the UK only those considered by the CJD Incidents Panel to be 'at risk of vCJD for public health purposes' on account of exposure to implicated surgical instruments, blood components or plasma products, and those who themselves have received blood components, are deferred (http://www.hpa.org.uk/infections/topics_az/cjd). There is considerable complexity relating to the introduction of similar donor deferral criteria in the context of cell, tissue and organ donation. Broadly, whilst all forms of donation are excluded for patients with CJD or those considered potentially infected, donation of haematopoietic stem cells and solid organs is permitted from those considered 'at risk for public health purposes' and those previously transfused, subject to a risk assessment that weighs the risk of vCJD transmission against the potentially life-saving nature of an otherwise suitable transplant. Donation of other tissues is based on the same donor deferral criteria as blood. Donor deferral criteria remain, however, blunt risk management tools with potential deleterious effects on blood, tissue and organ supply.

Importation of blood components

Since our last report (Ludlam & Turner, 2005) the use of imported methylene-blue treated fresh frozen plasma (FFP) has been extended to all patients under the age of 16 years and to high users. Solvent detergent-treated FFP is recommended for patients undergoing plasma exchange for thrombotic thrombocytopenic purpura on the grounds that there is some evidence to suggest that methylene-blue treated FFP has a deleterious impact on outcome in this patient group (Alvarez-Larran *et al*, 2004). Consideration continues to be given around the possibility of importing FFP and cryoprecipitate for additional groups of patients. Importation of platelets is likely to be impractical given the short shelf-life of these products. However, it may be possible to import red cell concentrates for some groups of patients, for example for children up to 16 years of age. Consideration also has to be given to cost, quality and regulatory requirements and countervailing risks of transmission of other infectious diseases or of component shortages.

Advances in the development of a screening test

As previously noted (Ludlam & Turner, 2005), neither nucleic acid transmission nor immunological responses have been clearly identified in association with transmission of prion diseases, rendering standard molecular and serological screening assays unfeasible. Surrogate markers, such as 14-3-3, S100 and erythroid differentiation-related factor, have thus far proved insufficiently sensitive and specific to be of clinical value. Considerable progress has however been made in the development of assays for the abnormal conformer of prion protein, PrP^{TSE}.

Normal prion protein (PrP^{C}) is a widely expressed 35 kDa 230 amino acid glycosyl-phosphatidylinositol anchored membrane glycoprotein with two N-linked glycosylation sites and a secondary structure that includes three alpha helices and a single beta-pleated sheet. During the development of prion diseases there is a change in secondary and tertiary structure with a substantial increase in the proportion of beta-pleated sheet which leads to a change in the physico-chemical characteristics of the molecule, rendering it relatively resistant to breakdown by endogenous proteases and leading to deposition of amyloid-like plaques in affected tissues. Because PrP^{C} and PrP^{TSE} have the same primary structure and post-translational modifications, both forms tend to be recognised by most conventional monoclonal antibodies. PrP^{TSE}-based assays, therefore, have to utilise alternative ways of distinguishing the normal from the abnormal conformational form. PrP^{TSE} was originally defined by its resistance to digestion by proteinase K (PK). However this is a relative phenomenon; PrP^{TSE} can be digested by higher concentrations and longer exposure to proteolytic enzymes and, in addition, there is recent evidence for proteolysis-sensitive forms of PrP^{TSE} (Safar *et al*, 2005).

