently it was possible to simulate this stainless steel by coating optically polished silica glass with chromium and this material was not subject to the limitations of stainless steel itself. Using this technology prion concentrations as low as 62.5 μg/ml have been detected, although the detection limit of this technology has not yet been determined. Recently improvements have been made by employing novel high frequency acoustic generators which can increase sensitivity still further.

The efficacy of UV-ozone in cleaning these materials has been assessed by using X-Ray Photoelectron Spectroscopy to measure elemental nitrogen. Initial results however indicate that this method can remove only 95% of the total protein bound to the contaminated surface.

Denise Dear, also of the Institute of Biotechnology, has developed an enzyme linked immunosorbent assay (ELISA) using 5 mm steel discs to confirm the results obtained from MARS. This assay can detect PrP at between 100 and 10 ng/ml, although initial data suggest that changes in the confirmation of protein upon binding to the steel surface requires careful choice of the epitope specificity of the detector antibody.

The Centre for Applied Microbiology and Research (CAMR) group has developed a high sensitivity ELISA, based on thermostable adenylate kinases and capable of detecting material bound to solid surfaces at femtomolar or attomolar concentrations. In addition, a number of better thermostable enzymes from several thermophilic bacteria and archaea have been identified. The most suitable, from *Sulfolobus acidocaldarius*, has been cloned into *Escherichia coli* and expressed at a high level.

During the past year the group at the University of Southampton has developed rapid visual and epimicroscopy techniques to detect prions on steel surfaces. The technology is readily automated and could be adapted to screen instruments both before and after processing in a hospital SSD. This work has progressed rapidly and an agreement to exploit this technology has been signed with the commercial company Microgen Bioproducts.

Novel chemical and enzymic inactivants

CAMR is evaluating a series of highly efficient thermostable proteins, in conjunction with the biotechnology company GENENCOR.

Workers at NPU are studying the biochemical properties of PrP^{sc} which correlate with the relative differences in resistance to inactivation observed in various strains of TSEs. This group has also confirmed earlier observations that the disappearance of PrP^{sc} does not always correlate with inactivation and thus this may not always be a suitable surrogate marker for infectivity. Future work by this group will extend these studies to evaluate the ability of a number of enzymes, detergents and chaotropic agents to enhance the inactivation of TSEs. The ability of current hospital autoclave protocols to inactivate vCJD is also being evaluated.

Physical methods of inactivating prions

This year two research contracts have commenced, one to the commercial company CSMA and the other to the University of Edinburgh, to study the effects of high-energy gas plasmas on prions. Initial results show that this technology is capable of efficiently inactivating conventional micro-organisms and cleaning stainless steel surfaces. Experiments to study the effect on prion infectivity are under way and will be reported later this year.

The CSMA group is developing novel plasma generators and the Edinburgh group isare assessing commercially available equipment, but isare also developing novel fluorometric methods for detecting low levels of proteins on steel surfaces.

Detecting infectious prions bound to solid surfaces

Research in this area is carried out by Charles Weissmann, John Collinge and their colleagues at Imperial College. They have demonstrated that clean stainless steel wires exposed to the brains of scrapie-infected mice, or to brain homogenates, for as little as 5 minutes can efficiently transmit infectivity to indicator mice. These workers have also shown that infectivity bound to the wires persists for far longer in the brain than injected homogenates and prions remaining bound to the wires can transmit disease efficiently. Similar results are obtained with wires exposed to animals in both the preclinical and clinical stages of disease and with wires treated with infected spleens.

Some chemicals, such as sodium hydroxide and sodium isothiocyanate, were shown to efficiently remove infectivity bound to the wires, but formaldehyde did not. This group has also developed a mix of enzymes and detergents which they claim can efficiently remove prions from steel surfaces.

They have also shown that phosphatidylinositol-specific phospholipase C and a prion specific monoclonal antibody can not only prevent scrapie infection *in vitro*, but also cure chronically infected cells.

The group based at the Moredun Institute is carrying out similar studies using standard stainless steel spheres to provide a validated method whereby the efficacy of several potential inactivation agents can be assessed *in vivo*. Their first studies indicate that allowing material to dry onto surfaces increases by several orders of magnitude the resistance of prions to inactivation.

ACTIVITIES BY COMMERCIAL COMPANIES

1. Microgen Bioproducts plan to market the detection technology developed by Southampton University.
2. The MRC Prion Unit are approaching commercial companies about marketing its cocktail of decontamination chemicals
3. The Japanese-French company MENICON will shortly market its hypochlorite-based reagents for removing prions from contact lenses
4. The Canadian company TSO_3 has received FDA approval to market its UV Ozone technology in the USA and will shortly wish to market it in Europe.
5. The American company Steris Inc. are developing improved chemical methods for inactivating prions.
6. The alkali autoclave manufactured by WR^2 is being evaluated by NPU.
7. Thermostable prokaryotic enzymes for decontamination are being jointly developed by HPA-Porton and GENENCORE

Science and Engineering Group

From the rapid progress being made in this area a number of DH contractors are nearing the stage where they will be able to offer novel reagents or protocols for

formal evaluation. In addition, it is apparent that at least 3 commercial companies, MENICON, TSO_3 and Steris Inc. have reagents or technologies which are also close to formal evaluation or being released into the marketplace. Several research groups funded by DH have also formed partnerships with commercial companies or are about to do so. Consequently it was agreed at the January 2002 meeting of the Working Group on the Decontamination of Surgical Instruments to set up a Science and Engineering Group. This group, chaired by Darryn Kerr of NHS Estates, will consider ways in which these new processes can be formally evaluated and, where appropriate, brought into practice by the NHS. A pilot group to decide the remit and composition of this group met in May 2002.

資料一覧

資料１

http://www.oie.int/eng/info/en_esbmonde.htm

*Number of reported cases of bovine spongiform encephalopathy (BSE) worldwide**
(excluding the United Kingdom)

Updated: 10.06.2004 (fr)

	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Austria	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	...
Belgium	0	0	0	0	0	0	0	0	1	6	3	9	46	38	15	7(c)
Canada	0	0	0	0	1(b)	0	0	0	0	0	0	0	0	0	2(h)	...
Czech Republic	0	0	0	0	0	0	0	0	0	0	0	0	2	2	4	1(c)
Denmark	0	0	0	1(b)	0	0	0	0	0	0	0	1	6	3	2	0(c)
Finland	0	0	0	0	0	0	0	0	0	0	0	0	1(c)	0	0	...
France	0	0	5	0	1	4	3	12	6	18	31(a)	161 (d)	274(e)	239(f)	137 (g)	23(c)
Germany	0	0	0	1(b)	0	3(b)	0	0	2(b)	0	0	7	125	106	54	14(c)
Greece	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	...
Ireland	15(a)	14(a)	17(a)	18(a)	16	19(a)	16(a)	73	80	83	91	149 (d)	246(e)	333(f)	183 (g)	47(c)
Israel	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	...
Italy	0	0	0	0	0	2(b)	0	0	0	0	0	0	48	38(a)	29	...
Japan	0	0	0	0	0	0	0	0	0	0	0	0	3(e)	2	4(g)	2(c)
Liechtenstein	0	0	0	0	0	0	0	0	0	2(c)	0	0	0	0	...	...
Luxembourg	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0(c)
Netherlands	0	0	0	0	0	0	0	0	2	2	2	2	20	24	19	4(c)
Poland	0	0	0	0	0	0	0	0	0	0	0	0	0	4(f)	5	6(c)
Portugal	0	1(b)	1(b)	1(b)	3(b)	12	15	31	30	127	159	149	110	86	133	36(c)
Slovakia	0	0	0	0	0	0	0	0	0	0	0	0	5	6	2	2(c)
Slovenia	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1(c)
Spain	0	0	0	0	0	0	0	0	0	0	0	2	82	127	167	53(c)
Switzerland	0	2	8	15	29	64	68	45	38	14	50	33(d)	42	24	21(g)	0(c)
United Kingdom	see particular table															

* Cases are shown by year of confirmation.
... Not available

(a) *France: includes 1 imported case (confirmed on 13 August 1999).*
Ireland: includes imported cases: 5 in 1989, 1 in 1990, 2 in 1991 and 1992, 1 in 1994 and 1995.
Italy: includes 2 imported cases.
Portugal: includes 1 imported case (confirmed on 22 November 2000).

(b) *Imported case(s).*

(c) *Belgium - Data as of 30 April 2004.*

Czech Republic *– Data as of 17 January 2004.*
Denmark *– Data as of 30 April 2004.*
Finland *– Date of confirmation of the case: 7 December 2001.*
France *– Data as of 30 April 2004. Clinical cases = 6. Cases detected at rendering (bovines at risk) = 11. Cases detected as result of systematic screening at the abattoir = 6.*
Germany *– Data as of 31 March 2004.*
Ireland *– Data as of 31 March 2004. Clinical cases = 12. Cases detected by the active surveillance programme = 35.*
Italy *– Data as of 30 January 2002.*
Japan *– Data as of 11 March 2004.*
Liechtenstein *– Date of the last confirmation of a case: 30 September 1998.*
Luxembourg *– Data as of 31 May 2004.*
Netherlands *– Data as of 30 April 2004.*
Poland *– Data as of 26 May 2004.*
Portugal *– Data as of 30 April 2004*
Slovakia *– Data as of 31 March 2004.*
Slovenia *– Data as of 29 March 2004.*
Spain *– Data as of 3 June 2004.*
Switzerland *– Data as of 28 May 2004.*

(d) ***France year 2000*** *– Clinical cases = 101. Cases detected within the framework of the research programme launched on 8 June 2000 = 60*
Ireland year 2000 *– Clinical cases = 138. Cases identified by active surveillance of at risk cattle populations = 7. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 4.*
Switzerland year 2000 *– Clinical cases = 17. Cases detected within the framework of the investigation programme = 16*

