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ORIGINAL ARTICLE *Transfusion transmitted disease*

Risk reduction strategies for variant Creutzfeldt–Jakob disease transmission by UK plasma products and their impact on patients with inherited bleeding disorders

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Summary. The appearance and rapid evolution of BSE in UK cattle in the mid 1980s, with compelling data supporting variant Creutzfeldt–Jakob disease (vCJD) as its human manifestation, pose a potentially severe threat to public health. Three clinical cases and one asymptomatic case of vCJD infection have been reported in UK recipients of non-leucodepleted red cell transfusions from donors subsequently diagnosed with vCJD. Plasma from both these and other donors who later developed vCJD has contributed towards plasma pools used to manufacture clotting factor concentrate. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Surveillance Study has detected asymptomatic vCJD postmortem in a haemophilic patient treated with UK plasma products including two batches of clotting factor linked to a donor who subsequently developed vCJD. Over 4000 bleeding disorder patients treated with UK plasma products are recorded on the UKHCDO National Haemophilia Database. The risk of vCJD transmission by plasma products is not known. However, public health precautions have been implemented since 2004 in all UK inherited bleeding disorder patients who received UK-sourced plasma products between 1980 and 2001 to minimize the possible risk of onward vCJD transmission. We evaluate vCJD surveillance and risk management measures taken for UK inherited bleeding disorder patients, report current data and discuss resultant challenges and future directions.

Keywords: haemophilia, inherited bleeding disorders, UK plasma products, variant Creutzfeldt–Jakob disease

Introduction

The first reports of a prion disease in humans, Creutzfeldt–Jakob disease (CJD), appeared in the 1920s [1,2] with a distinct clinico-pathological variant being described in 1996, variant Creutzfeldt–Jakob disease (vCJD) [3] in which significant involvement of lymphoreticular tissues was demonstrated [4,5]. Compelling epidemiological, clinical, neuropathological and experimental data support vCJD as the human manifestation of bovine spongiform encephalopathy (BSE) [4,6,7], an epidemic of which occurred in UK cattle in the 1980s and early 1990s. The incidence of BSE peaked in 1993, and while the precise origin of the BSE epidemic remains unclear, there is little doubt that the rendering practices employed at that time significantly contributed to its rapid spread throughout the UK. Feeding cattle and sheep ruminant-derived protein was

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banned in 1988 [8], with an ensuing fall in the number of BSE cases. However, such measures were not taken in time to prevent the introduction of BSE-infected cattle carcasses into the human food chain. By January 2010, 167 clinical cases of vCJD attributable to dietary exposure had been reported in the UK by the National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU), a majority of which have been confirmed by neuropathological examination [9]. Much lower but increasing numbers of cases have been reported worldwide, the majority of which are believed to have contracted vCJD in their country of origin [10], probably as a result of the export of UK animals and/or ruminant feed. Although the annual incidence of clinical vCJD in the UK has been steadily declining since 2000 and the extent of the primary vCJD outbreak has been several magnitudes less than previously predicted [11,12], limited information is available to provide accurate estimation of the number of future clinical cases. Where genetic information is available, all confirmed clinical cases of vCJD have thus far been shown to be homozygous for the methionine residue at codon 129 of the prion protein gene (*PRNP*). However, a suspected clinical case of vCJD in an individual heterozygous for methionine/valine has recently been reported [13].

Transfusion transmission of vCJD: early perception of risk, risk reduction measures and plasma product recalls

