PLASMA PRODUCT TRANSMISSION OF vCJD: SUGGESTED REVISIONS TO RISK ASSESSMENT

Prepared for the ACDP TSE Risk Assessment Subgroup, meeting 30th April 2012

Purpose:

Following a risk assessment of exposure to vCJD infectivity in blood and blood products by Det Norske Veritas (DNV) consulting on behalf of the Department of Health (DH) in 2004, and the announcement in December 2003 of a transfusion-associated case of vCJD, the CJD Incidents Panel (CJDIP) recommended that all bleeding disorder patients who had received UK-sourced plasma products between 1980 and 2001 should be informed that they were "at risk" for public heath purposes. This "umbrella" notification approach included approximately 4000 patients, most of whom had not received implicated batches from a vCJD donor.

In 2011, in response to the lack of clinical cases in blood transfusion recipients which suggested that the assumptions in the DNV risk assessment may have been too precautionary, the DH developed a revised blood risk assessment. The DH risk assessment includes new assumptions pertaining to level of infectivity, the time-period during which blood is considered infective, and prevalence. The DH risk assessment was accepted by SEAC's (Spongiform Encephalopathy Advisory Committee) successor: the Advisory Committee on Dangerous Pathogens (ACDP) Transmissible Spongiform Encephalopathy Risk Assessment Subgroup (TSE RA SG), in January 2012. Its implications for the risk of secondary transmission of vCJD via plasma products should now be considered.

This paper sets out proposals to review the plasma product risk assessment and the notification of patients, as a result of the DH risk assessment.

Background:

The 2004 DNV risk assessment was conducted to inform the management of individuals who had received implicated batches of blood and plasma products. This model was based on the various published animal experimental data, to model the potential vCJD infectivity in blood and its components (including plasma products). It quantified the infectivity of plasma fractions using ID_{50} (median Infective Dose), and used a value of 900 intra-venous (i/v) ID_{50} per unit of whole blood.

Following consideration of the DNV risk assessment, the CJDIP advised that bleeding disorder patients should be notified of their "at risk" status. The DNV risk assessment infectivity estimates were combined with batch-specific manufacturing data in a Product Risk Calculator (developed by the DH and refined by the HPA in 2004), to estimate the potential vCJD infectivity in each batch of implicated plasma product. Each batch required individual calculation because of variations in the manufacturing process. Patients who had received UK-sourced plasma products between 1980 and 2001 were considered at risk. The start-date of 1980 is when Bovine Spongiform Encephalopathy (BSE) could have entered the human food chain and the end-date of 2001 was derived from the expiry date of the last batches of blood products manufactured by Bio Products Laboratory (BPL) (the UK National Blood Service plasma fractionators) from UK plasma.

The Product Risk Calculator classified batches into high, medium and low risk:

1. High risk plasma products: Factor VIII, Factor IX, and anti-thrombin. These were considered high risk because a single dose of these products, as used in clinical practice, was estimated to contain sufficient potential vCJD infectivity to cross the 1% "at risk" CJDIP threshold (which equates to and exposure of 0.02 ID_{50}). These plasma products were used to treat patients with bleeding disorders (patients with congenital and acquired haemophilia (Haemophilia A and Haemophilia B), von Willebrand's Disease, other congenital bleeding disorders and congenital antithrombin III deficiency). Approximately 4000 patients who were treated with UK-sourced clotting factor concentrate between 1980 and 2001 were considered "at risk" in this group.
2. Medium risk plasma products: IV Immunoglobulin and 4.5% albumin. These were considered medium risk because the >1% threshold would be reached by an individual who had received more than one unit, within range of therapeutic use. Assessment at the individual level had to be carried out to determine whether an individual had received sufficient quantities to reach the 1% threshold. Eleven individuals were identified as "at risk" following receipt of medium risk plasma products.
3. Low risk plasma products: 20% albumin and Factor VIII products using albumin as an excipient. These were considered very unlikely to expose patients to a 1% or greater potential additional risk because several thousand vials of the implicated product would be needed, and this was not likely to occur in clinical practice. Since the people receiving these products were considered not at risk, they were not followed-up, and so numbers are not known.

