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ORIGINAL ARTICLE *Transfusion transmitted disease*

The risk of variant Creutzfeldt-Jakob disease among UK patients with bleeding disorders, known to have received potentially contaminated plasma products

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Summary. The risk of variant Creutzfeldt-Jakob disease (vCJD) from potentially infected plasma products remains unquantified. This risk has been assessed for 787 UK patients with an inherited bleeding disorder prospectively followed-up for 10–20 years through the UK Haemophilia Centre Doctors' Organisation (UKHCDO) Surveillance Study. These patients had been treated with any of 25 'implicated' clotting factor batches from 1987 to 1999, which included in their manufacture, plasma from eight donors who subsequently developed clinical vCJD. Variant CJD infectivity of these batches was estimated using plasma fraction infectivity estimates and batch-manufacturing data. Total potential vCJD infectivity received by each patient has been estimated by cumulating estimated infectivity from all doses received during their lifetime. Of 787 patients, 604 (77%) were followed-up for over 13 years following exposure to an implicated batch. For these 604 patients, the estimated vCJD risk is ≥1% for 595, ≥50% for 164 and 100% for 51. This is additional to background UK population risk due to dietary exposure. Of 604 patients, 94 (16%) received implicated batches linked to donors who developed clinical vCJD within 6 months of their donations. One hundred and fifty-one (25%) had received their first dose when under 10 years of age. By 1st January 2009, none of these patients had developed clinical vCJD. The absence of clinical vCJD cases in this cohort to date suggests that either plasma fraction infectivity estimates are overly precautionary, or the incubation period is longer for this cohort than for implicated cellular blood product recipients. Further follow-up of this cohort is needed.

Keywords: haemophilia, inherited bleeding disorders, risk assessment, UK plasma products, variant Creutzfeldt-Jakob disease

Introduction

The bovine spongiform encephalopathy (BSE) epidemic in UK cattle occurred from 1980 to 1996. Evidence has been presented that a distinct clinicopathological variant of Creutzfeldt-Jakob disease (vCJD), first described in 1996 [1], is the human manifestation of BSE [2–4]. Concerns that vCJD may be transmissible by blood and blood products, and actions taken to reduce the risk to UK patients with an inherited bleeding disorder, have recently been reported [5].

The vCJD risks from plasma products linked to donors who later developed vCJD, remain unquantified. Det Norske Veritas's (DNV) risk assessment informed the introduction of further public health measures for recipients of UK-sourced plasma products in 2004 [6]. These recipients included patients with inherited bleeding disorders who had been treated with UK-sourced plasma products between 1980 and 2001. On the advice of the CJD Incidents Panel (CJDIP), and facilitated by the Health Protection Agency (HPA), these patients were informed of their risk by the UK Haemophilia Centres Doctors' Organisation (UKHCDO) *via* their

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Haemophilia Centres and asked to implement public health measures to reduce the possible risk of vCJD spreading to others [5].

The nature of the blood-associated vCJD agent and the impact of processing technologies on the nature and distribution of vCJD infectivity in human blood components and plasma products were unknown. Therefore, the DNV risk assessment was based on data from published animal studies and a number of assumptions [6]. Three options were developed: (i) the fractionation step with the largest clearance of infectivity represents the entire process, (ii) the reduction in infectivity when separating blood into blood components and plasma fractions is the only step that reduces infectivity when producing plasma products, and (iii) the infectivity level correlates with the protein content of plasma products. Option (iii) was rejected as it was considered scientifically invalid. The CJDIP adopted option (ii) rather than (i) on the basis that it was more precautionary and because there were uncertainties around the clearance values in option (i).

This article presents the application of this risk assessment to 787 bleeding disorder patients who have received implicated clotting factor batches linked to donors who later developed clinical vCJD. The identification of the abnormal prion protein associated with asymptomatic vCJD postmortem in a patient in this cohort has prompted this assessment [7]. The implications to inform further public health responses are discussed.

Materials and methods

Implicated plasma product batches

In the UK, a total of 178 plasma product batches have been linked to 25 plasma donations from 11 donors who subsequently developed clinical vCJD [8]. These include 25 implicated clotting factor[1] batches linked to 18 plasma donations from eight donors that have been used to treat 787 UK patients with inherited bleeding disorders. The batches had expired before the 2004 patient notification.