Distinct from the number of new clinical cases is the unknown prevalence in the UK of presymptomatic, or subclinical, vCJD infection, i.e. where asymptomatic individuals harbour vCJD infection as discussed elsewhere [10,14]. It is from this group of individuals that the risk of secondary vCJD transmission arises, with the characteristic prominent lymphoreticular phase giving rise to the possibility of transmission via surgical instruments, blood and blood products and organ (including bone marrow) transplantation. This differs from classical sporadic CJD, which has been shown to be transmissible by neurosurgical instruments, pituitary derived hormones and corneal transplants but in which transmission by blood or blood products has not been demonstrated [15–21]. The widespread transmission of hepatitis C and human immunodeficiency virus (HIV) infections by plasma products prior to 1986 raised ongoing concerns about the possible emergence of new blood-borne pathogens. These led to the publication of therapeutic guidelines by the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) recommending, where possible, that plasma-derived factor VIII (FVIII) and factor IX (FIX) concentrates be replaced with recombinant products in the treatment of patients with haemophilia A and B [22]. The first report of clinical vCJD cases in 1996 [3] raised concerns amongst UK haemophilia clinicians that the infective agent may be transmissible by blood products [23]. Around the same time, a collaborative study, the Transfusion Medicine Epidemiology Review (TMER), was established between the NCJDSU and the four UK blood services (UKBS) with the aim of identifying any association between CJD (including variant) and blood transfusion [24]. At that time, 17 patients were recorded as having donated blood prior to being diagnosed with vCJD and there was concern that there may be many more infected, yet asymptomatic individuals amongst the donor population. It was estimated that even a modest prevalence of vCJD in the general population could result in an infected donation entering the plasma pools from which clotting factor concentrates were prepared. Together with the almost exclusive restriction of vCJD to the UK at that time, these concerns greatly influenced the UKHCDO's decision in 1997 to recommend the use of bovine material-free recombinant products, as well as fractionated products from non-UK plasma donations [23]. Treatment with recombinant factor concentrates was funded in 1998 for haemophilic patients aged <16 years and was extended to include all adult patients by ascending age from 2003/2004 and completed in 2005/2006.

In the absence of a test to detect preclinical vCJD infection, a number of precautionary donor selection and component processing measures have been introduced since 1998 to minimize the possible risk of secondary vCJD transmission by blood and its components (Table 1) [25–29]. The uncertainty of vCJD transmissibility by plasma products led to the recommendation by the Committee for Proprietary Medicinal Products that a product be recalled where a donor subsequently diagnosed with vCJD had contributed to the plasma pool (termed an 'implicated' batch) [30]. In 1997, there were two Bio Products Laboratory (BPL, the plasma fractionator for the UK National Blood Service) recalls of clotting factor concentrates [31], both of which included batches of in-date FVIII concentrate.

The first risk assessment of plasma vCJD infectivity

Theoretically, the degree of exposure of an individual recipient to vCJD infection is dependent on the prevalence of subclinical infection within the donor

Table 1. Measures taken in the UK to minimize risk of variant Creutzfeldt–Jakob disease (vCJD) transmission by blood and plasma product transfusion.

I. Rationalization of clinical use of blood and blood products. Department of Health initiatives: Better Blood Transfusion 1998, 2002, 2007
II. Donor selection
a. Use of non-UK donors for plasma product fractionation (announced 1998, implemented 1999)
b. Use of non-UK plasma donors in under 16 s or adult recipients of large plasma volumes (2002)
c. Exclusion of recipients of blood transfusion since 1980 from donor pool (2004)
d. Exclusion of individuals from donor pool who are unsure whether they have received a blood transfusion since 1980 (2004).
e. Exclusion of donors where recipients have developed vCJD where blood transfusion cannot be excluded as source of vCJD and where no infected donor has been identified (2005)
III. Component processing
a. Leucodepletion of all blood products to white cell concentration $<10^6$ L^{-1} (announced 1998, implemented 1999)
b. Use of recombinant factors in selected patients with haemophilia A and B (1998) and all others (2003–2005)
IV. Product recall where donor confirmed as suffering from vCJD found to have contributed to plasma pool

Table 2. Possible determinants of risk of variant Creutzfeldt–Jakob disease (vCJD) transmission by transfusion of blood and plasma products.

I. Levels of infectivity in donor population
a. Prevalence of sub-clinical infection – geographical variation
II. Exposure of recipient to infected donors
a. Infectivity of donation within incubation period
b. Quantity of plasma/leucocytes within component
c. Number of donors contributing towards component/size of plasma pool
d. Number of transfusions received
e. Manufacturing process: e.g. leucodepletion, plasma fractionation, inactivation procedures
III. Susceptibility of recipient
a. Genotype e.g. codon 129 *PRNP*
b. Age
c. Other