Based on the DNV risk assessment, Product Risk Calculator results, and recognition that vCJD had been transmitted by blood transfusion in at least one case, the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) advised an "umbrella" notification approach in 2004. This was endorsed by the CJDIP, DH and the Haemophilia Society. In 2004 (and a further patient notification in 2006), all patients with bleeding disorders (congenital and acquired haemophilia (Haemophilia A and Haemophilia B), Von Willebrand Disease, other congenital bleeding disorders and congenital antithrombin III deficiency) who had received certain UK-sourced plasma products between 1980 and 2001 were informed of their increased risk of developing vCJD and that they were considered "at risk" for public health purposes. Only a small proportion of these patients had received plasma from an implicated batch. An implicated batch is one to which a donor subsequently diagnosed with vCJD had contributed. All patients were given the option to find out whether or not they had received implicated batches.

The reasons for the umbrella approach were:

- A single dose of implicated clotting factor would contain enough infectivity for a recipient to be at >1% additional risk.
- At this stage of the primary epidemic, it was thought likely that there would be more implicated clotting factors identified if there were future vCJD clinical cases who had donated plasma.
- As bleeding disorder patients receive large quantities of plasma products over a prolonged period, an umbrella approach avoided anticipated additional notification exercises each time future implicated batches were identified.

- The use of Factor VIII and Factor IX was increasing, with BPL having manufactured 32-78% of Factor VIII between 1980 and 2001, indicating that the proportion number of bleeding disorder patients who had received UK-sourced plasma products was likely to be high.

Risk assessment review:

Patients with bleeding disorders who received implicated batches of clotting factors:

Of bleeding disorder patients who received UK-sourced clotting factor concentrate between 1980 and 2001, 787 patients are documented to have received implicated clotting factor (although only 53.6% of the 23.7 million units of implicated batches released have been accounted for) (Zaman et al. 2011). When the estimated infectivity from all implicated batch doses received during their lifetime was cumulated, 98% of patients received an estimated vCJD infectivity above the 1% threshold ($\geq$0.02 ID_{50}).

There has been one post-mortem report of a vCJD infected haemophilia patient who died from non-neurological causes (Peden et al. 2010). Receipt of UK-sourced plasma products was considered their most likely source of infection.

The lack of clinical cases in this group suggests that either the plasma fraction infectivity estimates are overly precautionary, or that the incubation period is longer for this cohort than for implicated cellular blood product recipients.

DNV risk assessment assumptions:

The DNV model contained several assumptions. Those which have already been revised in the DH risk assessment are:

1. Infectivity is present (and constant) throughout the incubation period (using a value of 900 intra-venous (i/v) ID_{50} per unit of whole blood).
2. The median incubation period for vCJD derived from blood is 15 years (90% range of 5-30 years).
3. All recipients are equally vulnerable.

Those which may warrant review include:

1. The effect of plasma fractionation on infectivity, for which DNV gave two options:
   a. Largest single clearance factor
   b. No additional clearance
      - This worst case scenario of a "no additional clearance" was chosen by the CJDIP Subcommittee (10th April 2003) based on it being the most precautionary approach.
2. The entirety of one infected dose in whole blood is present in all components derived from the whole blood.

Recent revisions to blood risk assessment:

In response to the lack of clinical cases in blood transfusion recipients, DH analysts developed a model calibrated to the number of observed clinical cases (with allowance for possible under-ascertainment), with input from the TSE RA SG. This model combined

precautionary inputs for several parameters into a four step process: i.) Prevalence of infectivity in the donor population; ii.) Percentage of units infective; iii.) Number of recipients infected; iv.) Estimation of secondary clinical cases. The variables that had the greatest impact in calibrating the model to the data were susceptibility to vCJD infection and the incubation period.