Calculation of infectivity of plasma products

Plasma from many thousands of donations is pooled prior to fractionation. The DNV risk assessment provided estimates of potential infectivity of different plasma fractions. Infectivity was quantified using the ID_{50}, where one ID_{50} is the dose required to produce infection in 50% of recipients.

[1]Factor concentrates are made from pooled plasma and include FVIII, FIX, FVII, FXI, FXIII and prothrombin complex concentrates as well as antithrombin.

In 2004, the HPA used a 'Product Risk Calculator' tool to estimate the infectivity of each implicated batch (Appendix 1 Supporting information). The tool combined the DNV infectivity estimates with fractionators' batch-manufacturing data. For each batch, it calculates the dose estimated to contain 0.02 ID_{50}. This represents a 1% risk of infection in addition to the general background population risk from potential dietary exposure. This is the level of risk the CJDIP considered sufficient to warrant patient notification and public health action [9]. The cumulated lifetime infectivity received by each patient was estimated using the data on each batch and the total quantity received.

Identification and management of patients with bleeding disorders

A policy decision was taken that all bleeding disorder patients treated with UK-sourced clotting factors from 1980 to 2001 (rather than just those who had received implicated clotting factors) should be considered 'at risk' of vCJD for public health purposes [5]. This decision was made because: (i) a single dose of implicated clotting factor was thought to contain sufficient infectivity for a recipient to cross the 1% additional risk threshold (high risk plasma product), and (ii) it was considered likely that further implicated clotting factors would be identified if future clinical vCJD cases were found to have donated plasma.

Haemophilia clinicians used locally held or National Haemophilia Database (NHD) records to identify all recipients of UK-sourced plasma products from 1980 to 2001 and used product information from two UK fractionators to identify patients who had received implicated clotting factors. Patients notified as being 'at-risk' of vCJD for public health purposes were able to choose whether or not to find out if they had received implicated clotting factors. Haemophilia clinicians were encouraged to report these patients (unless they had withheld consent) to the NHD, for follow-up. This has been in the UKHCDO vCJD Surveillance Study following ethical approval from the London Multicentre Ethics Committee (MREC/01/2/11).

National haemophilia database

Data on product type and batch number of implicated batches, total doses received and start and completion dates of each treatment were collected by haemophilia centres. The NHD is updated annually by individual UK haemophilia centres with treatment data sets and information about new diagnoses and deaths. All deaths and causes of death are verified as patients are flagged with the Office for National Statistics. Person-years at risk of vCJD were calculated by subtracting the date of

the first dose of an implicated batch from either 1st January 2009 or the date of death as appropriate.

Results

Patient population in NHD

A total of 8547 patients with inherited bleeding disorders were registered on the NHD on 1st January 2009 (Table 1). Of these, 3735 have been identified as having received UK-sourced clotting factors between 1980 and 2001 and therefore are defined as 'at risk' of vCJD for public health purposes. Of these, 787 had received implicated clotting factors batches ('implicated batch') linked to donors who later developed clinical vCJD. Auditing notification data for each centre against implicated batches supplied to them by the two UK fractionators show that 11 million IUs (about 50%) of implicated batches remains unaccounted for [5]. As a result of this under-notification, it is estimated that the 787 patients represent approximately 50% of all patients who had received implicated batches. The following results/data concern these 787 implicated batch recipients.

Outcome, deaths and autopsy

No clinical cases of vCJD have been observed in these patients as of 1st January 2009. Fifty-one (6.5%) deaths were reported by 1st January 2009 but none was related to vCJD. Only four autopsies have been performed in this cohort. Abnormal prion protein, indicating vCJD infection, has been detected in a single postmortem spleen sample of a haemophilia patient who died of causes unrelated to vCJD 11 years after receiving 9025 IUs (estimated vCJD infectivity ID_{50} 0.21) from two implicated FVIII batches [7]. These batches were linked to two plasma donations from a donor who developed vCJD within 6 months of the second donation.