Five general approaches have been developed for the detection of PrP^{TSE}

Differential proteinase-K digestion. Immunohistochemistry distinguishes PrP^{TSE} from PrP^{C} by disrupting the latter through the use of proteolytic enzymes or chaotropic agents, coupled with the use of standard anti-PrP monoclonal antibodies and *in situ* visualisation for detection. This technique enables the demonstration of PrP^{TSE} deposition in the central nervous system and, in the case of vCJD, in follicular dendritic cells in lymphoid tissue of clinically affected patients. Western blot relies on the extraction of PrP^{TSE} from blood or tissues, proteolytic digestion and electrophoresis with visualisation by anti-PrP monoclonal antibodies. Proteolysis leads to complete digestion of PrP^{C}, but removes only the membrane-distal part of PrP^{TSE}, leading to three bands on gel electrophoresis which corresponds to the three different glycosylation states. The migration rates of these bands vary between different strains of prion disease, allowing clarification of strain type (Collinge *et al*, 1996). Partially selective precipitation of PrP^{TSE} from large sample volumes by sodium phosphotungstic acid coupled with enhanced detection of bound antibody by chemiluminescence have been used to enhance the sensitivity of Western blot and demonstrate PrP^{TSE} in a variety of peripheral tissues in both sporadic and vCJD (Wadsworth *et al*, 2001). The World Health Organisation Working Group on International Reference Materials for the Diagnosis and Study of Transmissible Spongiform Encephalopathies oversaw a collaborative study in which a number of different laboratories used their versions of the immunoblot (Minor *et al*, 2004). Generally it was concluded that, at present, immunoblot is not sufficiently sensitive to detect PrP^{TSE} in the peripheral blood of animals or humans with clinical prion disease.

Immunocapillary electrophoresis was amongst the first methods that claimed to be able to detect PrP^{TSE} in the peripheral blood. The test material is treated with proteinase and subject to a competitive antibody inhibition assay using a labelled peptide (as the competitor) and a monoclonal antibody that recognises both PrP^{TSE} and the peptide (Schmerr *et al*, 1999; Yang *et al*, 2005). The technique has however proved difficult to reproduce in other laboratories and failed to discriminate between infected and uninfected blood samples in a blinded study (Cervenakova *et al*, 2003b).

Epitope unmasking/masking. More success has been achieved with the conformation-dependent immunoassay (CDI), which is predicated on the observation that some PrP epitopes are masked within the PrP^{TSE} aggregate. An increase in signal intensity produced by a labelled monoclonal antibody by a sample denatured using guanidine hydrochloride when compared with the native (un-denatured) sample denotes the presence of PrP^{TSE} (PrP^{C} gives the same signal intensity under both conditions). The sensitivity of the technique is increased through the use of highly sensitive dissociation-enhanced lanthanide fluorescence immunoassay for antibody detection and, in some versions of the assay, the use of PK to reduce background signal (Safar *et al*, 1998, 2002). CDI appears to achieve greater sensitivity than immunoblot (Bellon *et al*, 2003) and, in the format including PK, may approximate the sensitivity of infectivity assays (Bruce *et al*, 2001). In the absence of PK it appears able to detect PK-sensitive forms of PrP^{TSE}, though it remains unclear as to whether these are infectious or not (Bellon *et al*, 2003).

The epitope-protection assay developed by Amorfix uses a chemical modification process which alters epitopes on normal PrP but not those buried within PrP^{TSE} aggregates. The latter are then disaggregated and the conserved epitopes detected using immunodetection methods (http://www.amorfix.com).

PeopleBio have developed an approach where a single antibody is used for both capture and detection steps leading to the blocking of available epitopes by the capture of PrP^{C} but not PrP^{TSE}.

PrP^{TSE}- specific monoclonal antibodies. Several antibodies have now been developed that appear to be specific for conformation-dependent epitopes present in PrP^{TSE} but not PrP^{C} (Korth *et al*, 1997; Paramithiotis *et al*, 2003; Curin Serbec *et al*, 2004; Zou *et al*, 2004). On these, the antibody 15B3, described by Korth *et al* (1997) and manufactured by Prionics, is the best characterised and has proved capable of detecting infectivity in the peripheral blood of scrapie-infected sheep and BSE-infected cattle in the absence of PK digestion (http://www.fda.gov/ohrms/dockets/AC/06/slides/2006-4240S1_9.ppt). Three other antibodies (Paramithiotis *et al*; 2003; Curin Serbec *et al*, 2004; Zou *et al*, 2004) also appear specific to PrP^{TSE} but have not yet been translated to routine assay format.

PrP^{TSE} – specific ligands. A variety of other ligands have been shown to bind selectively to the abnormally conformed molecule. Plasminogen has been proposed as a means of selective binding PrP^{TSE}, but as it can also bind to a variety of other proteins it is therefore unlikely to be sufficiently specific for assay development (Fischer *et al*, 2000).