(e) ***France year 2001*** *– Clinical cases = 91. Cases detected at rendering (bovines at risk) = 100 (out of 139,500 bovines tested). Cases detected as result of routine screening at the abattoir = 83 (out of 2,373,000 bovines tested).*
Ireland year 2001 *– Clinical cases = 123. Cases identified by systematic active surveillance of all adult bovines = 119. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 4.*
Japan year 2001 *– Clinical cases = 1. Cases detected as result of screening at the abattoir = 2.*

(f) ***France year 2002*** *– Clinical cases = 41. Cases detected at rendering (bovines at risk) = 124 (out of 274,143 bovines tested). Cases detected as result of systematic screening at the abattoir = 74 (out of 2,915,103 bovines tested). The active BSE surveillance programmes implemented in France in 2002 led to routine examination of cattle aged over 24 months, which were slaughtered for consumption purposes, were euthanised or died due to other reasons.*
Ireland year 2002 *– Clinical cases = 108. Cases detected by the active surveillance programme = 221. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 4.*
Poland year 2002 *– Clinical cases = 1. Cases detected as result of routine screening at the abattoir (cattle over 30 months) = 3.*

(g) ***France year 2003*** *– Clinical cases = 13. Cases detected at rendering (bovines at risk) = 87. Cases detected as result of systematic screening at the abattoir = 37.*
Japan *– Data as of 5 November 2003. The 9th case was a bullock aged 21 months.*
Ireland year 2003 *– Clinical cases = 41. Cases detected by the active surveillance programme = 140.*
Switzerland year 2003 *– Clinical cases: 8. Cases detected within the framework of the official surveillance programme: 11. Cases detected through voluntary testing following routine slaughter: 2.*

(h) 1 case diagnosed in Canada in May 2003 + 1 case diagnosed in the United States of America in December 2003 and confirmed as having been imported from Canada

資料２

http://www.dh.gov.uk/PublicationsAndStatistics/PressReleases/PressReleasesNotices/fs/en?CONTENT_ID=4074900&chk=553JlD

Monthly Creutzfeldt Jakob disease statistics March 2004

Published: Monday 1 March 2004
Reference number: 2004/0084

The Department of Health is today issuing the latest information about the numbers of known cases of Creutzfeldt Jakob disease. This includes cases of variant Creutzfeldt Jakob disease (vCJD) - the form of the disease thought to be linked to BSE. The latest results which are correct as at *1 March 2004 can be seen by clicking on the link below.

Summary of vCJD cases

Deaths

Deaths from definite vCJD (confirmed): 103
Deaths from probable vCJD (without neuropathological confirmation): 35
Deaths from probable vCJD (neuropathological confirmation pending): 1
Number of deaths from definite or probable vCJD (as above): 139

Alive
Number of definite/probable vCJD cases still alive: 7

Total number of definite or probable vCJD (dead and alive): 146
The next table will be published on Monday 5th April 2004

Referrals: a simple count of all the cases which have been referred to the National CJD Surveillance Unit for further investigation in the year in question. CJD may be no more than suspected; about half the cases referred in the past have turned out not to be CJD. Cases are notified to the Unit from a variety of sources including neurologists, neuropathologists, neurophysiologists, general physicians, psychiatrists, electroencephalogram (EEG) departments etc. As a safety net, death certificates coded under the specific rubrics 046.1 and 331.9 in the 9th ICD Revisions are obtained from the Office for National Statistics in England and Wales, the General Register Office for Scotland and the General Register Office for Northern Ireland.

Deaths: All columns show the number of deaths that have occurred in definite and probable cases of all types of CJD and GSS in the year shown. The figures include both cases referred to the Unit for investigation while the patient was still alive and those where CJD was only discovered post mortem (including a few cases picked up by the Unit from death certificates). There is therefore no read across from these columns to the referrals column. The figures will be subject to retrospective adjustment as diagnoses are confirmed.

Definite cases: this refers to the diagnostic status of cases. In definite cases the diagnosis will have been pathologically confirmed, in most cases by post mortem examination of brain tissue (rarely it may be possible to establish a definite diagnosis by brain biopsy while the patient is still alive).

Probable vCJD cases: are those who fulfil the 'probable' criteria set out in the Annex and are either still alive, or have died and await post mortem pathological confirmation. Those still alive will always be shown within the current year's figures.

Sporadic: Classic CJD cases with typical EEG and brain pathology. Sporadic cases appear to occur spontaneously with no identifiable cause and account for 85% of all cases.

Probable sporadic: Cases with a history of rapidly progressive dementia, typical EEG and at least two of the following clinical features; myoclonus, visual or cerebellar signs, pyramidal/extrapyramidalsigns or akinetic mutism.

Iatrogenic: where infection with classic CJD has occurred accidentally as the result of a medical procedure. All UK cases have resulted from treatment with human derived pituitary growth hormones or from grafts using dura mater (a membrane lining the skull).

Familial: cases occurring in families associated with mutations in the PrP gene (10 - 15% of cases).

GSS: Gerstmann-Straussler-Scheinker syndrome - an exceedingly rare inherited autosomal dominant disease, typified by chronic progressive ataxia and terminal dementia. The clinical duration is from 2 to 10 years, much longer than for CJD.

vCJD: Variant CJD, the hitherto unrecognised variant of CJD discovered by the National CJD Surveillance Unit and reported in The Lancet on 6 April 1996. This is characterised clinically by a progressive neuropsychiatric disorder leading to ataxia, dementia and myoclonus (or chorea) without the typical EEG appearance of CJD. Neuropathology shows marked spongiform change and extensive florid plaques throughout the brain.

Definite vCJD cases still alive: These will be cases where the diagnosis has been pathologically confirmed (by brain biopsy).

ANNEX

DIAGNOSTIC CRITERIA FOR VARIANT CJD

I A) PROGRESSIVE NEUROPSYCHIATRIC DISORDER
B) DURATION OF ILLNESS > 6 MONTHS
C) ROUTINE INVESTIGATIONS DO NOT SUGGEST AN ALTERNATIVE DIAGNOSIS
D) NO HISTORY OF POTENTIAL IATROGENIC EXPOSURE

II A) EARLY PSYCHIATRIC SYMPTOMS *
B) PERSISTENT PAINFUL SENSORY SYMPTOMS **
C) ATAXIA
D) MYOCLONUS OR CHOREA OR DYSTONIA
E) DEMENTIA

III A) EEG DOES NOT SHOW THE TYPICAL APPEARANCE OF SPORADIC CJD *** (OR NO EEG PERFORMED)
B) BILATERAL PULVINAR HIGH SIGNAL ON MRI SCAN

IV A) POSITIVE TONSIL BIOPSY

DEFINITE: IA (PROGRESSIVE NEUROPSYCHIATRIC DISORDER) **and** NEUROPATHOLOGICAL CONFIRMATION OF vCJD ****

PROBABLE: I **and** 4/5 OF II **and** III A **and** III B

or I **and** IV A

* depression, anxiety, apathy, withdrawal, delusions.

** this includes both frank pain and/ or unpleasant dysaesthesia

*** generalised triphasic periodic complexes at approximately one per second

****spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum.

Related links

Download CJD Statistics (PDF, 3K)

Notes to editor

1. For further information contact the Department of Health Media Centre.

Contact Media Centre

Phone **Press Officer**
020 7210 4860/5287

資料３

The Epidemics of BSE and vCJD in the UK

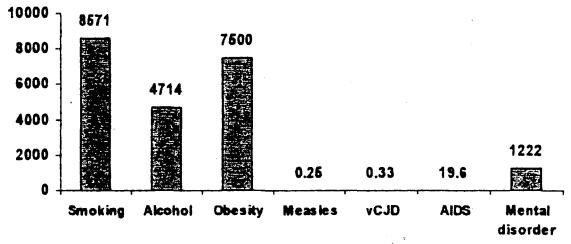
THE EPIDEMICS OF BSE AND vCJD IN THE UK

Peter Smith

Department of Infectious and Tropical Diseases
London School of Hygiene & Tropical Medicine

Chair, Spongiform Encephalopathy
Advisory Committee (SEAC)

Deaths per BBC news story
(Harrabin et al 2003)



Why has vCJD attracted attention disproportionate to the size of the epidemic?

- a new disease.
- the average incubation period is of unknown length, many more cases may appear in the coming years.
- caused by an "infectious protein", the prion, with remarkable survival characteristics.
- affected predominantly young people and clinical course is inexorable and it is currently untreatable, very distressing and uniformly fatal.
- high proportion of the UK population, as well as visitors and consumers of exported beef products may have been exposed to the agent.
- the BSE epidemic has impacted substantially on world trade and has caused concern about the safety of a widely consumed food product.
- cost of the epidemic of BSE has exceeded $5 billion and substantial additional costs will continue to be incurred in the future.

TRANSMISSIBLE	can be experimentally transmitted to same or different species - usually by inoculation
SPONGIFORM	group of holes (vacuoles) seen in brain tissue sections on microscopy
ENCEPHALOPATHY	degenerative condition of the brain

TSE's are caused by "unconventional agents":

- stimulate no detectable immune response
- extraordinarily resistant to inactivation by ultra-violet and ionising radiation, chemical disinfectant and heat
- nature and structure of agent largely unknown

Prp host coded protein that becomes modified in infected tissue and accumulates around CNS lesions (prion protein)

Main naturally occurring transmissible spongiform encephalopathies reported before 1986

HOST	DISEASE	DISTRIBUTION
Man	**Creutzfeldt-Jakob disease (CJD)** (described in 1920's) (sporadic c.85%, familial c.<15%, iatrogenic c.1%)	**Worldwide** (incidence about 1/million/yr)
	Kuru (reported 1957)	**Papua New Guinea** Declined to rarity
Sheep (Goats)	**Scrapie** (known for 250 years)	**Widely distributed** (not reported in some countries - eg. Australia, New Zealand, Argentina)
Mule deer, Elk	**Chronic wasting disease**	**North America** (localised)

ORIGINS OF THE FIRST CASE(S) OF BSE?