population, the manufacturing process of a given blood component and the number of transfusions received (Table 2). The partitioning of prion infectivity during the manufacture of plasma products has been extensively investigated and is reported elsewhere [32–37]. In addition, there is individual variation in susceptibility to infection, with possible influences including age and *PRNP* genotype. An independent assessment of the risk to patients of exposure to vCJD infectivity in blood products was carried out on behalf of the Department of Health (DH) by Det Norske Veritas Consulting (DNV) and reported in 1999 [38]. To estimate the numbers of new infections and possible resultant vCJD cases, the authors attempted to estimate the proportion of UK blood donations that may be infected with vCJD, the possible level and distribution of vCJD infectivity in blood components and plasma products derived from those donations and the likely level of exposure to infectivity of defined sets of patient groups. Substantive data surrounding several of the variables used in these calculations were lacking, necessitating various assumptions and that data be extrapolated from spiked animal models [39,40]. Based on the assumption that blood is equally infective throughout the incubation period of the disease, the likely proportion of infected donations was estimated as between 1/200 and $1/10^6$, depending on the median incubation period of the disease. Over the same range of infected donations, the recipient's risk of infection was predicted to range between unity and $1/10^6$, depending on the patient group. Each infected donation was estimated to result in 2.6 infected recipients (assuming roughly equal contributions from red cell and plasma product transfusions), approximately 80% of whom may live long enough to develop vCJD [38].

The subsequent confirmation of a further clinical case of vCJD in an individual whose blood donations had previously contributed towards plasma pools resulted in a further BPL recall in 2000 [41]. Unlike the 1997 recalls, all batches of clotting factor concentrate had passed their respective expiry dates at the time of this recall. In Scotland, two donations from an individual later diagnosed with vCJD had contributed to the Scottish National Blood Transfusion Service (SNBTS) fractionation pools, and the affected FVIII and FIX products that had been issued to centres in Scotland and Northern Ireland between 1987 and 1989 were described in the SNBTS notification of 2001.

Management of early plasma product recalls

At the time of the 1997 and 2000 BPL and 2001 SNBTS notifications, the haemophilia centres issued with implicated batches of clotting factor were asked to return any remaining stock and recall any remaining unused batches supplied to patients. No public health precautions were advised at the time of these recalls. The 1997 product recall letters from BPL to haemophilia centres cited the following advice that had been provided by the ethics committee local to the NCJDSU: 'the recipients (patients) should not be informed that the product that they

had received has been recalled for this reason [subsequent diagnosis of vCJD in donor] [31]'. In response to queries raised by clinicians and hospital trusts about this directive, the DH confirmed to medical directors that patients who had received implicated blood products should not be informed [42]. This was based on three considerations: first, that it was not known (the word used was 'unlikely') whether vCJD was transmissible by blood products; secondly, that there was no diagnostic test in existence, and finally that no preventative treatment was available. The consensus given by the DH at the time was that patients would 'not benefit from this knowledge, and that uncertainty created by informing patients could cause unjustified worry and create a permanent blight on their lives' [42]. However, many haemophilia physicians either directly informed patients who had received an implicated batch, or provided all their patients with information about vCJD, giving them the option to be informed whether or not they had received an implicated batch(es). In the case of paediatric patients, parents were similarly contacted. The establishment of the CJD Incidents Panel (CJDIP) in 2000 on behalf of the Chief Medical Officer provided an independent expert committee that advised on issues involving possible vCJD transmission in healthcare settings.

vCJD surveillance in UK patients with inherited bleeding disorders

Over 20 000 UK patients with inherited bleeding disorders are currently registered on the National Haemophilia Database (NHD) of whom around one-fifth have been treated with clotting factor concentrate derived from UK-sourced plasma donations. A pilot retrospective histopathological study of the brains of 22 haemophilic patients who died of HIV-related illnesses during part of the period of potential vCJD infection showed no evidence of vCJD [43]. A 5-year surveillance study of patients with haemophilia was commissioned and funded by the DH in 2000 and co-ordinated by the UKHCDO following ethical approval being given by the London Multi-Centre Research Ethics Committee (MREC/01/2/11). The aims of this study were to determine the extent of exposure of individual patients with inherited bleeding disorders to implicated batches of clotting factor concentrate, to analyse tissue biopsies and autopsy material for vCJD and to notify possible and confirmed clinical cases of vCJD in the UK haemophilic population. It was hoped that all haemophilic patients undergoing surgical procedures involving the central nervous system and lymphoid tissue (including tonsil, lymph nodes and spleen) would consent to participate in the study. It was anticipated that in addition to facilitating the appropriate monitoring and long-term follow-up of patients, the findings from this study would inform future assessments of the risk of vCJD transmission posed by plasma products. The control group comprised haemophilic patients who had not received known implicated batches of clotting factor. At the outset of the study, haemophilia centres were provided with details, including issue dates of known implicated BPL or SNBTS batches they had received and requested to provide recipient data identifiable only by the patient's unique NHD number and date of birth. Participation in this study was voluntary. The data to be collected and recorded in a special file on the NHD was the degree of exposure to UK plasma products between 1980 and 2001, including the dates of first and last exposure to an implicated batch and its quantity.