Polyanionic compounds are known to selectively bind PrP^{TSE} and this property has been employed in the Seprion assay (Lane *et al*, 2003), which uses coated magnetic beads to capture the molecule. The assay is not dependent on PK treatment and is not species-specific provided a suitable detection antibody is used. It is licensed for postmortem diagnosis of BSE and Chronic Wasting Disease and is reported to be able to distinguish between infected and uninfected blood in scrapie-infected sheep and a small number of human samples.

The approach developed by BioMerieux involves PK digestion, precipitation and denaturation followed by reticulation by streptomycin, chemical capture by calyx-6-arene and detection of the macromolecular aggregates by labelled monoclonal antibody (http://www.fda.gov/ohrms/dockets/AC/06/slides/2006-4240S1_9.ppt). Detection of PrP^{TSE} in a small number of plasma samples from scrapie-infected sheep, BSE-infected cattle and CJD-infected humans has been reported.

Adlyfe have developed a third approach utilising a synthetic peptide based on the region of the PrP molecule involved in the PrP^{C}–PrP^{TSE} conformational transition. The peptide sequence is coupled to its mirror image as a palindromic molecule fluorescently labelled at each end. When incorporated into PrP^{TSE} the peptide folds into a hairpin with a beta-sheet conformation and the flurophores stack and change their fluorescence wavelength. Further, the folded ligand induces further molecules to adopt the folded conformation and thus amplifies the signal (Grosset *et al*, 2005). The assay is reported to have discriminated infected from uninfected plasma in natural and experimental scrapie, BSE and CJD.

Chiron have utilised (http://www.fda.gov/ohrms/dockets/AC/06/slides/2006-4240S1_9.ppt) a synthetic PrP polypeptide to capture PrP^{TSE} on magnetic beads with detection by monoclonal antibody in an ELISA format.

Amplification. Two methods have been used to amplify the detection signal. Screening for intensively fluorescent targets utilises double labelled antibodies, more of which bind to PrP^{TSE} aggregates than to PrP^{C} and giving rise to a stronger fluorescence signal (Bieschke *et al*, 2000). Immuno-polymerase chain reaction (PCR) also provides a method of amplifying the signal from an antibody or ligand conjugated to a nucleotide sequence utilising the PCR (Barletta *et al*, 2005).

Two further approaches have been developed that result in the amplification of PrP^{TSE} itself. The first of these, protein misfolding cyclic amplification (PMCA) has given rise to considerable excitement. PrP^{TSE} seeded into an excess of PrP^{C} leads to formation of new PrP^{TSE}. That PrP^{TSE} is then

fragmented through sonication or shaking and leads to a new round of PrP^{TSE} formation (Kocisko *et al*, 1994; Saborio *et al*, 2001). Recurrent cycles therefore of incubation and fragmentation lead to amplification of the original PrP^{TSE} (Castilla *et al*, 2005). Immunoblot and CDI have been used for detection of PrP^{TSE} and infectivity. Studies show that 140 sonication cycles produced an increase in signal intensity of around 6000-fold, whilst a second 'nested' set of 118 cycles with a fresh source of normal PrP led to an approximate 10^7-fold amplification. The technique has proved capable of discriminating infected from uninfected blood from hamsters experimentally infected with scrapie, however there are recent reports of detection of PrP^{TSE} in uninfected animal brain implying the possibility of low levels of abnormally conformed PrP in 'normal' individuals.

A number of cell-based amplification techniques have been described in which the rodent cell lines N2a (Nishida *et al*, 2000), PK-1 (Klohn *et al*, 2003), Rov9 (Birkett *et al*, 2001) and CAD-5 are infectable by natural or experimental strains of scrapie and demonstrate amplification of PrP^{TSE} detected by immunoblot. No cell-based amplification has yet been successfully reported for CJD.

Both these kinds of amplification take several days (PMCA) to weeks (cell-based assays) and would therefore be better positioned as confirmatory rather than screening assays.

Considerations with regard to assay assessment. Whilst the above is not a comprehensive list of all the assays under development, it does provide a flavour of the range and variety of approaches and their relative strengths and weaknesses. Some of these are now approaching the point at which they may be Council of Europe (CE) marked and marketed as potential clinical assays. There are, therefore, a series of further considerations relating to the potential assessment and utility of prion assays prior to clinical implementation.