Origin of first BSE infection is unknown

Most widely favoured hypotheses:

- mutated cattle-adapted form of scrapie
- strain of scrapie at low level in sheep population
- sporadic case in cattle (as "sporadic" CJD occurs in humans)

but other causes cannot be excluded

RECOGNITION AND INVESTIGATION OF THE EPIDEMIC

- First cases of BSE diagnosed in 1986 shortly after diagnosis of spongiform encephalopathy in nyala from British zoo
- Further cases into 1987 - recognition of start of epidemic?
- Epidemiological studies initiated:
  - South > North
  - Dairy > Beef
  - No association:
    - imported animals or products
    - vaccines and chemicals
    - contact with sheep
    - cattle breed
- Common factor - use of meat and bone meal (MBM) as supplementary feed

Hypothesis - epidemic due to sudden exposure of cattle to MBM containing scrapie like agent in early 1980s, followed by disease after 4-5 year incubation period

ORIGINS OF THE EPIDEMIC OF BSE?

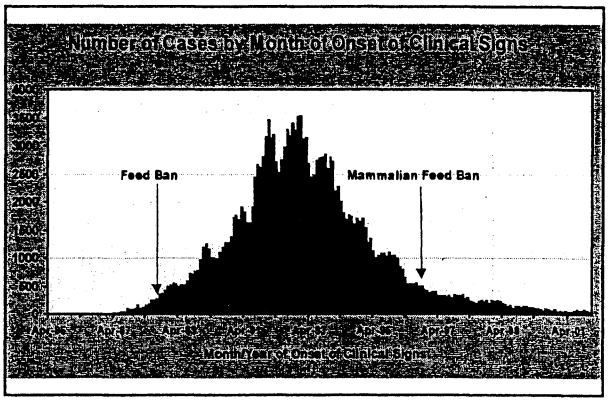
- Rendering of cattle and sheep offal to produce high protein supplement feed, fed to sheep and cattle
- BSE introduced into the rendering process - source unknown
- Infectious agent recycled in feed to multiply the epidemic (similar to kuru?)
- Long incubation period delayed recognition of problem until epidemic well established
- But why in the UK and why in the 1980's?

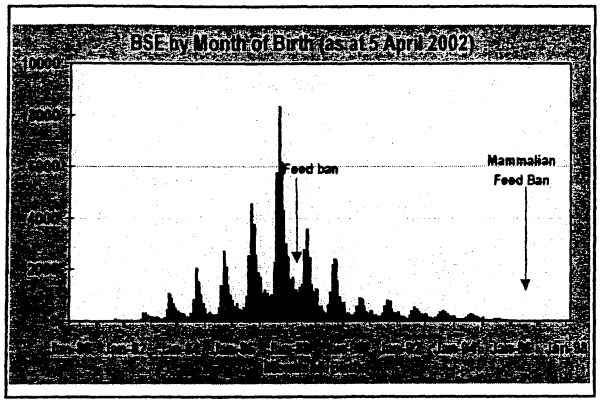
WHY IN THE UK AND WHY IN THE 1980'S?

- Unlucky (for the UK) chance?
- Ratio of sheep to cattle entering rendering higher in UK than most other places
- Early 1980's reduction in use of solvents and live steam stripping - increased exposure of cattle to scrapie and emergence of cattle-adapted strain
- Practice started of feeding MBM to very young calves

INITIAL CONTROL MEASURES & SURVEILLANCE

Jul 1988	Ban on feeding ruminant protein to ruminants (but still allowed to pigs and poultry)
Aug 1988	Ban on BSE affected cattle from entering the food chain
Nov 1989	Ban on Specified Bovine Offals (SBO) for human consumption (including brain, spinal cord and intestines)
May 1990	Intensified CJD surveillance started (though risk to humans was judged to be "remote")





Main control measures to prevent animal transmission

Jul 1988	Ruminant feed ban
Sep 1990	SBO ban extended to any animal feed
Nov 1994	Any mammalian protein banned from ruminant feed
Mar 1996	Ban on mammalian protein to all farmed animals (measure introduced across the EU in Jan 2001)
Jun 1996	Mammalian MBM recalled

DECLINE OF BSE EPIDEMIC IN GB

		% reduction from prev. year
1995	14,301	40
1996	8,013	44
1997	4,310	46
1998	3,179	26
1999	2,256	29
2000	1,311	42
2001	781	40
2002	445	42

03.07.03

Cases of BSE born in the UK after 1 Aug 1996

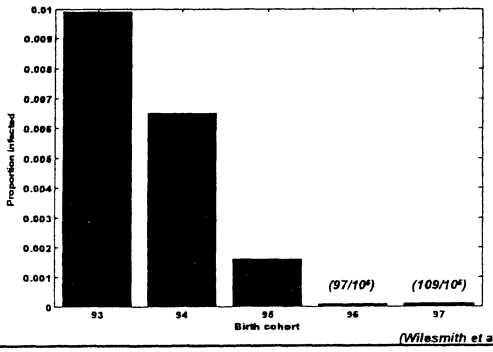
Year of birth	No. cases
1996	17
1997	40
1998	19
1999	6
TOTAL	82

Source	No. cases
Passive	21
Cas./Fall. Stock	46
OTMS	15
TOTAL	82

14 Jan 2004

Proportion of animals infected in annual birth cohorts

(birth cohort 93 corresponds to animals born between 1 July 1993 – 30 June 1994, etc)



(Wilesmith et al, 2003)

BSE in cattle exported to EC from the UK

Cattle exported 1985 - 90	57,900
"Expected" BSE cases (at UK rates)	1668
"Observed" BSE cases	18

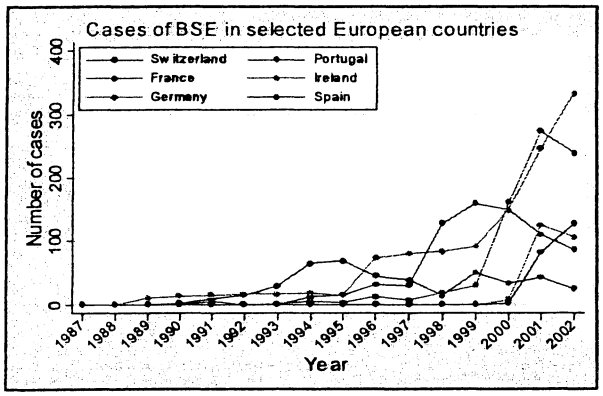
(Vet. Record June 96)

Sequence of first report of BSE in native-born cattle

1986 UK
1989 Ireland
1990 Portugal, Switzerland
1991 France
1997 Belgium, Luxembourg, Netherlands
1998 Liechtenstein
2000 Denmark, Germany, Spain
2001 Austria Czech Republic, Finland, Greece, Italy, Japan, Slovakia, Slovenia
2002 Israel, Poland
2003 Canada

CASES OF BSE IN OTHER EUROPEAN COUNTRIES

http://ourworld.cs.com/j1braakman/BSE.htm?f=fs 10 Feb 2003



TESTING FOR BSE IN CATTLE DESTINED FOR FOOD CHAIN IN EU COUNTRIES (DATA FOR 2001)

	>30 mo. Tests (some >24 mo.)	No. +ve
Ireland	636,930	34
Portugal	28,384	19
France	2,382,225	83
Belgium	359,435	28
Netherlands	454,649	11
Germany	2,565,341	36
Spain	328,517	35
Denmark	250,414	3
Italy	377,201	27
TOTAL (EU)	7,670,176	279

CONCLUSIONS REGARDING THE BOVINE EPIDEMIC

- Control measures since 1988 (and especially since 1996 in the UK and since 2001 in rest of EU) have brought the epidemic well under control
- Likely that the consistent decline over the last decade will continue though "disappearance" is difficult to predict.
- The numbers of infected animals entering the food chain now (especially those in the late stage of the incubation period) is likely to be at a very low level.
- The bovine tissue controls in place should ensure that any risks to human health are very low and diminishing year on year.
- Disease in cattle is no longer a significant public health problem, provided existing controls are enforced.
- However, many challenges remain!