Important decisions made by the TSE RA SG on 14th July 2011 regarding model calibration were:

1. Models should predict no more than 10 clinical vCJD cases to have occurred so far due to transmission via blood components.
2. An infectivity estimate of the order of 1 Infectious Dose (ID) per unit of non-leucodepleted red cells (based on Gregori *et al.* (Gregori, Yang, and Anderson 2011)) should be used instead of the hundreds/thousands used in previous scenarios. This equates to there being "several" IDs per whole blood donation.
3. The Hilton *et al.* appendix study data (Hilton et al. 2004) are supported by the interim results of the current HPA appendix study, which also extends its finding to a wider age cohort.
4. Detectable prion protein in lymphoid tissue should remain an indicator of infectivity in blood.
5. Where there is no indication of infection in any specific donor, historical exposure to blood components is estimated to carry a 1 in 30,000 chance of leading to vCJD infection, for each unit transfused from 1990 onward. (This was endorsed subject to production of a short note setting out the logic in more detail. The note itself, "Estimating the risk of vCJD infection from past receipt of blood components", (Peter Bennett, 3rd August 2011), was then signed off by the TSE RA SG in correspondence).

Review of assumptions and implications for plasma product risk assessment:

While the DH risk assessment deals with vCJD transmission risks via blood components, the new input assumptions affect the assessment of vCJD transmission risk via plasma products.

There are three main changes in assumptions that may affect the assessment of risk via plasma products:

1. Infectivity in a unit of whole blood. In the existing DNV risk assessment this is 900 intra-venous (i/v) ID_{50} per unit of whole blood. In the new blood risk assessment this is 9 ID_{50} per unit.
2. Date from when infectivity may have been present in the UK blood supply. In the DNV this is 1980, in the new blood RA this is 1990.
3. Prevalence of infectivity within the population. In the DNV risk assessment it was assumed that only 1 infected donor per batch. In the new blood risk assessment, a prevalence of 1 in 4,000 donations (based on the Hilton *et al.* study) is used.

Proposed review of the risk assessment for plasma products:

We propose carrying out three analyses:

1. <u>Reviewing the Product Risk Calculator:</u>

Based on the modified assumptions outlined above, we propose to revise the inputs for the Risk Product Calculator, to see whether the risk classification of plasma product batches changes.

We propose to first make three input changes to the Risk Product Calculator:

i. Calculating batch infectivity using a whole blood infectivity of 100 fold less than the 900 intra-venous (i/v) ID_{50} per unit of whole blood used in the DNV risk assessment.

- This would equate to 9 ID_{50} per unit, consistent with the assumption of "several IDs" endorsed by the TSE RA SG, based on the infectivity demonstrated in the Gregori *et al.* (2011) paper.

ii. Only including products from blood donated between 1990 and 2001.

- As noted above, the TSE RA SG has adopted the approach of counting all donations from 1990 onward as potentially infective for the components risk assessment, and we propose to treat plasma products in the same way.
- There is currently no scientific reason to change the end date of 2001 (when the last BPL batches expired.

iii. Calculating batch infectivity allowing for there being more than one infected donation per pool:

- Using a prevalence of 1 in 4,000 (based on the Hilton *et al.* study), which equates to five infected donations in a batch containing 20,000 donations.
- Using the prevalence estimated from the ongoing appendix study, endorsed by the TSE RA SG.

The revised risk calculations will show:

- Whether plasma products previously assessed as high risk (i.e. treatment with 1 unit resulted in a 1% additional infectivity risk) should now be assessed as lower risk.
- Whether the plasma products previously assessed as medium risk should now be assessed as high or low risk.

2. <u>Reviewing the infectivity risk to patients treated with implicated batches:</u>
We propose applying the new infectivity batch information to the implicated batches received by patients with bleeding disorders. This will show how many remain above the 1% risk threshold. However, this will only be based on the implicated batches received by these patients.

3. <u>Review of total plasma product treatment received by at risk patients:</u>
The HPA proposes working with UKHCDO to review the treatment of "at risk" patients in the umbrella group. Depending on available resources and timescale, this work could include:

i. Ascertaining the amount of non-implicated batches received by the 787 patients who received implicated batches. This would give the total treatment for this sample of patients.
ii. Carrying out individual risk assessments to see how many remain above the 1% threshold level.

iii. Could see impact of changing from 1980 to 1990 on umbrella group. How many would no longer be at risk.
iv. Choosing other samples of patients (for example, those with good data) to see impact of new risk calculations on individual patient risks.