Estimated infectivity of implicated batches

Table 2 is the list of implicated batches showing the quantities of each batch used with their estimated infectivity, and the number of patients treated with each batch. Two hundred and sixty three (33%) patients received >1 implicated batches and 229 (29%) patients received implicated batches linked to >1 donors. A total of 12.7 million IUs of implicated FVIII and FIX was used to treat 787 patients from 1987 to 1999. On average each patient received 10 000 IUs (median) (range 240–169960) and estimated vCJD infectivity 0.443 ID_{50} (median) (range 0.010–9.593). A total of 773 (98%) patients received estimated vCJD infectivity ≥0.02 ID_{50} (Fig. 1). Of 604 (77%) patients who have been followed-up for over 13 years, which is the predicted incubation period of primary vCJD [10,11], 595 have ≥1%, 164 have ≥50% and 51 have 100% estimated vCJD risk in addition to the background UK population risks due to potential dietary exposure.

Donors linked to implicated batches

Table 3 is the list of eight donors showing data on implicated batches and the number of recipients linked to each of them. These donors developed vCJD 88 months (median) (range 6–143) following their last donations. One hundred and forty-nine (19%) patients received implicated batches linked to donors who developed vCJD within 6 months of donation and 552 (70%) linked to donors who developed vCJD within 6 years of donation. When estimated infectivity is plotted against interval between donation and onset of vCJD in donors the distribution of patients for these parameters can be clearly seen (Fig. 2). The patient in whom the abnormal prion protein associated with vCJD was found at postmortem received two implicated batches from donor 1 [7]. For one of these batches, the interval between donation and onset of vCJD in the donor is 6 months but with a relatively

Table 1. Patients with inherited bleeding disorders registered in the National Haemophilia Database on 1st January 2009 by diagnosis and subgroups at risk of vCJD for public health purposes.

	Number of patients with bleeding disorders by diagnostic subgroups				
Patient group and subgroups	Haemophilia A	Haemophilia B	von Willebrand	Other	Total
Total registered in the National Haemophilia Database (NHD)	3 281	729	2 996	1 541	8 547
Registered patients who are at risk of vCJD: (treated with UK sourced plasma products between 1980 and 2001)	2 246	562	518	409	3 735
Registered patients at risk of vCJD who are known to have received implicated clotting factor batches	556	168	39	24	787*

*11 million IUs (about 50%) of implicated batches remain unaccounted for [5]. As a result of this under-notification, it is estimated that the 787 patients represent approximately 50% of all patients who had received implicated batches.

Table 2. Description of each implicated clotting factor batch used to treat 787 patients with inherited bleeding disorders.

Batch number	Brand name†	Donor IDs linked to implicated clotting factor batches*	Months between donation and onset of vCJD in donors	Estimated infectivity (ID_{50}) per IU for each batch†	Total quantities (IUs) of each batch used	Estimated total infectivity (ID_{50}) received from each batch	Total number of patients registered as treated with each batch (n = 787)‡
FHB4547§	8Y	1	6	0.0000199	873 821	17.424	61
FHB4596	8Y	6	31	0.000043	1 054 410	45.340	93
FHC4237§	8Y	1	46	0.0000472	983 977	46.444	117
FHB4189	8Y	8	112	0.0000486	735 725	35.756	71
FHB4419	8Y	3	15	0.0000584	656 600	38.345	55
FHB4116	8Y	2	31	0.0000774	280 710	21.727	34
FHC0369	8Y	8	139	0.000088	199 060	17.517	52
FHC0289	8Y	2	59	0.0000948	266 960	25.308	46
FHC0059	8Y	5	143	0.0001135	58 560	6.645	10
FHM4054	High purity F8	8	127	0.0000662	304 500	20.158	33
FHM3990	High purity F8	8	134	0.0000738	169 055	12.476	11
FHE4548§	Replenate	1	6	0.0000246	965 400	23.749	88
FHF4625	Replenate	7	58	0.0000262	1 035 900	27.141	47
FHE4536	Replenate	6	40	0.000029	1 224 270	35.504	97
FHE4437	Replenate	8	82	0.0000388	818 095	31.742	73
0304-70510	Z8	4	134	0.0009526	16 150	15.385	3
FJA4308	9A	8	94	0.0000343	379540	13.031	20
FJA4239B§	9A	1	46	0.0000548	141435	7.755	9
FJA0092	9A	2	59	0.0000735	92990	6.835	18
FJA0020	9A	5	143	0.0000948	88025	8.349	10
3502-70210	HT Defix	4	138	0.0001391	216220	30.083	26
FJM4327	Replenine	8	98	0.0000226	1129915	25.536	80
FJM4625	Replenine	7	58	0.0000434	22145	0.961	4
FJM4437	Replenine	8	82	0.0000592	379380	22.459	29
FJM4596	Replenine	6	31	0.0000604	592380	35.780	49