TSE's in Exotic Species in the UK (Mar 2002)

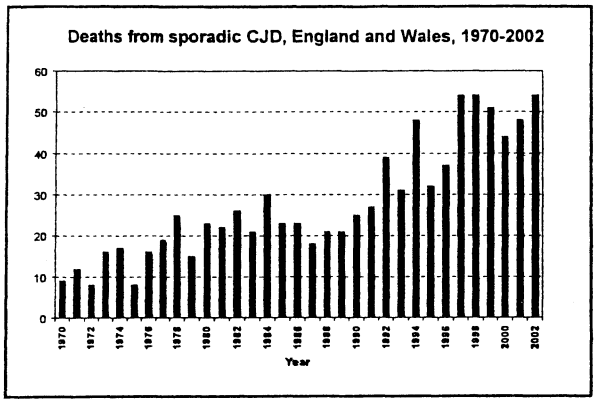
Nyala	1	Puma	2
Gemsbok	1	Tiger	3
Kudu	6	Ocelot	3
Oryx	2	Ankole cow	2
Eland	6	Bison	1
Cheetah	5	Lion	4

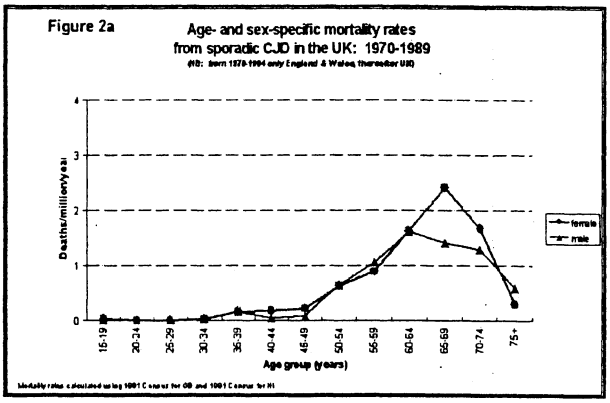
Cat (domestic)* 89

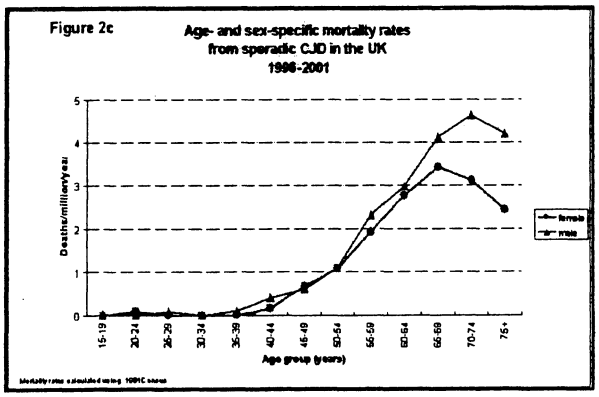
Cases in domestic cats

1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
12	12	10	11	16	8	8(1)	6(2)	4(2)	2(1)	1(1)	1(1)

*Plus: 1 in N Ireland, 1 in Norway, 1 in Lichtenstein, 2 in Switzerland
( ) born after Sept 1990 when SBO ban was extended to any animal feed







KNOWN CASES OF CJD IN THE UK, 1970 - Mar 96, DYING AGED LESS THAN 45 YEARS

(excludes known iatrogenic and inherited cases)

	<30y	30-34	35-39	40-44
1970-79	0	2	3	2
1980-84	1	1	3	1
1985-89	0	0	3	3
1990-94	0	0	1	2
1995-96(Mar)	5(1)	2(1)	0	1

() patients alive

NEUROPATHOLOGICAL FEATURES OF CASES OF THE NEW VARIANT OF CJD (vCJD)

- Spongiform changes
- Extensive PrP plaques (Kuru-type plaques surrounded by zone of spongiform change - "florid plaques")
- Not seen in any of 175 cases of sporadic CJD investigated

BASIS OF "CAUSATIVE" LINK BETWEEN BSE AND vCJD IN MARCH 1996

- Geographical limitation of vCJD and BSE to UK
- Temporal occurrence of vCJD consistent with incubation period 5-10 years after BSE exposure
- Biologically plausible
- No other persuasive explanation

SUPPORTIVE EVIDENCE FOR CAUSATIVE LINK IN YEAR FOLLOWING MARCH 1996

- No cases of vCJD found with onset before 1994
- Only one case described outside the UK (France)
- Similar pathology when BSE injected into macaque
- Strain typing studies

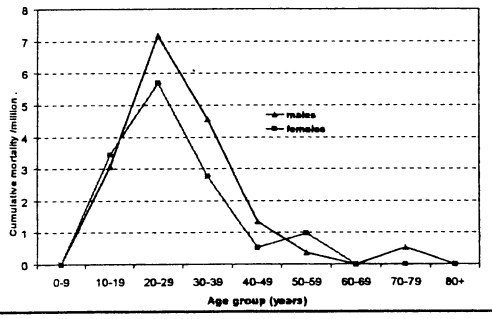
CASES OF vCJD IN UK (as at 2 Feb 2004)

Year died	Number of cases
1995	3
1996	10
1997	10
1998	18
1999	15
2000	28
2001	20
2002	17
2003	18
2004	0
Total deaths	139*
Cases alive	7
Total cases	146

*Includes 36 without neuropathological confirmation

Cases outside UK: France 6; Ireland 1*; Italy 1; US 1*: Canada*
*resided in the UK for substantial period

Cumulative age- and sex-specific mortality rates for vCJD in the UK up to 31st December 2002

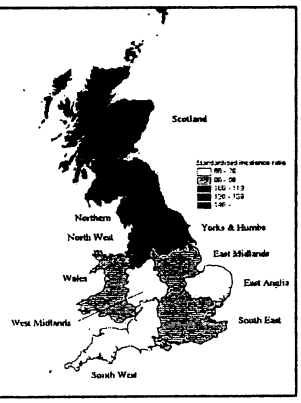


GENETIC SUSCEPTIBILITY TO CJD POLYMORPHISM OF THE PrP GENE

Codon 129	General Population	Sporadic CJD	vCJD
MM	37%	82%	100%
VV	12%	8%	0
MV	51%	10%	0

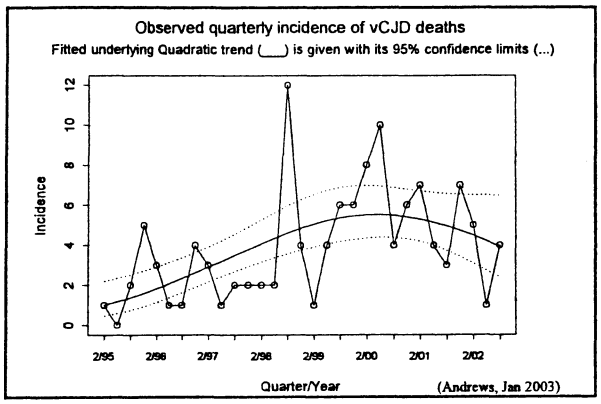
Standardised incidence ratio of vCJD by Standard Region - based on cases' place of residence in 1991

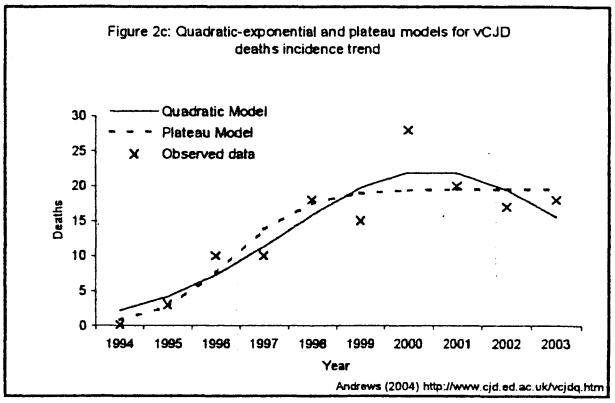
(Cousens et al 2003)



PREDICTIONS OF THE SIZE OF THE vCJD EPIDEMIC

Authors	Case data used	Range of predictions for epidemic size
Cousens et al (1997)	13 cases with onset before 1996	**Less than 100 cases to 80,000** assuming mean incubation period up to 25 years
Thomas & Newby (1999)	23 deaths in 1995 to 1997	**Less than few hundred** and mean incubation period 6-16 years
Ghani et al (2000)	55 deaths to end 1999	**Less than 100 to 136,000** assuming mean incubation periods of up to 90 years.
Huillard et al (2001)	82 cases with onset before 2000	**At most several thousand cases** but cannot predict number of infections
Ghani et al (May 2003)	121 deaths to end 2002	**Best estimate 161 cases**, 95% confidence interval 130 to 661





Some current issues

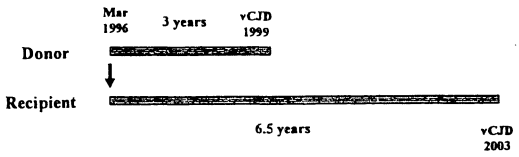
- When to lift the OTM Rule?
- BSE/scrapie in sheep?
- Iatrogenic transmission - blood transfusion, re-use of surgical instruments
- Large-scale surveys of prevalence of (late-stage) infection (tonsils and appendices)
- Development of (blood) test for infection

Changing the OTM rule

Option for change: allow into food chain after BSE testing -	Est. cost 2y 2004-2006 (£m)	vCJD cases from 2004-9 exposure*
All cattle	48	.04 (<2)
Born after 01.08.96	380	.02 (<1)
Born after 01.10.98	486	
Born after 01.01.01	552	
No change	736	

*based on "pessimistic" assumption of total of 5000 cases from exposure to date

Transmission of vCJD through blood transfusion?



資料４

National CJD Surveillance Unit

National CJD Surveillance Unit

Established 1990
identify any changes in CJD that may be linked to BSE

Now:

- Identify all cases of sporadic & variant CJD in UK
- Investigate risk factors of sporadic & variant CJD
- Investigate the geographic distribution of CJD
- Estimate short & long term trends
- Identify mechanism of transmission of BSE to humans
- Evaluate potential risks of onward transmission
- Identify any novel forms of human TSEs
- Evaluate case definitions & diagnostic tests

National CJD Surveillance Unit

- Surveillance
  - Patient review & examination
  - Risk factor questionnaire
    - demographic details, occupational & educational histories
    - surgical & medical histories, dietary histories
- Case - control study

CASE CONTROL STUDY OF RISK FACTORS FOR VARIANT & SPORADIC CJD

Case control study for risk factors

Cases- those with CJD (sporadic & variant) } interview relative

Controls- those without CJD

Risk Factor Questionnaire

Medical & surgical
Dietary
Occupational
Residential
Educational
Animal/ farm contact
} histories

Case control study

1998- 2002: 3 different control groups

Hospital controls

Suspect cases

General practice recruited community controls

BUT:

Disadvantages of each control group

Response rate poor from letter from GP- 24%

Ethical approval

Case Control Study

2002- 2005
Further funding from DH
Ethics committee approval (MREC)

4 groups of controls

Hospital controls (n=74)

Suspect cases (n=34)

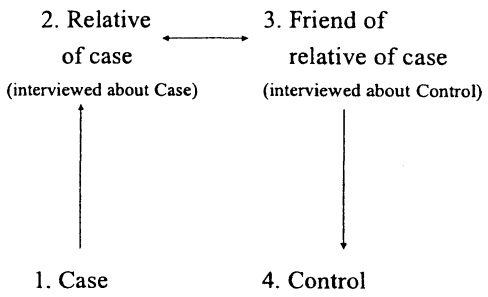
Relative nominated controls

General population controls (n=922)

Hospital controls

- Neurologist to seek permission from clinician caring/ cared for case
- Clinician to nominate a member of staff for Research nurse to contact
- Research nurse contact member of staff & together identify suitable hospital control
- Consent will be sought, if not obtained next suitable patient will be approached

Relative nominated controls



General population controls

National Centre for Social Research (NatCen)
Largest, independent social research institute in UK

Postcode Address File- randomly pick 4000 addresses

1000 interviews- trained interviewers
700 10- 50 years
300 >50 years

Research nurse to complete GP Medical History Forms

Results from case control study.....