The required sensitivity is difficult to gauge because the level, spatial distribution and temporal variation of infectivity in the blood of patients with vCJD or healthy individuals with subclinical infection is unknown. The generalizability of experimental data from mouse and hamster experiments to the human condition cannot be assumed (Castilla *et al*, 2006). Moreover, the relationship between infectivity and PrP^{TSE} is complex. Although many authorities believe PrP^{TSE} to be causal, there is experimental evidence both of infectivity with very low levels of PrP^{TSE} and of the presence of PrP^{TSE} in the absence of infection in human brain (Yuan *et al*, 2006). Recent studies have shown that following PK digestion, particles in the size range 300–600 kDa have the highest associated specific infectivity (Silveira *et al*, 2005), suggesting that a PrP^{TSE} oligomer of 14–28 might represent an infectious dose. The contribution of PK-sensitive PrP^{TSE} to infectivity is uncertain. It is reasonable, therefore, to regard PrP^{TSE} as a marker of infection, provided it is recognised that there is not a simple linear correlation with the level of infectivity or the development of disease. The National Institute of Biological Standards and Controls have established a reference panel of homogenised human CJD-infected brain and spleen spiked into plasma, peripheral blood from natural and experimentally infected animals and a small number of peripheral blood samples from patients with vCJD, to provide independent evaluation of the sensitivity of prion assays (http://www.nibsc.ac.uk).

Whereas the sensitivity of an assay is mostly related to its technical aspects, the specificity is also highly dependent on the population into which it is deployed. Thus an assay which may be highly specific (i.e. a high proportion of true to false positives) in a group of patients with suspect clinical disease, can show very poor specificity in a normal population where the number of false positives may significantly exceed the number of true positives. This point is demonstrated in Fig 1. The UK Blood Services have established a Test Assessment Facility containing samples from 5000 UK and 5000 US blood donors to evaluate the likely positivity rates amongst the general population.

Finally, there are a number of other considerations in weighing the likely impact of the introduction of a vCJD assay. Such an assay is unlikely to only be used amongst blood donors, it may also be used in patients with suspect CJD or other psychiatric or neurological conditions (to exclude CJD); in those considered 'at risk for public health purposes' on account of exposure to implicated surgical instruments, blood components or plasma products; or for population prevalence studies and the 'worried well'. In the absence of a true confirmatory assay (i.e. the ability to demonstrate infectivity) it will prove difficult to discriminate between false and true positive individuals and, of course, the likelihood of a truly positive individual developing clinical vCJD is unknown.

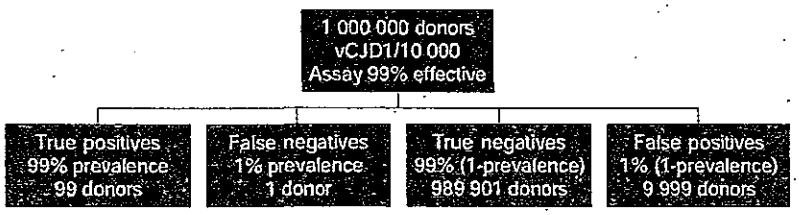

Fig 1. Outcome of screening of a 'normal' population of one million donors in whom there is a true positive prevalence of 1/10 000 for subclinical variant Creutzfeldt-Jakob disease using an assay with a sensitivity and specificity of 99%. As can be seen, a very poor specificity results where the number of false positives greatly exceeds the number of true positives.

Blood donors would not be able to continue to donate if they tested positive, it is illegal for example to take the donation with the intent of discarding it, even if the donor consents to such a strategy. Test positive individuals will therefore have to be told of this outcome and (presumably) managed as 'at risk for public health purposes'. Clearly this will cause significant distress and give rise to psychological and social problems for some people, act as a disincentive to blood donation and therefore a negative impact on the blood supply. Moreover, it is likely that previous recipients of blood components from these donors will also have to be traced and contacted (lookback), giving rise to a much larger group of individuals in the population considered 'at risk of public health purposes' and requiring specific precautionary measures to be taken in the event of surgery or medical investigation (see below). A comprehensive health and economic evaluation will therefore have to weigh the positive impact of reducing potential secondary transmission of vCJD against these potential negative consequences.