Second risk assessment and CJDIP recommendations

Concern about the possibility of vCJD transmission by blood and blood products was heightened following the demonstration of blood transmission of BSE in a sheep model [44]. Unlike previous experimental models in which prions were inoculated by the intracerebral route, the sheep in this study had been orally infected with BSE and were therefore more representative of the situation in humans. Furthermore, transmission was shown to occur with blood taken during both the preclinical and clinical stages of infection [45].

A second DNV risk assessment undertaken on behalf of DH was reported in 2003 [46]. This was conducted to inform the management of individuals who had received implicated batches of blood and plasma products. The assessment was based on the various published experimental data in animals to model the potential vCJD infectivity in blood and its various components including plasma products [15,45,47]. The assumptions of this risk assessment were accepted by the Spongiform Encephalopathy Advisory Committee, the Committee on the Microbiological Safety of Blood and Tissue, and by the Committee on Safety of Medicines. CJDIP advised that surviving recipients of implicated red cell concentrates be informed and public health precautions implemented to minimize the risk of secondary vCJD transmission. Together with batch-specific manufacturing data, the risk assessment was used by CJDIP to estimate the potential vCJD infectivity in each batch of implicated plasma product. The likely risk

to treated patients was compared with the 'at-risk' threshold developed by CJDIP to guide the management of other 'at-risk' patient groups [48]. If patients had been exposed to a 'threshold' of 1% or greater potential risk of infection over and above the general risk to the UK population believed to have resulted from dietary exposure to the BSE agent, CJDIP advised that they should be notified and requested to take public health precautions. This 1% additional risk equates to an exposure of 0.02 ID_{50}, which is the equivalent level of infection at which public health precautions are implemented for patients exposed to vCJD via surgical instruments [49]. For each of the major assumptions underlying the risk assessment, the most precautionary option was chosen. The implicated plasma products were divided into three groups based on the assessed risk [50]. Amongst those considered to pose a high risk were FVIII, FIX and antithrombin concentrates, of which as little as one vial of treatment led to an exposure in excess of the defined risk threshold. Products in the medium-risk group included those in which exposure to substantial quantities was required to reach the risk threshold such as immunoglobulins, and the low-risk group comprised products with such low levels of potential infectivity as could effectively be ignored as causing any additional vCJD risk. The low-risk group also included some FVIII products that had been manufactured using implicated albumin as an excipient. Details of the majority of batches of implicated plasma products and their distribution directly to centres or through consignees were provided by BPL and SNBTS. To reduce the possibility of onward transmission of vCJD, it was recommended by CJDIP in 2004 that public health precautions be taken in recipients of 'high risk', and 'medium risk' implicated plasma products who had exceeded the 1% additional risk threshold.

Transmission of vCJD by blood transfusion

The CJDIP recommendations to implement public health measures in 'at-risk' recipients of implicated red cell and plasma products were reinforced by the subsequent recognition of the first case of vCJD transmission by blood transfusion [51]. TMER surveillance of the 66 recipients of red cell transfusions derived from the 17 vCJD patients who had previously donated blood has established that of the 24 identified recipients who survived more than 5 years following transfusion, three to date have shown evidence of vCJD infection [52]. In addition to these three clinical secondary cases of vCJD [51,53,54], a further asymptomatic case has been reported, in which the patient died from unrelated pathology with no evidence of neurological disease, but with post-mortem evidence of prion accumulation in lymphoreticular tissue [55]. All affected red cell donations are known to have been made relatively close to the onset of clinical symptoms in the donor, consistent with the increasing level of prion infectivity demonstrated throughout the incubation period in some animal models [56]. The incubation period in these secondary transfusion transmitted cases was around half the length of that estimated for primary oral infections from BSE. All three clinical cases were methionine homozygotes at codon 129 [51,53,54], while the asymptomatic case was methionine/valine heterozygous [55]. As a significant proportion of patients in the TMER recipient cohort did not survive long enough to develop clinical disease should they have been infected by vCJD, it is possible that the observed number of infected recipients underestimates the transmissibility of vCJD by blood transfusion. Likewise, it is possible that other surviving recipients are currently harbouring subclinical infection.