Preliminary results: diet, surgery, occupation (case n=51)

GP controls (n=116)- DIET
Consumption of sausages >1/week: OR 8.4 (2.2-32.5)*

Consumption of MRM >8/month: OR 4.4 (1.5-12.7)*
*p<0.01

BUT, ? recall bias
Consumption in suspect non-cases: findings consistent with above, but not significant

Problems with case control study

- Rare disease
- Surrogate witness
- Recall bias
- Ethical approval

vCJD and PUBLIC HEALTH

Local reporting of CJD cases

Geographically Associated Cases ('clusters')

CJD Incidents

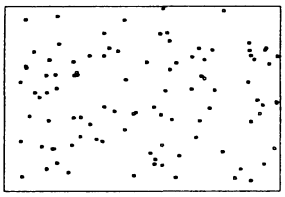
TMER

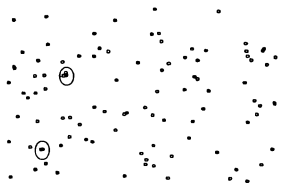
LOCAL REPORTING OF CJD

- Neurologist/clinician notifies case to local CCDC
- Local CCDC- action- 'invasive incidents', infection control, care, media
- Quarterly tables to CCDC via SCIEH (REs)

GEOGRAPHICALLY ASSOCIATED CASES of vCJD

A random distribution





The Leicester cluster$_1$

5 cases of variant CJD lived in Leicestershire (population 870, 000)

Cumulative incidence:

UK 1.5/ million Leicester 5.7/ million

4/5 from Charnwood (142, 000): 28.2 / million

Kulldorff's method- spatial scan statistic-

Leicestershire- most likely cluster ($p<0.004$)

No other significant clusters ($p<0.05$), including Kent

(Cousens et al. Lancet 2001; 357: 1002- 1007)

The Leicester cluster

- All cases ate beef frequently
- 4/5 were reported to have bought meat from butchers who processed whole carcass beasts & split the heads to remove the brains for commercial purposes
- Friesian cross cattle- locally reared & slaughtered around 36 months of age

The Leicester cluster

Hypothesis: the BSE agent entered the food chain as a result of cross- contamination of beef with brain during the process where butchers split heads to remove the brain

Tested- case- control study- matched each case to 6 community controls

OR 15 (1.6- 139)

The Leicester cluster

If true: minimal incubation- between 10- 16years

Does this explain other cases in UK & in other countries?

BUT

BIAS- recall & interviewer

Interview with butchers- 'unblinded'

Brain- where did it go?- food chain.....

GEOGRAPHICALLY ASSOCIATED CASES (GACs)

National protocol developed (on NCJDSU web site)

Collaborate with colleagues at:-

London School of Hygiene & Tropical Medicine

Communicable Diseases Surveillance Centre (Noel Gill & Anna Molesworth)

Local Health Protection Teams, Environmental Health, Vets etc.

Report to SEAC Epidemiology Sub Group

vCJD - "CLUSTERS"

Geographically associated cases (GACs):

2 or more cases vCJD where there is an association between the cases because of:

a) Geographical proximity of residence at some time, either now or in the past;

b) Other link with the same geographic area, eg. attending the same school or work place or attending functions in the same area.

GEOGRAPHICALLY ASSOCIATED CASES (GACs)

How to detect GACs (NCJDSU, local, families, media)

5km analysis

Other factors eg. same school

Decision as to whether to investigate- size of population & local factors

Investigation- with local Public Health & other colleagues

Descriptive epidemiology

GEOGRAPHICALLY ASSOCIATED CASES (GACs)

Current situation in the UK

21 areas identified with with 2 or > geographically associated cases by 5km analysis

13 areas, including Leicester, with 2 or > geographically associated cases selected for investigation to date

11 areas, including Leicester, finished investigation

GEOGRAPHICALLY ASSOCIATED CASES (GACs)

Results to date

5 cases in Leicestershire remain the only statistically significant cluster

No evidence of transmission through surgery (iatrogenic)

No evidence of butchering practice as suggested in Leicestershire

BUT: same beef supplier (6 locations), same school (3), social contact (2), same GP, dentist or hospital (4), vaccine batch (1)

National CJD Surveillance Unit

Neurology Bob Will & Richard Knight

Neuropathology James Ironside, Director

Statistics Dawn Everington

Genetics Matthew Bishop

CSF Biochemistry Alison Green

Protein Biochemistry Mark Head

Care co-ordinator Gordon Maclean

Health Protection Agency

Noel Gill

Anna Molesworth

Nicky Connor

Katie Oakley

Helen Janecek

Nick Andrews

London School of Hygiene & Tropical Medicine

Peter Smith

Simon Cousens

CJD INCIDENTS

CJD Incidents Panel

Protocol developed

risk assessment & management

Tissue infectivity in CJD

	Variant CJD	Sporadic CJD
Central nervous system	High	High
Optic nerve & retina	High	High
Other eye tissues	Medium	Medium
Lymphoreticular system- tonsil, appendix, spleen	Medium	Low
Blood	Low (?)	Low
Other tissues	Low	Low

CJD INCIDENTS

Risk assessment

- Gathering invasive incident history (surgical, dental & blood donation/ transfusion)
- CJD Incidents Panel

Management of risk

- Instruments
- People

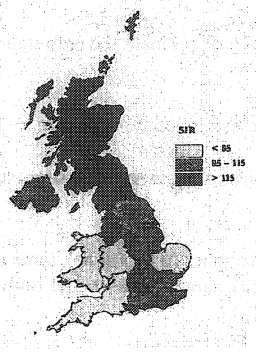
CJD INCIDENTS

People

Potential risk- contact- public health

RESIDENCE IN NORTH OF UK

STANDARDISED INCIDENCE RATIOS (SIRs) UP TO 31 JANUARY 2003 OF vCJD BY STANDARD REGION ON 1 JANUARY 1991



Variant CJD - GEOGRAPHY

Distribution of 51 variant CJD cases by region of residence in 1991

Standard region	Population aged 16-54 at the 1991 census (%)	Number (rate/million) of vCJD cases
Scotland	2,684,004 (9)	8 (2.98)
Northern	1,592,257 (5)	5 (3.14)
North-West	3,293,814 (11)	6 (1.82)
Yorkshire & Humberside	2,567,630 (9)	7 (2.73)
Wales	1,461,006 (5)	2 (1.37)
West Midlands	2,749,699 (9)	1 (0.36)
East Midlands	2,121,678 (7)	4 (1.89)
East Anglia	1,072,018 (4)	1 (0.93)
South-West	2,379,370 (8)	3 (1.26)
South-East	9,469,745 (32)	14 (1.48)
Total	29,393,174 (100)	51 (1.74)

Comparison of cumulative incidence in the "North" of the UK (excluding Northern Ireland) with that in the "South"

Region	Population aged 10 years and above at the 1991 census	Number (rate/million) of vCJD cases by place of residence at 1st January 1991	
		First 51 cases	Total
"North" (North West, Yorks & Humbs, Northern, Scotland)	16.6 million	26 (1.57)	58 (3.49)
"South" (South West, South East, Wales, West Midlands, East Midlands, East Anglia)	31.2 million	25 (0.80)	67 (2.15)
Total (rate ratio)	47.8 million	51 (1.94)	125 (1.65)

Variant CJD- GEOGRAPHY

Dietary & Nutritional Survey of British Adults

- 1986 - 1987
- 2197 adults aged 16 to 64 years
- weighed, 7 day dietary records

Household Food consumption & Expenditure Report

- 1984 - 1986
- 20, 000 households
- One week records of all foods entering home for consumption

OTHER POTENTIAL RISK FACTORS
FOR vCJD

- Diet
- Occupation
- Social class, race, urban/rural residence
- Secondary transmission- surgery, blood transfusion
- Medicines, vaccines
- Contact between cases

資料５

National Creutzfeldt-Jakob disease Surveillance Protocol

NATIONAL CREUTZFELDT JAKOB DISEASE SURVEILLANCE PROTOCOL

DISEASE OR SYNDROME

Sporadic, familial, iatrogenic and variant Creutzfeldt Jakob Disease (CJD), including Gerstmann-Straussler-Scheinker Syndrome (GSS) and Fatal Famial Insomnia (FFI).

RATIONALE FOR SURVEILLANCE

Following the identification in UK cattle of bovine spongiform encephalopathy (BSE) as one of the transmissible spongiform encephalopathies, the Southwood Report recommended that CJD should be monitored. The National CJD Surveillance Unit (CJDSU) was established in 1990 with the primary aim of identifying any changes in the characteristics of CJD that might be linked to BSE. In 1996 a new variant of CJD (vCJD) was identified and evidence has since gathered that links vCJD causally to BSE. The exact mechanism of transmission of the BSE agent to the human population has not been identified, but dietary exposure to BSE contaminated beef products remains the most likely hypothesis.