These calculations will show the likely impact of the proposed changes on the numbers of patients currently categorised as "at risk" of vCJD following treatment with UK-sourced plasma products. These calculations could then be used to inform the Panel's decision on whether the umbrella approach should remain, be modified, or be replaced by individual patient risk assessments.

Potential other calculations and risk assessment considerations:

The DNV risk assessment used precautionary assumptions, which could also be reconsidered. We propose that the DH analysts could conduct the following analyses:

1. The worst case scenario of a "no additional clearance" effect of plasma fractionation on infectivity was chosen by the CJDIP Subcommittee (10th April 2003) as it was the most precautionary approach. In this scenario, the entire infectivity load present in the fraction is assumed to be present in the appropriate derivative. The CJDIP Subcommittee had however noted that it was unlikely that successive purification steps would not result in any reduction in infectivity.
   - A less pessimistic approach, such as that of "largest single clearance factor (CF)", could be taken, where any infectivity in plasma is assumed to be reduced by the same proportion as found in animal experiments in which plasma was spiked with infective material derived from the brain. However, the CJDIP decided against this, as it would require accepting the applicability of spiking experiments using brain-derived material to endogenous infectivity in blood.
2. The DNV risk assessment considers the entirety of one infected dose in whole blood is to be present in all components derived from the whole blood. Although this is not physically possible, there has been no scientific basis for any other assumption.
   - Analyses could be conducted to estimate how infectivity could be partitioned between products.
3. Reviewing the 2001 "end date" of risk exposure by investigating whether it is possible to trace who received the UK batches not accounted for, and what proportion of the total supply this represents.
4. As an additional consideration, a recent paper (Beringue et al. 2012) has suggested that there may be different vCJD strains, the more common being lymphotropic (causing long-term asymptomatic carrier-state infection) rather than neuroinvasive (causing relatively rapid onset of clinical symptoms). If so, receipt of product from an "implicated" batch, containing material from donors who went on to develop clinical vCJD, would imply exposure to a neuroinvasive strain, whereas receipt of other batches would be more likely to involve exposure to a lymphotropic strain. The importance of exposure to an implicated batch may therefore be more important than considered in current risk assessments, especially in terms of the risk of recipients developing clinical vCJD.

Summary:

The following process is proposed for applying a revised risk assessment to plasma product recipients:

a) To adapt the existing risk calculations by:
   1. Using a whole blood infectivity level of 9 i/v ID_{50}/unit.
   2. Using a batch infectivity using a prevalence:
      i. Of 1 in 4,000 donations.
      ii. As estimated by the current appendix study.
   3. Blood being considered as potentially infective for donations between 1990 and 2001.

b) Apply the new risk batch infectivity calculations to implicated batches.

c) HPA and UKHCDO to review the treatment of "at risk" patients in the umbrella group.

The results of these calculations will be considered before considering the effects of any further revisions. Further revisions may be appropriate if considered potentially "decision-critical", for example, if the initial re-calculations place substantial numbers of recipients near the CJDIP notification threshold.

d) If further calculations are deemed appropriate, advice will be sought from the ACDP TSE RA Subgroup on the potential case for two further revisions, proposed to be conducted by the DH:
   4. Including an impact of plasma fractionation on infectivity, such as the largest single CF approach.
   5. Re-assessing the distribution of infectivity amongst blood derivatives.

e) The Subgroup's advice is also sought as to whether the risk assessment should attempt to distinguish between exposure to neuroinvasive and lymphotropic strains (from "implicated" and "non-implicated" batches respectively), or whether this should await more direct evidence of the existence of different human strains.

Reference List

Beringue, V. et al. "Facilitated cross-species transmission of prions in extraneural tissue." Science 335.6067 (2012).

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Hilton, D. A. et al. "Prevalence of lymphoreticular prion protein accumulation in UK tissue samples." J.Pathol. 203.3 (2004).

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