2004 vCJD plasma product patient notification exercise

UKHCDO advice

By the time of the 2004 CJDIP recommendations, the fate of products manufactured from 23 plasma donations derived from nine UK plasma donors who later developed vCJD had been established. These donations had undergone fractionation to produce albumin, immunoglobulin and clotting factor concentrates, including 16 batches of FVIII and eight batches of FIX that were distributed in the UK. TMER surveillance identified that these donations included plasma from at least one donor who, it is likely, had already transmitted vCJD via red cell concentrates [57]. At this time, it was considered likely that further batches of UK-sourced plasma products would become implicated as future vCJD cases arose. Therefore, to prevent secondary spread to other patients a 'population' or 'umbrella' approach was implemented in patients with inherited bleeding disorders who had received UK plasma-sourced products between 1980 and 2001. This policy was advised by UKHCDO and endorsed by CJDIP, DH and the Haemophilia Society, the UK charity representing patients with inherited bleeding disorders. As a result, all patients with bleeding disorders who had been treated with UK-sourced pooled factor concentrates between 1980 and 2001 were considered to be 'at-risk' of vCJD for public

health purposes and precautions were required to minimize the potential risk of secondary transmission. The start date of 1980 was when BSE was believed to have entered the human food chain and the end date of 2001 was the last possible expiry date of any product manufactured by UK fractionators and sourced from UK donors. This approach was based on the assumption that many further vCJD implicated batches of clotting factor concentrate would subsequently be identified and that only small volumes of implicated FVIII or FIX treatment were required for the recipient to be deemed 'at-risk' of vCJD. It was anticipated at that time that extending the 'at-risk' group of patients with inherited bleeding disorders and anti-thrombin deficiency in this way would significantly reduce the risk of secondary vCJD transmission. Such an approach differed from that taken in patients with primary immunodeficiency disorders in whom immunoglobulin forms the mainstay of treatment. As much larger quantities of this product are required to reach the 'at-risk' threshold, individual risk assessments were undertaken in these patients.

National advice: HPA responsibilities

The patient notification exercise was conducted in September 2004 and coordinated on behalf of the DH by the Health Protection Agency (HPA) in England, Wales and Northern Ireland, and the Scottish Centre for Infection and Environmental Health. Several professional and patient organizations, support groups and other stakeholders were involved in the consultation, planning and training for the notification exercise for patients with bleeding disorders, including representatives of UKHCDO, UKBS, the plasma fractionators and the Haemophilia Society. All clinicians responsible for the care of patients with bleeding disorders were provided with information to enable them to notify their patients and advise those for whom public health precautions were required. A date for contacting patients and their general practitioners was specified, which coincided with a national press release. At the same time, the Haemophilia Society informed its members by post about the notification process and provided a fact sheet on vCJD.

Haemophilia clinicians were provided with information sheets and a template letter to patients drafted by HPA/UKHCDO. Haemophilia centres were required to trace all recipients of clotting factors sourced from UK plasma between 1980 and 2001 and document their 'at-risk' status in the patient's medical records including details of exposure to implicated batches. Where a patient's care had been transferred to another centre, clinicians were instructed to forward recipient treatment details to the current centre, which was then responsible for informing the patient. All patients with bleeding disorders were to be notified, provided with written information and given an opportunity to discuss and find out whether they had received UK sourced plasma clotting factors in the specified time period (and were therefore considered 'at-risk'), as well as being given an option to find out whether or not they had received implicated batches. 'At-risk' patients were advised to inform providers of medical, surgical or dental treatment so that appropriate measures could be taken to minimize the risk of secondary vCJD transmission by instruments. They were also advised to inform their families in the event that a future emergency situation should arise and advised not to donate blood, tissues or organs which, in any event, this patient population is precluded from. 'At-risk' patients were advised that their clinical care should not be compromised in any way and invited to discuss the implications of the notification exercise. The original ethical approval was amended to facilitate recording of these relevant data for surveillance purposes on the NHD as previously described. Patients were requested to contact their clinician should they not wish their details to be recorded in this way.

BPL responsibilities

Haemophilia clinicians were contacted directly by BPL or SNBTS with details of any vCJD implicated batches they had been issued. While this accounted for the majority of the implicated batches, the data were incomplete at the time of the 2004 notification exercise, and the eventual tracing of product distribution of FVIII and FIX concentrate issued in 1988 through consignees resulted in a further patient notification in 2006 by which time, this information had become available.