The primary aim of CJD surveillance in the UK is to inform the scientific community, policy makers and, ultimately, the general public of changes in the epidemiology of CJD and vCJD and of potential risk factors, in order to plan for and to reduce the potential consequences of this disease.

The main objective of the CJDSU is to identify all cases of CJD in the UK and to investigate each case further by clinical examination, clinical investigations, neuropathological examination, genetic analysis, molecular biological studies, collecting basic epidemiological data and carrying out a case-control study in order to:

- provide accurate data on the incidence of CJD, including vCJD;
- investigate risk factors for CJD, including vCJD;
- identify the mechanism of transmission of BSE to the human population;
- provide estimates of short-term and long-term trends in the rate of occurrence of vCJD;
- evaluate the potential risks of onward transmission of vCJD, including through iatrogenic routes;
- identify any novel forms of human spongiform encephalopathy;
- evaluate case definitions of CJD, including vCJD; and
- evaluate diagnostic tests for CJD, including vCJD.

CURRENT SURVEILLANCE

ROUTINE SURVEILLANCE

Referral of suspect cases to the CJDSU occurs in three ways:

- **Clinical**- passive ascertainment: neurologists, neuropathologists and neurophysiologists are reminded annually of the need to refer any individuals in whom CJD or vCJD is considered a possible diagnosis to the CJDSU.

- **Death certificates**- passive ascertainment: the Office for National Statistics for England and Wales and the General Register Offices for Scotland and Northern Ireland supply all death certificates coded under the rubrics 046.1 and 331.9 (9th ICD revision).
- **Other sources**- passive ascertainment: pyschiatrists, paediatricians, geriatricians, other health professionals and members of the general public may refer cases to the CJDSU.

CLASSIFICATION

Suspect cases are classified according to the criteria below by a neurologist from the CJDSU. This is an on-going process, being constantly up-dated as more information is ascertained. The date of any change of classification and the reason for that change is recorded. In addition, the classification is recorded at the following key stages:

- At notification;
- When the suspect case was first seen in life by a neurologist from the CJDSU;
- The highest classification on the basis of clinical information alone (ie. not including neuropathological information); and
- When review by the CJDSU is complete (ie. when the case-file is 'closed').

CLASSIFICATION CRITERIA

SPORADIC CJD (Rotterdam 1998)

I		Rapidly progressive dementia
II	**A**	Myoclonus
	B	Visual or cerebellar problems
	C	Pyramidal or extrapyramidal features
	D	Akinetic mutism
III		Typical EEG

DEFINITE SPORADIC CJD	Neuropathological/immunocytochemical confirmation.
PROBABLE SPORADIC CJD	I *and* 2 of II *and* III **OR** possible sporadic CJD *and* positive 14-3-3.
POSSIBLE SPORADIC CJD	I *and* 2 of II *and* duration < 2 years.
IATROGENIC CJD[1]	Progressive cerebellar syndrome in a pituitary hormone recipient **OR** sporadic CJD with a recognised exposure risk, *eg. dura mater transplant.*
FAMILIAL CJD[1]	Definite or probable CJD plus definite or probable CJD in a first degree relative **OR** neuropsychiatric disorder plus disease- specific PRNP mutation.

VARIANT CJD (UK, 2000)

I	**A**	Progressive neuropsychiatric disorder.
	B	Duration of illness > 6 months.
	C	Routine investigations do not suggest an alternative diagnosis.
	D	No history of potential iatrogenic exposure.
II	**A**	Early psychiatric symptoms*
	B	Persistent painful sensory symptoms**
	C	Ataxia.
	D	Myoclonus or chorea or dystonia.
	E	Dementia.
III	**A**	EEG does not show the typical appearance of classical CJD (after review by CJDSU staff)*** **OR** no EEG performed.
	B	Posterior thalamic high signal on MRI scan (after review by

CJDSU staff).

IV	**A**	Positive tonsil biopsy.

DEFINITE VARIANT CJD	IA **and** neuropathological confirmation of vCJD****
PROBABLE VARIANT CJD	I **and** 4/5 of II **and** IIIA **and** IIIB **OR**
PROBABLE VARIANT CJD	1 **and** IV A
POSSIBLE VARIANT CJD	I **and** 4/5 of II **and** IIIA

*	depression, anxiety, apathy, withdrawal, delusions.[2]
**	including both frank pain and/ or unpleasant dysaesthesia.
***	generalised triphasic periodic complexes at approximately one per second.
****	spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum[3]

In addition, there are three additional sub-categories for those referrals that do not meet the criteria of possible CJD, which are:

- **Diagnosis unclear**- when the diagnostic criteria for possible, probable or definite CJD are not met *nor* is there a reasonable alternative diagnosis and, therefore, CJD remains a possibility;
- **CJD thought unlikely**- when information indicates that a clinical diagnosis of CJD is very unlikely because of atypical disease features, and/or an atypical course, and/or atypical clinical investigation results, and/or a reasonable alternative diagnosis is made, but is *not* confirmed. This category includes cases which improve clinically without another firm diagnosis being made; and

- **Definitely not CJD**- when information indicates that CJD is not the diagnosis *and* there is another definite diagnosis proven by clinical examination, clinical investigations or pathology.

FOLLOW UP OF SUSPECT CASES

Whenever possible all referrals to the CJDSU categorised as 'definite CJD', 'probable CJD', 'possible

CJD', and 'diagnosis unclear' are visited in life in order to carry out a physical examination, to take specimen samples and to gather systematic clinical information from the suspect case and their relatives. During such visits, a CJDSU neurologist completes a copy of the "Patient Review and Examination Form" and where possible makes a copy of the relevant sections of the hospital records and relevant investigation results, including EEGs. A request is also made for copies of any relevant MRI scans to be sent to the CJDSU. At the same visit, as part of the case control study to investigate risk factors for CJD, a close relative or nominated spokesperson is interviewed by a nurse practitioner/ research nurse, or deputy, from the CJDSU, who completes a copy of the risk factor "Questionnaire".

Following this visit a "Final Review Form" is opened for each suspect case and held in their file at the CJDSU. Incoming clinical, pathological and laboratory data are recorded on this form as they arrive at the CJDSU. Following the death of a suspect case, if a post-mortem is performed, every effort is made to obtain details of the report and review of any pathological material is organised. In addition, following the death of a definite or probable case of variant CJD, the general practice records are requested and used to update the "Final Review Form". This form is closed when it is apparent that no further data are likely to be forthcoming.

If notification to the CJDSU is made after death or death occurs soon after notification and before a visit can be performed, for definite cases (and in cases that the final classification is probable) hospital records are requested. In addition, an attempt is made to visit the relatives of the case in order to gather further clinical information. Data extracted from the hospital records and obtained from relatives are recorded on a copy of the "Late Referral Form" by a CJDSU neurologist. At the same visit, a close relative or nominated spokesperson is interviewed by a nurse practitioner/ research nurse, or deputy, from the CJDSU, who completes a copy of the risk factor "Questionnaire" . The "Late Referral Form" is closed when it is apparent that no further clinical, pathological or other laboratory data are likely to be forthcoming.

Changes in diagnostic criteria that occur as data is accrued in relation to suspect cases of CJD are noted on the "Change in Classification Form".

Notifications classified as probable or definite familial CJD, Gertsmann- Straussler- Scheinker Syndrome (GSS), Fatal Familial Insomnia (FFI) and iatrogenic CJD are not followed up, unless the diagnosis is unclear or a specific request is made by the local clinician for a visit by a neurologist from the CJDSU.

CESSATION OF FOLLOW UP

In order to obtain as much complete data on each case as is possible, following the death of a suspect case (or following recovery) the files are reviewed twice yearly. When it is apparent that no further clinical, pathological or other laboratory data are likely to be forthcoming, the case file is closed.

ENHANCED SURVEILLANCE

Paediatric surveillance

This is carried out through prospective active surveillance in conjunction with the British Paediatric Surveillance Unit. The aim is to identify cases of progressive intellectual and neurological deterioration and to determine whether or not cases of CJD are occurring in children resident in the UK aged under 16.

years at onset of symptoms.

Retrospective review of CJD and related disorders

This is a three-year project involving all the neuropathology laboratories in the UK, which commenced in 1999. The aim is to review cases of CJD which have been identified in diagnostic files back to 1970 (the earliest point of prospective clinical surveillance data) and to review selected groups of atypical dementia cases in order to determine whether any cases of CJD have been misclassified or missed altogether.

RECOMMENDED MINIMUM DATA ELEMENTS

The following minimum data sets are collected. Please note, the "Patient Review and Examination", "Late Referral" and "Final Review" forms are completed on those suspect cases outlined in the previous section, "Follow-up of Suspect Cases".

Notification Form

Identification information, notification details, history, examination at notification, investigations, risk factors, classification at notification.

Change in Classification Form

For each change in classification: classification, criteria for classification, date of change and reason for change.

Patient Review and Examination Form

Identification information, clinical history, state of patient at admission/ first seen by a neurologist, previous medical history, examination of the patient by CJDSU neurologist, history and examination related to current illness, investigations (including EEG, MRI and CSF), specimens collected and classification based on clinical information.

Late Referral Form

Identification information, clinical history, state of patient at admission/ first seen by a neurologist, previous medical history, history and examination related to current illness, investigations (including EEG, MRI and CSF), clinical and neuropathological materials available, post mortem results and classification history.

Final Review Form

Identification information, summary of clinical history and examination, investigations (including EEG, MRI and CSF), clinical and neuropathological materials available, post mortem results and classification history.