Table I. Residual infectivity distribution in a unit of leucodepleted red cell concentrate.

Log reduction in infectivity	Residual leucocytes	Residual plasma	Residual infectivity
Leucodepletion alone	0·2	130	130·2
1 Log	0·2	13	13·2
2 Log	0·2	1·3	1·5
3 Log	0·2	0·13	0·33
4 Log	0·2	0·013	0·213

The data represents the likely distribution of residual infectivity in a unit of leucodepleted red cell concentrate prepared by a bottom and top processing method (with a residual plasma volume of around 10 ml).
Assuming 10 ID/ml infectivity in whole blood with 40% (i.e.4 ID/ml) being removed by leucodepletion and the remainder residing in the plasma (i.e. for a haematocrit of 0·45 a plasma concentration of approximately 13 D/ml), around 130 ID remains in the unit's plasma. Hence up to approximately a 3 log further reduction is required to reduce the risk of transmission to <1 ID/unit.

Blood component processing

Universal leucodepletion was introduced in the UK in 1999 as a measure to reduce the risk of secondary transmission of vCJD. The experimental data from mice infected with the Fukuoka-1 strain of Gerstmann-Straussler-Scheinker disease (Brown *et al*, 1998, 1999) suggests that leucodepletion filters have little impact on plasma-borne infectivity. Studies in the 263K hamster model (Gregori *et al*, 2004) similarly suggest a 40–70% reduction in whole blood infectivity, consistent with the removal of leucocyte-associated infectivity, but not that present in the plasma. Table I illustrates the likely distribution of residual infectivity in a unit of leucodepleted red cell concentrate prepared by bottom and top processing method (with a residual plasma volume of around 10–15 ml). Assuming 10 ID/ml infectivity in whole blood, just over 130 ID would be left in the unit and that up to a 3 log further reduction is required to impact upon the risk of transmission (i.e. achieve <1 ID/unit). Red cell concentrates prepared by the more common top-top methodology contain greater amounts of residual plasma (around 20 ml) and would consequently require a 4-log reduction. The absence of data on the level of infection in human blood means an uncertainty of at least 1-log around these point estimates. It can be said in summary, however, that it is unlikely that current blood component processing will suffice to reduce the risk of transmission in most plausible infectivity scenarios.

Three companies are working on the development of prion reduction filters. One has a CE-marked dock-on filter which is used in series with a leucodepletion filter. Published studies using this filter material show >3 log reduction in infectivity on brain homogenate spikes and to the limit of detection (>1 log) in endogenous infectivity studies (Gregori *et al*, 2006). Two other companies are working on the development of combined leucodepletion/prion reduction filters. All prion reduction filters will have to undergo independent assessment of clinical safety and efficacy within a series of studies managed by the UK and Irish Blood Services and agreed with SEAC and the Advisory Committee on the Safety of Blood, Tissues and Organs (http://www.advisorybodies.doh.gov.uk/acsbto/index.htm). Part of the problem for both manufacturers and Blood Services is the absence of assays capable of detecting either PrP^{TSE} or infectivity in the peripheral blood of patients with vCJD. Assessment of the efficacy of the technology is therefore based on brain homogenate spikes (where baseline infectivity is sufficient to detect a 3–4 log reduction but the physico-chemical form of the spike is unlikely to be similar to that of plasma based infectivity), and endogenous infectivity studies (where the form of infectivity is likely to be more relevant, but the baseline infectivity is sufficiently low that little more than a 1-log reduction is detectable). There remain, therefore, fundamental questions relating to the clinical relevance of different forms of spike material and general applicability of these kinds of studies to the human situation. The potential for deleterious effects on the red cell concentrate itself are also a matter for concern, both in terms of the possibility of alterations to the rheological or antigenic profile of the red cells and the loss in the volume of the additional filter. The latter would have a particular impact if used in conjunction with bottom and top processing, the combined effect of which may reduce the red cell mass in a concentrate below current standards, necessitating additional transfusions for some individuals.