*These numbers have been assigned to anonymize the donors for this study.
†Sorted by brand name and estimated infectivity per IU.
‡15 patients were treated with the same batch of an implicated clotting factor in more than one treatment episode. 256 patients were treated with different batches of implicated clotting factors in more than one treatment episode.
§Four implicated clotting factor batches were linked to the donor whose donations were linked to vCJD infection of a patient with bleeding disorder [7]. This patient received implicated clotting factor batches: FHB4547 and FHC4237.

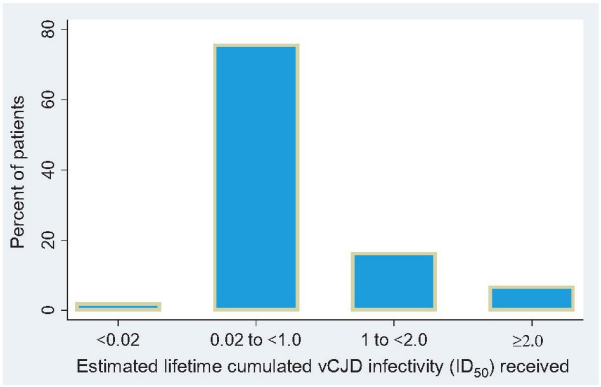

Fig. 1. Distribution of patients with bleeding disorders by estimated lifetime cumulated vCJD infectivity received (n = 787).

low estimated infectivity dose. Others have received higher estimated infectivity from the same donor and the same donation, but none of them has developed clinical vCJD.

Age at exposure and person-years at risk

The median age at which patients received their first dose of an implicated batch was 22 years (range 0.3–87). 174 (22%) patients were under 10 years, 362 (46%) under 20 years, and 628 (80%) were under 40 years of age when they received their first dose. The median age of patients who were alive on 1st-January-2009 (n = 736) was 35 years (range 13–92). The median follow-up time from the date of the first dose of an implicated batch to 1st January 2009 or the date of death was 15 years (range 2 days–22 years) (person-years at risk). Plotting the estimated infectivity against person-years at risk reveals many patients with more event free person-years at risk than the patient with known abnormal prion protein [7] (Fig. 3).

Discussion and conclusion

This article reports the absence of clinical vCJD cases among 787 patients with an inherited bleeding disorder who have been treated with high risk[2] implicated clotting factors. These include 604 (77%) patients who have lived longer after receiving the first doses of implicated clotting factors than the predicted incubation period of 13 years for primary vCJD [10,11]. Of them, one quarter (n = 164) have ≥50% estimated risk

[2]A single dose of implicated clotting factor was thought to contain sufficient infectivity for a recipient to cross the 1% risk threshold.

Table 3. Description of implicated donations, manufactured clotting factors, known quantities used, the number of identified patients treated, average quantities and infectivity received by each patient from individual donors.

