Department of Health

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URGENT -IN STRICTEST CONFIDENCE

See attached circulation list

5th December 2000

Dear Colleague

vCJD: POTENTIAL INFECTIVITY IN BLOOD AND FRESH FROZEN PLASMA

1. I am seeking your advice quickly on the current state of knowledge re the potential vCJD infectivity of Fresh Frozen Plasma (FFP). Please see attached a reference list and brief questionnaire which I hope are self-explanatory.

2. The context is the requirement by the Department of Health to appraise options for the sourcing of FFP, whether from within the UK as at present or from abroad (most probably from the US). We are in the process of building an analytical model to assist the appraisal, and it would be very helpful to have some additional information as set out in the attached short request. Your advice on the completeness of the attached reference list, and information on any current but unpublished information would also be of great help. The latter would be treated in confidence if requested.

3. You will see from the copy list that we are canvassing views from scientific members of SEAC, MSBT and other researchers in the field. If you feel I have missed someone out who could contribute please let me know.

4. As this option appraisal is required urgently, I should be grateful if you could e-mail or fax your views by return, or by Tuesday 12th December if at all possible. I apologise for the short deadline and for approaching you in this manner. Please feel free either to write suggestions against the relevant questions or to reply in any other form. Thank you for your help.

Yours sincerely

André Hare
Economic and Operational Research Division

p:\data\ah200\Dec\L12 SEAC and MSBT Blood FFP

External Circulation List

MSBT Scientific Members

Prof Zuckerman	Royal Free Hospital
Dr Gorst	Royal Lancaster Infirmary
Dr Mortimer	PHLS
Dr Wyatt	Mater Hospital Trust

SEAC Scientific Members

Prof Smith	Chair, SEAC
Prof Aguzzi	University Hospital Zurich
Prof Anderson	Imperial College London
Prof Bostock	Inst. Animal Health
Mr Bradley	VLA
Prof Collinge	Imperial College London
Prof Ironside	CJDSU
Prof Masters	University of Melbourne
Prof McConnell	University of Cambridge
Dr Safar	University of California

Other Scientific Experts

Dr Bruce	Inst. Animal Health
Prof Weissmann	Imperial College London
Prof Brown	Nat Inst. Health, Bethesda
Dr Minor	NIBSC
Dr Miller	CDSC
Dr Wallington / Dr Anstee	NBS (CJD Steering Group)
Dr Turner	Scottish National BTS

Internal Circulation List

Dr Pat Troop DCMO
Dr Mary O'Mahony PH6
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Dr John Stephenson RD2
Dr Peter Bennett EOR4
Mr Jeremy Townshend EOR4

Potential Transmission of vCJD through Fresh Frozen Plasma (FFP)

REFERENCE LIST

Economics and Operational Research Division (EOR), Department of Health

1 December, 2000

Query: Is this reference list below adequate for this rapid study? Are there any significant omissions?

Most Recent key papers

1) **F Houston, J D Foster, Angela Chong, N Hunter, C J Bostock. Transmission of BSE by blood transfusion in sheep *The Lancet* 2000; 356: 999-1000**

Articles Referenced:

a) Bruce ME, Will RG, Ironside JW, et al. Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature* 1997; 389: 488-501.

b) Schmerr MJ, Jenny A, Cutlip RC. Use of capillary sodium dodecyl sulfate gel electrophoresis to detect the prion protein extracted from scrapie-infected sheep. *J Chromatogr B Biomed Appl* 1997; 697: 223-29.

c) Foster JD, Bruce M, McConnell I, Chree A, Fraser H. Detection of BSE infectivity in brain and spleen of experimentally infected sheep. *Vet Rec* 1996; 138: 546-48.

d) Hill AF, Zeidler M, Ironside J, Collinge J. Diagnosis of new variant Creutzfeldt-Jakob disease by tonsil biopsy. *The Lancet* 1997; 349: 99-100.

e) Goldmann W, Hunter N, Smith G, Foster J, Hope J. PrP genotype and agent effects in scrapie: change in allelic interaction with different isolates of agent in sheep, a natural host of scrapie. *J Gen Virol* 1994; 75: 989-95.

2) **Brown P. BSE and Transmission through blood. *The Lancet* 2000; 356.**

Articles Referenced:

a) Ghani AC, Ferguson NM, Donnelly CA, Anderson RM. Predicted vCJD mortality in Great Britain. *Nature* 2000; 406: 583-84.

b) Brown P. Can Creutzfeldt-Jakob disease be transmitted by transfusion? *Curr Opin Hematol* 1995 Nov; 2(6): 472-7

c) Brown P, Cervenakova L, McShane LM, Barber P, Rubenstein R, Drohan WN. Further studies of blood infectivity in an experimental model of transmissible spongiform encephalopathy, with an explanation of why blood components do not transmit Creutzfeldt-Jakob disease in humans. *Transfusion.* 1999; 39: 1169-78

d) Rowher RG. Titer, distribution and transmissibility of blood-borne TSE infectivity. Presented at *Cambridge Healthtech Institute* 6th Annual Meeting; "Blood Product Safety: TSE, Perception vs Reality", MacLean, VA, USA, Feb 13-15 2000

e) Hill AF, Butterworth RJ, Joiner S, et al. Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. *The Lancet* 1999; 353: 183-189