With regard to platelet concentrates, re-suspension in optimal additive solution rather than plasma would reduce the amount of residual plasma by around 65% to 80–90 ml. This would still contain more than enough infectivity to transmit infection to the recipient under even the most

optimistic of the current infectivity assumptions and is likely to be ineffectual. Prion reduction filters are not currently applicable to either platelet concentrates or FFP.

Plasma product manufacturing

It is reassuring that to date no recipient of a pooled plasma product has developed vCJD. However in 1997, shortly after the first description of vCJD as a new condition, there was concern that the UK plasma supply might have the potential to transmit the infectious agent and that plasma collected from countries where there were few or no cases of vCJD might pose a lower risk (Ludlam, 1997). Although this view gave rise to controversy, the regulatory authorities moved to a position of allowing, and subsequently mandating that pooled plasma products manufactured in the UK should only be made from plasma imported from parts of the world at low risk of vCJD.

In an attempt to help define the risk of PrP^{TSE} transmission by plasma-derived products, detailed studies have been undertaken to assess how prions are partitioned during the plasma fractionation process, mainly by spiking the starting plasma with 'exogenous' prion derived from brain homogenates of experimentally infected animals. The strengths and weaknesses of this approach are similar to those described above in the discussion around the assessment of prion filters. In general there was least clearance of prion in the manufacture of factor VIII, IX and antithrombin concentrates, greater clearance in the preparation of intravenous immunoglobulin, and greatest clearance in the manufacture of albumin (Foster, 1999).

The way in which different countries responded to the risk that plasma products might transmit the infectious agent varied and depended partly on the perceived relative number of donors who might be infectious as well as details of the plasma fractionation techniques used in each country.

In the UK, using data on partitioning of prion infectivity during manufacture of plasma products, along with the animal data on the likely range of infectivity in individuals with subclinical infection, a risk assessment was undertaken to quantify the risk of recipients of such products being infected. The CJD Incidents Panel have taken the view that an individual with a >1% additional risk of exposure to an infectious dose of vCJD should be notified and managed as 'at risk for public health purposes'.

To date a total of 174 'implicated' batches of plasma products have been identified as having been manufactured from a pool of plasma to which an individual contributed who subsequently developed vCJD (Hewitt *et al*, 2006). For each of these batches a detailed risk assessment was carried out that included the total number of donations included in the pool, the details of the plasma fractionation process used during manufacture and (conservative) estimates of the likely cumulative reduction in infectivity over the manufacturing process. The outcome was expressed as the likely mass of product to which an individual would have had to be exposed to increase their risk of exposure to infection by 1% over background. Although these estimates varied between manufacturers dependent on the details of the manufacturing process, broadly speaking plasma products could be classified into 'high risk of exposure' products, such as coagulation factor concentrates, where a single adult dose would suffice to place a patient beyond the 1% additional exposure threshold; 'medium risk of exposure' products, such as immunoglobulin, where only patients receiving repeated doses of the implicated batch would be likely to pass the 1% threshold; and 'low risk of exposure' products, such as albumin, where unfeasibly large exposure to the implicated batch would be required to move the patient beyond the 1% threshold. Categorisation as 'at risk for public health purposes' requires that a patient be notified and that precautions be taken in the use of surgical instruments and other invasive medical interventions (such as endoscopy with biopsy), to reduce the risk of onward transmission to other patients.

Consideration was given to whether to categorise as 'at risk for public health purposes' only those who had been exposed to specific implicated batches, or whether to categorise all individuals who had received UK manufactured products between 1980 and 2001 (the dates between which implicated plasma products pools could have used). After much debate it was agreed that for 'low and medium risk of exposure' products (immunoglobulins and albumin), the former approach would suffice, whereas for 'high risk of exposure' products (coagulation factors), an umbrella approach would be more appropriate because it was uncertain how many batches of plasma might be 'infectious' from donors with subclinical vCJD and because if additional donors developed vCJD, it would be necessary to inform further groups of recipients, who might have previously been told they had not received 'implicated' batches.

Other countries have responded differently to the UK. In France the assessment took into account the local plasma fractionation processes and concluded that the risk posed by 'implicated' batches to recipients was very small and it was not appropriate to take any special precautions to prevent further spread by surgical instruments. A similar view was formulated in Germany, though no cases of vCJD have yet arisen in that country (Seitz *et al*, 2007).