Neuropathological

Post-mortem report with the referring pathologist's diagnosis, and any other relevant findings at autopsy. Review of the neuropathological material includes PrP immunocytochemistry and investigations on non-central nervous system (CNS) tissues, including lymphoid and peripheral nervous system tissues. All referring pathologists are encouraged to freeze CNS and other tissues for biochemical studies and (when necessary) DNA extraction.

Genetic

Prion protein gene (PRNP) analysis is performed in cases in which consent for genetic analysis is obtained.

Molecular biological

Prion protein ($PrP^{RES)}$ typing is performed where possible on the CNS and other tissues in cases in which frozen tissues are stored at post mortem.

RECOMMENDED DATA ANALYSIS, PRESENTATION, REPORTS

By case of variant CJD

Once relatives and local clinicians have been informed of the diagnosis of definite vCJD and in those cases that have a final classification of probable vCJD, the CJDSU informs the following:

- The Chief Medical Officer is notified by fax of the gender, date of death and vCJD classification. The DOH informs other government departments and the Spongiform Encephalopathy Advisory Committee (SEAC) Secretariat;
- The Public Health Laboratory Service Communicable Disease Surveillance Centre are notified of the CJDSU identification number, age at death, gender, date of onset, date of notification to the CJDSU, date of birth, date of death and date confirmed as 'definite/probable' vCJD.
- Colleagues in the EU Surveillance System, WHO Headquarters, CDC Atlanta, European

Commission, Alzheimer's Disease Society, Human BSE Foundation, BSE Enquiry and other interested parties are sent the gender, date of death, vCJD classification and the current total number of definite (and those with a final classification of probable) vCJD cases.

Transfusion Medicine

Transfusion Medicine Epidemiology Review (TMER)

The UK Transfusion services are informed six monthly of all definite and probable cases of sporadic and familial CJD who were reported as blood donors ("main TMER") and those that were reported as blood product recipients ("reverse TMER"). The basic information they are sent is the name, maiden name, gender and date of birth of the case. In addition, for blood donors, they are informed of the year of donation(s), the home address at the time of donation(s) and where the donation(s) was given and, for transfusion recipients, they are informed of the year of the transfusion(s), the home address at the time of transfusion(s), the hospital where the transfusion(s) occurred and the indication for the transfusion(s). Similar details for controls are also given. The information sent is 'blinded' with regards to whether it relates to cases or controls.

Variant CJD: As soon as a suspect case is classified as 'probable', the Medical Director(s) of the relevant (according to residential history) Transfusion Service(s) is notified with the following information (Appendix 8): forename, surname, maiden name, gender, date of birth, residential history, whether a donor, donation dates, places of donation, vCJD classification and country (England, Wales etc.) notified. An anonymised copy is sent to the appropriate Department of Health(s). Details on controls of probable vCJD cases are also sent to the relevant Transfusion Service(s), which are the forename, surname, maiden name, gender, date of birth, residential history, whether a blood donor and whether received a blood/ blood product transfusion. The information sent is not 'blinded' with regards to whether it relates to cases or controls.

Monthly

Numbers of referrals for investigation, numbers of sporadic, iatrogenic, familial, GSS and vCJD cases by year are published by the Department of Health (press release and web-site), on the CJDSU web-site and in the SCIEH weekly report.

Annually

The CJDSU annual report contains the following minimum information:

Sporadic CJD

- Deaths from sporadic CJD by region (England and Wales, Scotland and Northern Ireland) by year;
- Cases of sporadic CJD by year of death and by age;
- Age- and sex- specific mortality rates from sporadic CJD;
- Trends in mortality rates from sporadic CJD by time;
- Standardised mortality ratios by Region; and
- Analysis of risk factors, depending on available information.

Variant CJD

- Cases of vCJD by date of onset;
- Geographical distribution of places of residence (UK only) at onset of vCJD; and
- Analysis of risk factors, depending on available information.

Web sites

UK (www.cjd.ed.ac.uk)

- Table of referrals and deaths from definite and probable sporadic, iatrogenic, familial and variant CJD and GSS by year.
- Latest annual report of CJDSU.
- CJD in Europe

Europe (www.eurocjd.ed.ac.uk)- tables of:

- Deaths (absolute numbers and annual mortality rates per million population) from definite and probable cases of sporadic, familial, GSS and iatrogenic CJD by country by year;
- Total number of cases of sporadic CJD (definite and probable cases and deaths) by country by year;
- Annual mortality rates from sporadic CJD by country by year;
- Total number of cases (deaths) of familial/genetic CJD and iatrogenic CJD by country; and
- Referrals of suspected CJD < 50 years old (from 1996 onwards) and number of cases of vCJD by country.

Ad hoc

As requested.

Principal uses of data for decision making

- Develop and test hypotheses about novel forms of spongiform encephalopathy;
- Track trends over time;
- Detect clusters;
- Detection of risk factors and mechanisms of transmission;
- Determine magnitude of public health problem;
- Inform prevention strategies; and
- Development and evaluation of diagnostic tests.

Special aspects

Collaboration with surveillance units within the EU and world-wide.

Reference section

1. Budka et al. Tissue handling in suspected Creutzfeldt-Jakob Disease (CJD) and other human spongiform encephalopathies (prion diseases). *Brain Pathology* 1995; 5: 319-322.
2. Will RG, Stewart G, Zeidler M, Macleod MA, Knight RSG. Psychiatric features of new variant Creutzfeldt-Jakob disease. *Psychiatric Bulletin* 1999; 23: 264- 267.
3. Ironside JW, Sutherland K, Bell JE et al. A new variant of Creutzfeldt-Jakob disease: neuropathological and clinical features. *Cold Harbour Symposia on Qualitative Biology* 1996; 61: 523- 530.

資料６

The vCJD in curve in UK

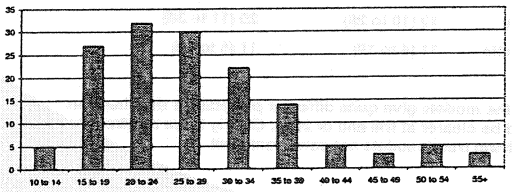
[redacted]

Outline

- vCJD incidence: The current situation
- Modelling the underlying incidence trend
- Has the epidemic peaked?
- Short-term projections
- Why hasn't the mean age of cases changes?
- Back-calculation models
- Further work

The current situation

- By March 9th 2004: 146 cases, 6 still alive
- Still all homozygous for methionine at codon 129
- Of 146 cases 82 males 64 females (p=0.16)
- Median age at onset of symptoms=26 (range 12-74)



Modelling the underlying incidence

Look at cases by year (and quarter)

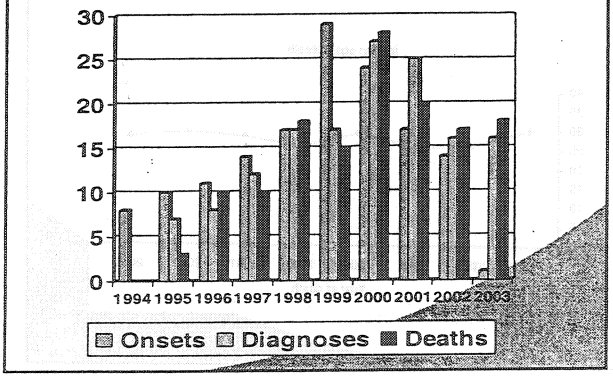
Analysis has been performed every quarter since 1996 (Paddy Farrington) – latest analysis can be found at: www.cjd.ed.ac.uk/vcjdq.htm

Should we look at cases by onset, diagnosis or death?

- Onset of symptoms> A Feature of the disease but need to allow for the delay from onset to diagnosis (average 11 months).
- Diagnosis> Changes in diagnostic criteria mean cases now diagnosed sooner by a few months – small bias.
- Death> Some cases still alive, treatment may delay death.

- In Practice we look at the data by all three dates

Onsets, Diagnoses and deaths by year



Shapes for the underlying trend

1. Linear (exponential) Model: $Y = \exp(b_1 t)$
2. Quadratic (exponential) Model: $Y = \exp(b_1 t + b_2 t^2)$
3. Plateau model: $Y = a/(1+\exp(b-ct))$

For diagnoses and deaths models are fitted to the data using Poisson regression.

The fit of the Models to the data can be compared

For comparing model 1 and 2 this allows us to determine whether the quadratic time effect is significant

For Onsets it is also necessary to model the delay from onset to diagnosis – this can be done using a gamma distribution for the delay. (Results not shown – see web document).

Results

Quadratic term significant (P<0.01) indicating that incidence is no longer increasing exponentially.

Quadratic model and Plateau model fit the data equally well

Figure 4c: Quadratic-exponential and plateau models for vCJD diagnoses incidence trend

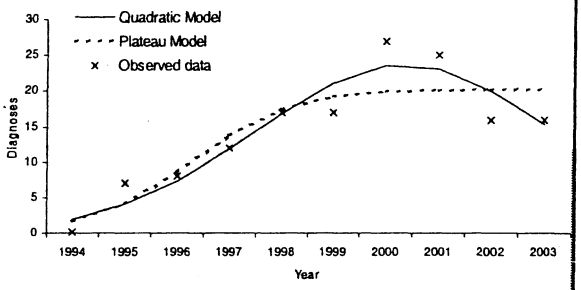
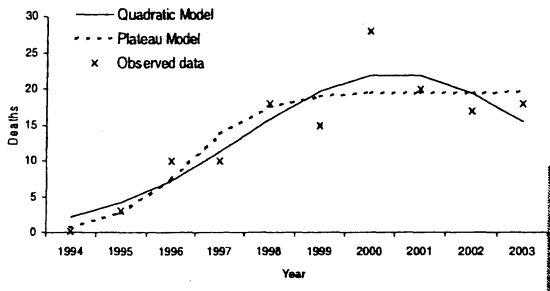


Figure 2c: Quadratic-exponential and plateau models for vCJD deaths incidence trend



How many Deaths or Diagnoses will there be in 2004?