Responses to the above articles:

3) **Sivakumaran M. Transmission of BSE by blood transfusion. *The Lancet* 2000; 356.**

4) **Holada K, Svimák J, Vostal JG. Transmission of BSE by blood transfusion. *The Lancet* 2000; 356.**

Articles Referenced (excluding any repeated references):

a) Barclay GR, Hope, J, Birkett CR, Turner ML. Distribution of cell-associated prion protein in normal adult blood determined by flow cytometry. *Br. J. Haematol.* 1999; 107:804-14

b) MacGregor I, Hope J, Barnard G, et al. Application of a time-resolved fluoroimmunoassay for the analysis of normal prion protein in human blood and its components. *Vox Sang* 1999; 77:88-96

c) Holada K, Mondoro TH, Muller J, Vostal JG. Increased expression of phosphatidylinositol-specific phospolipase C resistant prion proteins on the surface of activated platelets. *Br. J. Haematol.* 1998; 103: 276-82

d) Holada K, Vostal JG. Different levels of prion protein (PrPc) expression on hamster, mouse and human blood cells. *Br J. Haematol.* 2000; 110: 472-80

Further References:

Possibilty of transmission of vCJD through blood and blood products

5) Turner M , Universal leucodepletion to reduce potential risk of transmission of new-variant Creutzfeld-Jakob disease. *British Journal of Haematology* 2000; 110/3 (745-747)

6) Hervé P, Transfusion Safety: emergent or hypothetical risks. *Transfusion Clinique et Biologique* 2000; v7 n1 (feb) 30-38

7) Milton A, How is Creutzfeldt-Jakob disease acquired? *Neuroepidemiology* 2000; 19: 55-61.

8) Turner ML, Ludlam CA, Variant Creutzfeldt-Jakob disease. *Transfusion Medicine Reviews* 2000; 14: 216-222.

9) Williamson LM, New variant Creutzfeld-Jakob disease and leukocyte depletion of blood components. *Infusionstherapie und Transfusionmedizin.* 26 (suppl. 2) 1999; 24-30

10) Moor ACE, Dubbelman TMAR, Vansteveninck J, Brand A, Transfusion-transmitted diseases: risks, prevention and perspectives. *European Journal of Haematology*, 1999; 62(1) 1-18

11) Cash J, Boyd K, Blood transfusion: Bayer's initiative (commentary). *The Lancet* 1999; 353: 691

12) Brown P, Rowher RG, et al. The distribution of infectivity in blood components and plasma derivatives in experimental models of transmissible spongiform encephalopathies. *Transfusion* 1998; 38, 810-6

13) Brown P. Donor pool size and the risk of blood borne Creutzfeldt-Jakob disease. *Transfusion* 1998; 38, 312-5

14) Brown P, Gibbs CJ, Rodgers-Johnson P, et al. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. *Ann. Neurol.* 1994; 35: 513-29

Prion protein

15) Soto C, Kascsak RJ, Saborio GP et al., Reversion of prion protein conformational changes by synthetic beta-sheet breaker peptides. *The Lancet* 2000; 355, 192-197

16) Binding Of Disease-Associated Prion Protein To Plasminogen. Michael B. Fischer, Christiane Roeckl, Petra Parizek, Hans Peter Schwarz & Adriano Aguzzi. *Nature* 2000; 408, 479-483

17) Sivakumaran M, Saunders P, Cobbold M et al. Qualitative analysis of leukocyte fragments in pres-storage leukodepleted blood products. *Blood* 1999; 94 (suppl 1): 459a

Other useful References

18) Peto S. A dose response equation for the invasion of micro-organisms. *Biometrics* 1953; 9, 320-35

Search Process

A *Medline* (www.ncbi.nlm.nih.gov/PubMed/) serach was carried out for the last two years with the key words "BSE", "variant Creutzfeldt-Jakob disease", "vCJD", "blood" and "Fresh Frozen Plasma". Relevant articles identified from the abstract list were ordered and are listed above.

We also looked at the recently published article by Bostock et al. in *The Lancet* (see article 1). Responses to this article and the editorial in *The Lancet* were obtained and cited references were followed up where appropriate.

Potential vCJD transmission and Fresh Frozen Plasma: QUESTIONNAIRE: REQUEST FOR SCIENTIFIC ADVICE

Economics and Operational Research Division (EOR) of Department of Health

4th December, 2000

Background

EOR has been tasked to assess urgently the possible risk of vCJD transmission via donated Fresh Frozen Plasma (FFP) from UK or other sources. This will form part of a wider assessment also covering the potential risk of importing viruses, the need to avoid any disruption of supply, etc.. We are therefore seeking your advice on some key variables associated with potential vCJD transmission, in particular the possible level of vCJD infectivity in FFP.