Donor IDs	Months between donations and onset of vCJD in a donor*	Number of batches of each product linked to a donor (n = 25)		Total quantities (IUs) of implicated clotting factors linked to a donor	Total number of patients linked to a donor (n = 787)†	Average quantities (IUs) received by each patient (median, range, quartiles)	Average vCJD infectivity (ID_{50}) received by each patient (median, range, quartiles)
1‡	6,§ 46§	8Y	2	2 963 633	257	9000	0.245
		9A	1			260–96000	0.010–4.531
		REPLENATE	1			3000–15700	0.118–0.481
2‡	31, 59	8Y	2	640 660	83	5900	0.483
		9A	1			255–29820	0.024–2.527
						1770–11000	0.145–0.914
3	15	8Y	1	656 600	55	9400	0.549
						470–54990	0.027–3.211
						4700–16000	0.274–0.943
4‡	135, 138	HT DEFIX	1	232 370	29	5520	0.883
		Z8	1			552–48852	0.077–9.593
						2760–8800	0.384–1.690
5	143	8Y	1	146 585	20	4800	0.502
		9A	1			240–35645	0.027–3.381
						1928–9650	0.197–1.089
6‡	31, 40	8Y	1	2 871 060	238	10000	0.373
		REPLENATE	1			500–102960	0.015–3.851
		REPLENINE	1			4755–15300	0.155–0.616
7	58	REPLENATE	1	1 058 045	51	13510	0.472
		REPLENINE	1			965–57900	0.025–1.517
						5150–30880	0.152–0.809
8‡	82, 94, 98, 112,	8Y	2	4 112 770	336	9700	0.376
	127, 134, 139	9A	1			460–100000	0.011–5.511
		HPF VIII	2			3475–15343	0.178–0.660
		REPLENATE	1				
		REPLENINE	2				

*Median interval between donation and onset of vCJD in donors was 88 months. 149 (19%) of patients received implicated batches linked to donors who developed vCJD within 6 months of donation and 552 (70%) linked to donors who developed vCJD within 6 years of donation.
†The figures in the column do not add to 787 because of exposure to multiple implicated donors. 557 patients were treated with implicated clotting factor batches linked to one donor, 182 to two donors, 45 to three donors, two to four donors, and one to five donors.
‡Donors 1, 2, 4, 6 and 8 donated more than once.
§The vCJD infected patient was treated with implicated clotting factor batches linked to two donations from this donor [7].

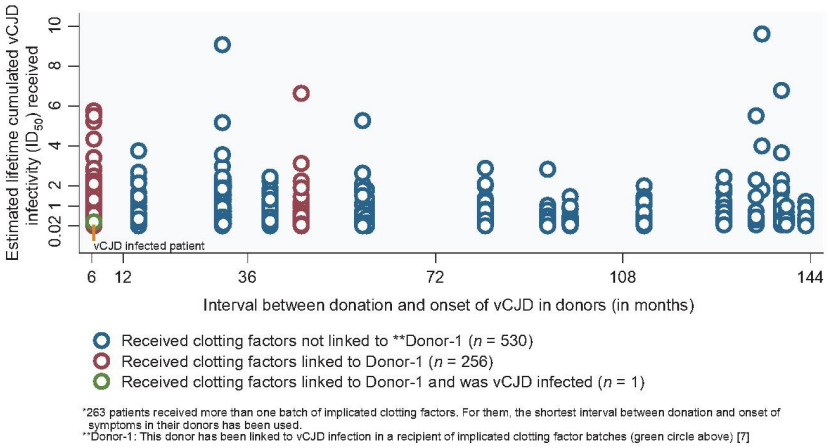

Fig. 2. Scatterplot showing estimated lifetime cumulated vCJD infectivity of implicated clotting factors received by patients with bleeding disorders by interval between donation and onset of symptoms in donors* (n = 787).

(received ≥1ID_{50}) and 8% (n = 51) have 100% risk (received ≥2ID_{50}) of vCJD in addition to background UK population risk due dietary exposure. Forty-nine of the 51 patients who have 100% risk were still alive on 1st January 2009. Thirteen of these 49 patients had received clotting factors linked to donors who developed vCJD within 6 months of their donation. The risk to these patients was calculated using estimates from the DNV risk assessment, and batch-manufacturing data.