Haemophilia clinician action

All 104 UK haemophilia centres received details of the 2004 exercise electronically 2 weeks prior to the date specified for notifying patients. The notification process comprised the identification of 'at-risk' patients, patient and general practitioner notification, NHD notification, responding to patient reply slips, implementation of patient counselling services and devising hospital policies through which the public health measures could be implemented. As

'at-risk' patients were identified, any who had recently undergone a surgical procedure involving specified tissues where the instruments used had not yet undergone 10 subsequent cycles of use/decontamination would need to be identified so that advice could be sought from CJDIP regarding the quarantine and handling of these instruments. Pertinent to the notification process was the adoption by hospital trusts of a multidisciplinary approach with collaborative links formed between haemophilia clinicians, infection control services, surgeons, gastroenterologists and others. Education of health care professionals in each hospital trust was imperative to enable the effective implementation of public health policies in 'at risk' patients. The number of patients with bleeding disorders registered at a given centre ranges from single figures to over 1500 and there was significant variation between centres in the resources available to implement the guidance within the specified time period. While the use of electronic records in many centres greatly facilitated the tracing of clotting factor concentrate, these frequently did not cover the early part of the 1980–2001 period, a difficulty that was compounded in some centres by incomplete or unavailable manual records. Infection control policies were informed by guidance from the Advisory Committee on Dangerous Pathogens TSE Working Group [58] and hospital trusts were required to devise means to implement the public health measures in 'at-risk' patients.

Variation in implementation of HPA guidance

Based on local knowledge of their patient group, some clinicians opted to contact only 'at-risk' patients to minimize any possible confusion and prevent unnecessary anxiety in the not insignificant proportion of patients registered with bleeding disorders who had never received UK plasma derived clotting factor concentrate. The UKHCDO requested that haemophilia centres pass on information in situations where patients had moved to another centre. The effectiveness of this varied; some patients were notified by more than one centre, and other patients may have remained untraced as they moved between centres. This difficulty in tracing and contacting patients is now being resolved as the UKHCDO moves towards a data-sharing approach between centres carrying out public health notifications. While there has been no formal evaluation of this notification, there have been anecdotal reports of clinicians notifying only patients known to have received implicated batches of their vCJD risk status. Furthermore, as the notification process requested patients to clarify their 'at-risk' status, it is possible that some patients remain unaware that they pose a public health risk unless specific action has been taken by clinicians to inform them.

A lack of understanding of the nature of the notification process has resulted in some 'at-risk' patients feeling stigmatized, and there have also been instances of patients being incorrectly labelled as having, rather than being at risk of, vCJD. Despite such difficulties, the telephone helplines set up for patients during the notification exercise as well as NHS Direct received few calls. Moreover, the findings from a study of other at-risk vCJD individuals are reassuring; no adverse long-term behavioural or emotional sequelae have been reported in individuals who have either undergone surgery involving contaminated instruments or who have donated blood to patients subsequently diagnosed with vCJD [59].

Endoscopy

A significant challenge that has arisen from the public health notification exercises surrounds endoscopic biopsy. The possible contamination of the biopsy forceps and the endoscope channel as a result of vCJD infectivity in the gut mucosa of subclinically infected individuals [60] led to the 2003 recommendation to quarantine endoscopes and retain their use only for the specified patient should invasive procedures such as biopsy or diathermy be required in an 'at-risk' patient [58]. For several years, the cost implications that resulted from the individualization of endoscopes in 'at-risk' patients requiring biopsy were borne by the hospital trust concerned. This resulted in variation between trusts in the threshold at which biopsies have been performed in these patients, thus raising the possibility that patient care may have been compromised in some cases. In 2008, the DH provided central funding for the refurbishment of suitable quarantined endoscopes used on patients at risk of vCJD [61]. Sufficient resources will similarly be required to ensure the continued implementation of appropriate public health measures in an ageing 'at-risk' bleeding disorder patient population while maintaining high standards of clinical care.

UK products distributed to other countries

As well as being supplied throughout the UK, implicated plasma donations contributed towards pooled plasma products that have been distributed to 13 countries: Belgium, Brazil, Brunei, Egypt, France, India, Ireland, Israel, Jordan, Netherlands, Oman,

Turkey and the United Arab Emirates. It is estimated that patients in at least four of these countries have been exposed to a level of infectivity exceeding the 'at-risk' threshold and the relevant Health Ministries have been contacted by the HPA and informed of the UK approach to risk assessment and patient notification. In the United States, a recent Food and Drug Administration risk assessment has concluded that the risk of vCJD infection from FVIII concentrate is very low [62].