Within the UK advice on prevention of spread of PrP^{TSE} by surgical, medical and dental instruments is given by the Advisory Committee on Dangerous Pathogens and advice on individual clinical incidents by the CJD Clinical Incidents Panel. Instrument contamination was estimated to be of 'high risk' where there was contact with tissue from the nervous system and 'moderate' risk if there was exposure to lymphoid tissue (http://www.advisorybodies.doh.gov.uk/acdp/index.htm). Surgery involving these tissues should be undertaken with disposable instruments where possible, and if not they should be 'quarantined' thereafter and not reused because it would not be possible to ensure adequate decontamination prior to use on the next patient. This guidance has led to major

difficulties in the performance of biopsies with gastrointestinal endoscopes because the samples obtained would probably contain lymphoid tissue. The financial implications are significant because the endoscopes cannot be decontaminated and must effectively be discarded. Both upper and lower gastrointestinal endoscopies without biopsy do not result in the instrument being considered as potentially 'contaminated' and it can therefore be reused on other patients after standard cleaning procedure. The concern about possible contamination of instruments has also led to an increased use of capsule endoscopies, which give good images but cannot be used to biopsy or treat gut lesions.

Although no individuals with haemophilia have thus far developed vCJD and a retrospective study of autopsy samples from individuals with haemophilia in 1998 showed no evidence of sub-clinical infection, it has been important to try and gather more data (Lee *et al*, 1998). This has not been easy and depends upon procuring appropriate tissue samples prospectively from individuals undergoing clinically necessary surgery in addition to consent for autopsy. In addition it has been important to try and develop a record of the extent of exposure of individuals to 'implicated' batches of concentrate, as well as all recipients of UK clotting factor concentrates over the 22-year period of exposure. This is being co-ordinated by UK Haemophilia Centre Doctors' Organisation by accumulating the data for subsequent anonymised studies.

Communication with patients and the general public

Keeping recipients of blood and blood products informed about the current state of knowledge and in particular informing individuals about their individual risks has proved challenging because of the complexity and uncertainty inherent in our understanding of the field. It has been important for there to be close collaboration between those able to assess the risk of vCJD infection, physicians responsible for clinical services and patient organisations representing those potentially affected. For those who have received blood components from donors who subsequently developed vCJD, the risk of exposure to vCJD is judged to be high and these individuals have been contacted on an individual basis and offered counselling and specialist follow-up. Similarly, blood donors who have donated blood administered to a patient who later developed vCJD have been contacted and are managed as 'at risk for public health purposes'. In 2004, all patients with haemophilia were sent a letter stating whether or not they had or had not received UK plasma-derived clotting concentrates between 1980 and 2001, irrespective of whether or not they had received UK plasma products, because in an earlier mailing about this topic only those in the 'at risk' group were contacted and this left non-recipients of letters not knowing whether they had not been potentially exposed or whether their letter had got lost in the post. All were offered the opportunity for individual counselling. It is this attention to the detail of how patients are informed that is critical in trying to ensure that individuals feel confident in the arrangements.

For patients potentially exposed to other implicated plasma products, the issue of traceability and notification have proved more problematic. Whilst patients with primary immunodeficiency share a similar close long-term relationship with their physicians, those receiving immunoglobulin for other clinical indications or high doses of albumin (for example during plasma exchange), are often discharged following their acute care. The absence of a general system of traceability for plasma products and of searchable clinical notes has made the follow-up of the latter groups of potentially exposed patients highly problematic.

Concluding remarks

Three years after our last review (Ludlam & Turner, 2005), the management of the risk of transmission of vCJD by blood and plasma products remains highly challenging. Whilst the diminishing number of clinical cases is reassuring, there are continuing uncertainties surrounding the prevalence of sub-clinical disease, the level of infectivity in peripheral blood of such individuals, and the overall risk of transmission and development of clinical disease. Much progress has been made in the development of new technologies, such as prion filters and prion assays, but assessment of these is problematic and cost and countervailing risks need to be considered. Accurate and timely communication with the general public and with those who are considered to be at increased risk of exposure remains essential given the continuing complexity and uncertainty of the field.

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