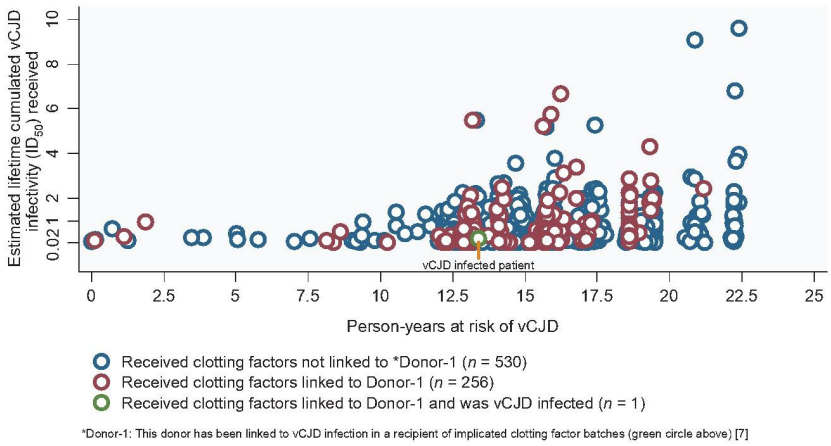

Fig. 3. Scatterplot showing estimated lifetime cumulated vCJD infectivity of implicated clotting factors received by patients with bleeding disorders by their person-years of exposure (n = 787).

The incubation period of vCJD within this at risk group may prove to be longer than the predicted incubation period of primary vCJD and secondary vCJD due to non-leucodepleted packed red cells transfusion. The infective dose in the plasma and red cell components is assumed equal but the implicated plasma is diluted in the plasma pool and then distributed between many vials. A large body of data from different experimental approaches (including endogenous infectivity models) consistently show that conventional bio-separation processes used in plasma product manufacturing are capable of removing prion agents to a significant extent [12,13]. These data question whether the highly precautionary approach as adopted in the UK is still judged as appropriate. It is possible that the infectivity clearance assumptions made in the DNV risk assessment, and the option chosen by the CJDIP are overly precautionary.

Other countries have adopted less precautionary approaches. Authorities in France concluded that the risk posed by implicated batches, even in the most pessimistic scenario, was very low. Consequently, they decided to continue to fractionate plasma sourced from domestic blood supply, introducing nano-filtration as an additional step in the process [14]. Authorities in Canada concluded that the risk of transmission of vCJD for patients who have received FXI linked to UK donors is in the range of 1 in 100 000 to 1 in 1 000 [15]. In their risk assessment, the US FDA included infectivity reductions associated with various processing steps in the production of FVIII and has concluded that the risk of vCJD infection is likely to be extremely low ranging from 1 in 9.4 million to 1 in 15 000 [16].

Age dependent susceptibility is required to fully account for observed age distribution of primary vCJD cases [11]. Age at treatment (8–10 years) with human growth hormone has been found to be a risk factor for secondary CJD in the UK [17]. If age dependent susceptibility is a risk factor for secondary vCJD, then the 174 (22%) patients who received their first dose of implicated clotting factors before 10 years of age may have an increased susceptibility to vCJD infection. The median follow-up time from first exposure in this subgroup is 16 years (range 12–22).

It is of interest that a recent publication links impaired scrapie agent neuroinvasion in aged mice with effects of host age on follicular dendritic cell status [18]. If immune function affects vCJD neuroinvasion in man, then it can be speculated that the immune modulation and deficiency associated with blood borne virus infections in some of this cohort may make subclinical vCJD infection more likely rather than clinical disease.

The dose response relationship has not been established for TSE infections. Experimental estimation of dose response relationship requires a large number of experimental animals, particularly if the level of infectivity is low. Unfortunately, there is very little data on dose response relationship in TSE infections. The DNV risk assessment considered different models on dose response relationship in TSE infections using available data and came up with the assumption that the dose-response function for vCJD infectivity is linear without any threshold [6]. More experimental data are required to validate this assumption to improve the risk assessment.

The DNV risk assessment assumes that risk from regular equal doses of vCJD implicated plasma product over a 1-year-period is additive, and it ignores doses received after the first year. Where the patients have received variable doses from different batches and/or from different donors during several years with wide variations in the estimated levels of infectivity, it is difficult, and somewhat meaningless to calculate an annual dose. Therefore, the CJDIP took a precautionary approach and decided to estimate cumulative lifetime infectivity.

While the under reporting of implicated batch recipients is a concern, it does not invalidate the descriptive data on risk assessment. These may inform any future risk assessment should vCJD develop in a patient who has received implicated batches of clotting factors.