Current results of the notification exercise and UKHCDO surveillance study

Patient exposure to UK plasma products including vCJD implicated batches

The collection of data of patients who received implicated batches and its entry on the NHD remains ongoing and has been greatly assisted by online registration. Annual returns historically provided by haemophilia centres to the NHD detail patient's treatment including product type and adverse events. From these data, it has been possible to estimate the number of patients treated with UK plasma products between 1980 and 2001. Furthermore, details of patient exposure entered into the database have been cross-checked against batch information provided to individual centres by BPL to establish the extent to which implicated batches are accounted for. Recently, similar total data for implicated batches supplied by SNBTS has been provided. This audit indicates that not all of the recipients for some of the batches have been notified to the NHD.

Using the NHD annual data, the estimated number of patients who received UK plasma products between 1980 and 2001 is 4581, of whom 792 are notified as having been treated with one or more than one implicated batch. The units of treatment received by the latter group of patients account for only 12.7 of the 23.7 million units of implicated batches released and 792 is therefore an underestimate of the number of patients treated with an implicated batch. The quantities of each released implicated batch supplied to UK haemophilia centres together with the units accounted for in the notification exercise is presented in Table 3. The percentage of each batch that is accounted for is also shown. For some of these batches, the accounting of use by the patient notification exercise is disappointingly low. The reasons for the low notification of

Table 3. Implicated batches of clotting factor concentrate by batch number, product name, release and expiry dates, and units released and used.

Batch number	Product name*	Factor type	Release date	Expiry date	Units released	Sum of units used	% Units accounted for
FHB4116	8Y	VIII	June 1992	April 1995	775 000	280 710	36
FHB4189	8Y	VIII	April 1993	March 1996	1 233 500	735 725	59
FHB4419	8Y	VIII	July 1995	June 1998	1 022 000	656 600	64
FHB4547	8Y	VIII	September 1996	September 1997	902 000	873 821	94
FHB4596	8Y	VIII	May 1997	March 2000	1 398 500	1 054 410	75
FHC0059	8Y	VIII	September 1988	July 1989	528 720	58 560	11
FHC0289	8Y	VIII	May 1990	March 1993	633 500	266 960	42
FHC0369	8Y	VIII	December 1990	October 1993	604 500	199 060	32
FHC4237	8Y	VIII	March 1994	October 1996	1 268 500	982 977	77.4
FJA0020	9A	IX	October 1988	August 1989	533 500	88 025	16
FJA0092	9A	IX	May 1990	April 1991	511 800	92 990	18
FJA4239	9A	IX	July 1993	December 1996	251 000	141 435	56
FJA4308	9A	IX	June 1994	April 1997	573 000	379 540	66
FHM399	High Purity F8	VIII	November 1991	April 1994	812 000	169 055	20
FHM405	High Purity F8	VIII	May 1992	October 1994	905 500	304 500	33
3502–70210	HT DEFIX	IX	Not known	Not known	230 184	216 220	93.9
FHE4437	REPLENATE	VIII	September 1995	July 1997	1 547 000	818 095	52
FHE4536	REPLENATE	VIII	September 1996	July 1998	2 069 000	1 224 270	59
FHE4548	REPLENATE	VIII	October 1996	September 1998	1 690 000	965 400	57
FHF4625	REPLENATE	VIII	July 1997	June 1999	2 290 000	1 035 900	45
FJM4327	REPLENINE	IX	October 1994	February 1996	1 607 500	1 139 915	70
FJM4437	REPLENINE	IX	November 1995	March 1997	832 500	379 380	45
FJM4596	REPLENINE	IX	April 1997	September 1998	838 500	592 380	70
FJM4625	REPLENINE	IX	July 1997	November 1998	875 000	22 145	2.5
0304–70510	Z8	VIII	Not known	Not known	123 690	16 150	13
0301–70320	Z8	VIII	Not known	Not known	125 440	Not known	0

*For further details [see ref. 22].

some implicated batches are not known, although patient refusal for the inclusion of their data may be a contributory factor. The last year an implicated batch was identified was 1999 and no further blood donors who donated plasma prior to developing vCJD have been identified since the 2004 notification.