Problem: Which underlying trend model do we use?

	Deaths (95% PI)	Diagnoses (95% PI)
Plateau	19 (10 to 29)	20 (11 to 30)
Quadratic	11 (4 to 19)	11 (4 to 19)

Since the models give quite different predictions the situation should be clearer at the end of 2004. Clearly there maybe other underlying trend models not considered yet.

Have we reached the peak?

If we assume the quadratic model is correct we can estimate the the time of 'the' peak and a confidence interval on this using boostrapping.

Diagnoses: August 2000 (September 1999-January 2002)

Deaths: December 2000 (March 2000-August 2002)

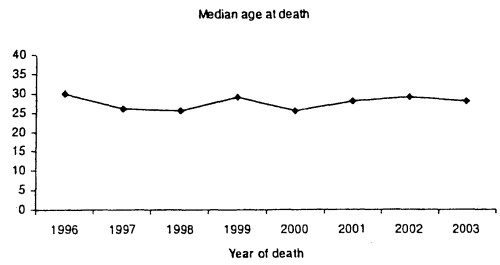
Problem

Assumes the quadratic model is correct

May not be THE peak – there may be future (larger) peaks

May be human-human transmission

The average age of the cases over time



Why hasn't the average age at death changed over time?

- Exposure to BSE was from 1986-1996.
- Therefore may expect age of cases to increase each year since we are a year further away from exposure.
- This hasn't occurred – needs explaining

Possible explanations

- Constant on-going exposure (unlikely)
- Age-specific incubation periods from exposure-onset (longer in those exposed when younger – not likely)

Most plausible:

Given a unit of BSE in the food chain, the risk of infection starts very low in under 5's then increases to peak late teens, then declines.

- A case born in 1980 is more likely to have been infected nearer the end of the BSE epidemic (1995)
- A case born in 1970 is more likely to have been infected nearer the beginning (1988)

Therefore, on average you see the 1980s cases later in the vCJD epidemic. This could give a constant age

Use back-calculation models to explore this further

Back –calculation models

- **These use**
- **Data on the BSE epidemic and control measures**
- **Data on vCJD epidemic (including age of cases)**

Simultaneously estimate age-specific risk of infection and the incubation period distribution

Also incorporate data on tonsil / appendix testing

Can be used to estimate the total epidemic size

Conclusions

Reasons for optimism

- **The vCJD epidemic has probably reached a peak (or at least a plateau)**
- **Projections for future cases are much lower than before**

Cautions

- **Possible epidemic in Methionine heterozygous**
- **Possible person-person spread**
- **Long tail to the epidemic**

Further work

More modelling work required

- **Further data on cases**
- **Further information form testing of tonsils for PrPsc**
- **Information on age-specific exposure to meat products**
- **Further models for current incidence**

PhD with London School of Hygiene and Tropical Medicine

資料７

National Anonymous Tonsil Archive(NATA) For Studies of Detectable Abnormal Prion Protein

National Anonymous Tonsil Archive (NATA) For Studies of Detectable Abnormal Prion Protein

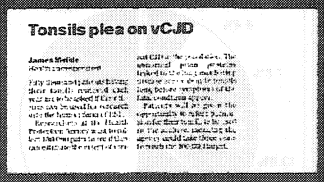
Collection Strategy

Carole Kelly
NATA Scientific Coordinator
CJD Team
CDSC
March 2004

Health Protection Agency

The Tonsil Archive

A National Anonymous Tonsil Archive for Studies of Detectable Abnormal Prion Protein


Tonsils plea on vCJD

Population Prevalence Survey
Tonsillar tissue that would otherwise be discarded
Routine tonsillectomies (all ages)
Unlinked anonymous method

Background to the NATA project

- The purpose of the archive is to establish an unlinked anonymous collection of leftover tonsil tissue from 100,000 individuals after routine tonsillectomy that will be used to study the population prevalence of abnormal prion protein
- Immediate establishment was recommended to the Chief Medical Officer by the Medical Research Council (MRC) / Department of Health (DH) Steering Group on Studies of Detectable Abnormal Prion Protein
- Multi-centre Research Ethics Committee approval was obtained to collect the tonsils without seeking explicit individual consent. Patients are given a patient information leaflet and an opportunity to object to their tissues being used in this study

Public health implications

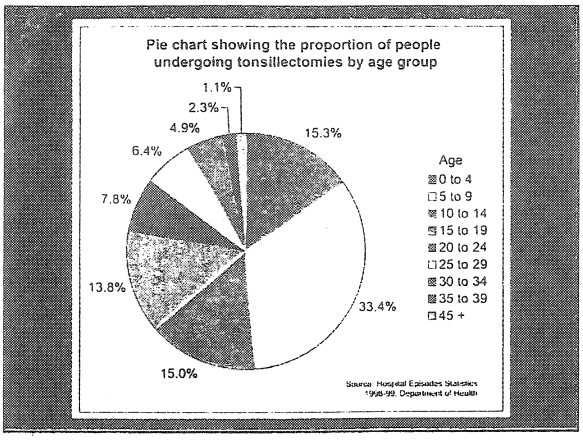
- Reliable prevalence estimates are essential for:
  - rational planning of interventions to limit the impact of the vCJD epidemic
  - planning of care provision for those who will develop the disease
- Predicting the likely number of vCJD cases is difficult without these estimates as:
  - the incubation period of vCJD may be >10 years
  - little is known about the pathogenicity of the BSE agent in humans
- Although the number of cases so far is relatively small, it is conceivable that a very large number of people are infected

Why tonsils?

- Evidence from animal models and limited data from humans suggest that the PrP^{Sc} will be detectable in peripheral lymphoid tissue during the pre-clinical phase of vCJD
- Outside of the central nervous system, tonsils appear to be the best tissue for the detection of PrP^{Sc} in humans with vCJD
- Retrospective studies of tissues (mostly appendixes) removed during routine operations or autopsies underway since 1997
- Prospective examination of fresh tonsil tissue is anticipated to be more sensitive as tonsil tissue seems to have a higher concentration of PrP^{Sc} than appendix tissue
- **HOWEVER** – the prognostic significance of a positive test for PrP^{Sc} in an asymptomatic person is not known

Tonsillectomies

- Only tonsil tissue collected from patients undergoing routine tonsillectomies
  - NOT from emergency operations or if clinical pathology requested
- Archive will be collecting tonsils for at least three years from patients of all ages, although exposure should not have occurred post 1996
  - Bovine offal banned in 1989 and cattle over 30 months excluded from human consumption in 1996
- All ages but most tonsillectomies carried out on <9 years of age
  - avoid confusion in operating theatres
  - negative control group
  - other exposure routes
- As the cohort of the UK population exposed to BSE ages, the availability of tonsils from people exposed through their diet will diminish

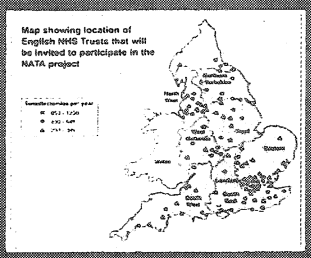


Unlinked anonymous method

- All specimens are irreversibly anonymised before any testing starts
  - no possibility of tracing the identity of the individual from whom the tissue originated, either directly or indirectly
  - This study will use only 'leftover' tissue
- The Tonsil Archive was established on an unlinked anonymous basis for the following reasons:
  - There is currently no effective treatment for vCJD
  - The prognostic significance of a positive test for PrP^{Sc} in an asymptomatic person is not known
  - Potentially serious psychological harm may arise from being told they may be incubating a fatal and incurable neurological illness
- After tonsillectomy, residual tissue remains present in the tonsil bed
  - A biopsy of tonsil tissue can be done at any time in the future should this be required for diagnostic purposes

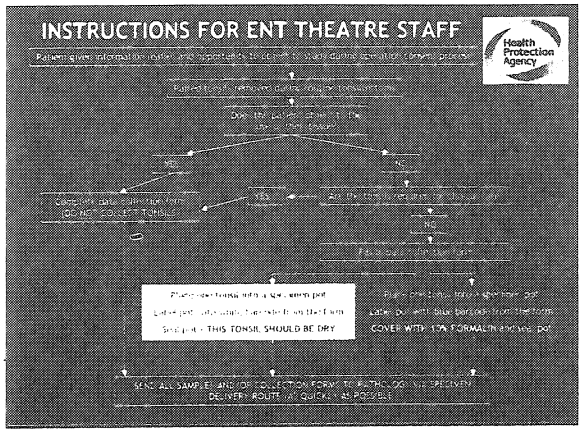
Hospitals

- The number of tonsillectomies undertaken annually have been declining. Approximately 45,000 tonsillectomies are carried out each year
- The project will aim to collect 80-100% of all tonsils removed in approximately 100 NHS Trusts reporting the largest number of tonsillectomies (>200 tonsillectomies per year)



INSTRUCTIONS FOR ENT THEATRE STAFF

Health Protection Agency



INSTRUCTIONS FOR PATHOLOGY STAFF

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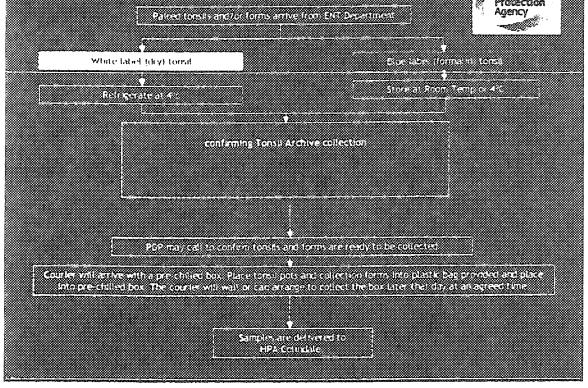

Many thanks for your attention!