Other factors, such as, prion protein genotype, age at exposure, interval between donation and development of vCJD in the donor, lifetime cumulative infectivity received and the number of donor exposures may also help assess the vCJD risk in this cohort. The continuance of this surveillance study especially with improved recruitment to its postmortem and biopsy arm may provide valuable information that aids our understanding of developing vCJD after exposure to implicated clotting factor batches and allows more informed risk counselling of patients.

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Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

1 Will RG, Ironside JW, Zeidler M *et al.* A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996; 347: 921–5.
2 Bruce ME, Will RG, Ironside JW *et al.* Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature* 1997; 389: 498–501.
3 Collinge J. Variant Creutzfeldt-Jakob disease. *Lancet* 1999; 354: 317–23.
4 Hill AF, Desbruslais M, Joiner S *et al.* The same prion strain causes vCJD and BSE. *Nature* 1997; 389: 448–50.
5 Millar CM, Connor N, Dolan G *et al.* Risk reduction strategies for variant Creutzfeldt-Jakob disease transmission by UK plasma products and their impact on patients with inherited bleeding disorders. *Haemophilia* 2010; 16: 305–15.
6 DNV Consulting. *Risk Assessment of Exposure to vCJD Infectivity in Blood and Blood Products for Department of Health*. London: Det Norske Veritus, 2003. Available at: http://www.dnv.com/binaries/vCJD_Update_Report_tcm4-74414.pdf. http://www.dnv.com/binaries/AppI-Blood_description_tcm4-74415.pdf. http://www.dnv.com/binaries/AppII_tcm4-74416.pdf. Accessed April 30, 2010.
7 Peden A, McCardle L, Head MW *et al.* Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. *Haemophilia* 2010; 16: 296–304.
8 Hewitt PE, Llewelyn CA, MacKenzie J, Will RG. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study. *Vox Sang* 2006; 91: 221–30.
9 CJD Incidents Panel. *Management of Possible Exposure to CJD through Medical Procedures: A Consultation Paper*. London, 2001. Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4078221.pdf. Accessed 28 April, 2010.
10 Ghani AC, Donnelly CA, Ferguson NM, Anderson RM. Updated projections of future vCJD deaths in the UK. *BMC Infect Dis* 2003; 3: 4.
11 Boelle PY, Cesbron JY, Valleron AJ. Epidemiological evidence of higher susceptibility to vCJD in the young. *BMC Infect Dis* 2004; 4: 26.
12 Ludlam CA, Turner ML. Managing the risk of transmission of variant Creutzfeldt Jakob disease by blood products. *Br J Haematol* 2006; 132: 13–24.
13 Flan B, Arrabal S. Manufacture of plasma-derived products in France and measures to prevent the risk of vCJD transmission: precautionary measures and efficacy of manufacturing processes in prion removal. *Transfus Clin Biol* 2007; 14: 51–62.
14 Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS). *Risk Analysis of New Variant Creutzfeldt-Jakob Disease Transmission by Blood and Blood products*. Paris, 2000. Available at: http://www.bpro.or.jp/publication/pdf_jptrans/fr/fr200012en.pdf. Accessed April 30, 2010.
15 Public Health Agency of Canada. *A Cursory Analysis Addressing the Question of the Assessment of Exposure to Particular Batches of Variant Creutzfeldt-Jakob Disease (vCJD) Implicated Plasma Products (Draft)*. Ottawa, Canada: Statistics and risk assessment section. Blood safety surveillance and health care acquired infections division. Centre for infectious disease prevention and control. Public Health Agency of Canada, 2004.
16 US FDA. *Draft Quantitative Risk Assessment of vCJD Risk Potentially Associated with the Use of Human Plasma-Derived Factor VIII Manufactured under United States (US) License from Plasma Collected in the US*. MD, USA: Center for Biologics Evaluation and Research. US Food and Drug Administration, 2006. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/UCM095104.pdf. Accessed 30 April, 2010.
17 Swerdlow AJ, Higgins CD, Adlard P, Jones ME, Preece MA. Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone. *Neurology* 2003; 61: 783–91.
18 Brown KL, Wathne GJ, Sales J, Bruce ME, Mabbott NA. The effects of host age on follicular dendritic cell status dramatically impair scrapie agent neuroinvasion in aged mice. *J Immunol* 2009; 183: 5199–207.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Users Guide to the Product Risk Calculator.

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