Tissue-based vCJD surveillance

Following the 2004 notification exercise, the vCJD surveillance study was extended and remains ongoing, although the number referred for postmortem remains low. There were 669 deaths in bleeding disorder patients between 2004 and 2008 including 269 treated with UK plasma products and 37 recipients of implicated batches. However, only a small number of study postmortems have been performed [63]. The report of the first asymptomatic case of probable transmission of vCJD by clotting factor concentrates [63] emphasizes the need for higher recruitment to this study if we are to improve our understanding of the risk of vCJD transmission via infected plasma products. Active vCJD surveillance of prospective tissue samples and autopsy material continues. The Office of National Statistics has provided information about deaths of haemophilic patients including whether the death certificate indicates that a postmortem was or may have been done. This is currently under investigation in the hope of providing further postmortem material for study.

Information to patients (February 2009)

The postmortem arm of the surveillance study has detected PrP^{res} in the spleen of a patient with haemophilia who had had no evidence of any neurological disorder while alive [63]. This patient was known to have been treated with at least one implicated batch of BPL FVIII 8Y. A decision was made to inform bleeding disorder patients of this finding even though the investigation of this case was continuing. A toolkit of letters and information sheets prepared by HPA/UKHCDO was electronically mailed to all Haemophilia Centres with instructions for patients to be informed as soon as possible by post. Many centres decided to post letters to only the patients in the at-risk group.

Further investigation of this patient's complete clinical records showed that he had received treatment with UK-sourced FVIII concentrates including two implicated batches of 8Y, each of which contained a plasma donation from the same donor who subsequently went on to develop vCJD. The patient had also been transfused with 14 units of red cells between 1998 and 2007 and had had invasive endoscopies. Further information about this is contained in a separate paper [63]. Of these potential risk factors, the only link to contact with a patient with vCJD was the two implicated 8Y batches. A further risk assessment by the Department of Health interprets the most likely source of vCJD in this patient as being treatment with UK plasma products [64].

Whilst to date no haemophilia or bleeding disorder patient has been diagnosed with, or died from, clinical vCJD, this information has increased anxiety among some at-risk patients as this is the first information linking treatment with an implicated batch and the detection of PrP^{res} in lymphoid tissue in a patient with haemophilia. However, it is too early to estimate the full implications of these findings on this group and other people treated with blood and plasma products produced in the UK from UK-sourced plasma.

Conclusions

The risk of transmission of viruses by plasma products including HIV and hepatitis C has been virtually eliminated since the introduction of improved donor selection and testing and the employment of effective viral inactivation processes in 1986. However, new concerns regarding the safety of UK blood and plasma products have arisen following the emergence of vCJD. An early precautionary approach was adopted in UK bleeding disorder patients with the aim of minimizing the possible risk of vCJD transmission and its secondary spread. These include their exclusion as blood and tissue donors; an approach that has subsequently been extended to include all recipients of cellular blood products in the UK. Public health measures were implemented in 2004 in all patients who had received UK pooled plasma clotting factor concentrates between 1980 and 2001, irrespective of whether these had contained plasma from a donor known to have later developed vCJD. Challenges have resulted from this approach and these have been discussed in this paper. Our understanding of the risk of vCJD transmission by plasma products has increased over time and informed risk reduction measures. Since the 2004 public health notification exercise, the numbers of new clinical vCJD cases in the UK have declined and no further vCJD patients have been identified as having previously donated implicated blood or blood products. However, the prevalence of subclinical vCJD infection in the general population, including the extent of infection among methionine/valine heterozygotes and valine/valine homozygotes, remains unknown. It is also not known how soon a suitable validated screening test for vCJD

will become available. Although the current risk assessment indicates that only small volumes of implicated clotting factor concentrates are sufficient to cross the additional 1% risk threshold at which public health measures are required, vCJD infectivity amongst implicated batches varies. The recent identification of the first case of asymptomatic vCJD in a haemophilic patient [63] as well as the report of vCJD in a methionine/valine heterozygous individual [13] highlight the need for the continued surveillance of individuals in the 'at-risk' population, including patients with inherited bleeding disorders. Attempts to improve the numbers of postmortem examinations by patients consenting in life or by consent of bereaved relatives needs urgent consideration. Patients who have received implicated batches are currently undernotified to the NHD. Taken together with the unknown prevalence of the abnormal prion protein associated with vCJD among blood donors and the absence of a validated test, continued employment of the population approach appears to be the best means of reducing secondary spread of vCJD between patients, including those with bleeding disorders. Further follow-up may lead to improved understanding of the risk of vCJD to this patient population and the re-evaluation of the current considered 'at-risk' groups for public health purposes.

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