This rapid study will have a tight focus, concentrating on the relative merits of three broad options for the supply of FFP, involving use of:

- UK-sourced plasma, supplied in single units and subjected to leucodepletion, as at present
- US single-unit FFP and
- US pooled FFP from a commercial supplier.[1]

Given the multiple uncertainties surrounding vCJD and its transmission, the study will not attempt predictions, but will consider a wide range of scenarios to clarify:

- the *possible* scale of onward infection associated with use of UK-sourced FFP, given different assumptions consistent with current knowledge
- the potential impact of substituting pooled or unpooled US plasma.

For present purposes, we are concerned *only* with the potential risk of vCJD transmission. It is recognised that options for sourcing plasma have other implications, and this study will be one contribution to a broader analysis.

Key Questions

The scale of any risk is dependent primarily on the potential infectivity (if any) of plasma, the effect of leucodepletion and of course the prevalence of vCJD in the UK – particularly amongst those of an age associated with blood donation. However it is not necessarily safe to assume *zero* prevalence of the disease within the US donor population – or indeed any other population - despite the lack of reported cases to date (and absence of a large historical BSE outbreak). Unless the prevalence of vCJD

[1] Though the US is considered as the most likely alternative, the same form of analysis will be applicable to any other potential donor population.

amongst US donors is zero, the effect of pooling plasma on the risk of onward infection must be taken into account.

Some suggestions as to plausible ranges of inputs for the variables just identified can be gleaned from published research, or indeed by reverting to the assumptions used by DNV in their Risk Assessment of blood[2], though direct evidence regarding vCJD in human blood is sparse as yet. Guidance and comment are therefore sought on the following topics, especially any emerging results from unpublished research.

We appreciate that not all recipients will feel qualified to address all questions: please therefore offer answers to as many as you think appropriate.

1. Infectivity of Blood Plasma

While it is not clear that plasma contains *any* vCJD infectivity, even low levels of infectivity are of concern given that individual patients typically receive substantial volumes – several hundred ml – of FFP. DNV estimated that plasma had a theoretical infectivity of approximately 1 ID_{50} per ml based on Brown et al.[3]

Queries:

1.1 What is the **maximum** vCJD infectivity (in some specified units – e.g. i/c ID_{50}s or IUs) of blood plasma consistent with current knowledge? (For example, can an upper limit be inferred from those animal experiments so far producing null results?)

1.2 Does this vary with the point within the incubation period at which blood was obtained? If so, roughly how?

1.3 How would the infectivity level(s) suggested relate to the probability of a recipient being infected by intravenous transfusion?[4]

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[2] Det Norske Veritas. Assessment of the risk of exposure to vCJD infectivity in blood and blood products. Final Report for the Spongiform Encephalopathy Advisory Committee and the Department of Health. *DNV*. February 1999.

[3] Brown P, Rohwer RG, Dunstan BC, MacAuley C, Gajdusek DC, Drohan WN. The distribution of infectivity in blood components and plasma derivatives in experimental models of transmissible spongifrom encephalopathy. *Transfusion* 1998. **38** 810-816

[4] For example, some researchers use the concept of ID_{50}s per ml together with a linear dose-response model. The probability of infection is then roughly half the number of ID_{50}s received, until certain infection is approached. Alternatively, Brown (Transfusion 1999) adopts the one-hit model of Peto (Biometrics 1953) in which the minimum amount of infectious material capable of transmitting disease contains a single *intracerebral* infectious unit (IU) and then considers two alternative models for the probability of infection via *intravenous* transfusion.

2. Effect of Leucodepletion

There appears to be little direct evidence on the effectiveness of leucodepletion. Brown (Transfusion 1999) seems to suggest that it could either increase or decrease infectivity. There is some evidence of PrP^{Sc} association with white cells (with some concerns about white cell fragments), but also new evidence of some association with plasminogen (Fischer et al, 2000).

Query: what is the likely range for the effect of leucodepletion on plasma infectivity?

3. Variation of infectivity with time

FFP may be stored at approximately -40°C for up to one year. If the unit (or pool) contains some infective material, the question arises as to whether prion conversion could continue to occur at a significant rate, so that infectivity of stored FFP would increase as time goes on?

Queries

3.1 Does the possibility of continued conversion appear realistic given current knowledge, or can infectivity be (provisionally) taken to be constant?

3.2 If prion conversion might continue in stored FFP, would it be reasonable to assume a rate no greater than that occurring when blood is still in the body?

4. End-point infectivity of FFP

Taking all the previous points into account, can a **range** of likely (rather than worst-case) values be given for the *intravenous* infectivity of leucodepleted blood derived *entirely* from an infected donor?

5. Relative prevalence of vCJD

The intention is to consider a very wide range of scenarios for the prevalence of vCJD amongst UK donors, from 1 in 100 down to 1 in 100,000. Scenarios for any US

prevalence will be defined relative to the UK, reflecting possible views as to the relative level of exposure to sources of infection.

Query: Would it be reasonable to consider a worst case in which US prevalence has reached $1/10^{th}$ that presumed for the UK? (If not, please suggest an alternative.)

6. Other variables

Finally, process variables regarding the use of FFP appear not to be subject to such great uncertainty as infectivity and prevalence. We have at least rough data on:

- amount of FFP derived from each donor
- number of transfusions, by age group (we are though seeking more on reasons for use and implications for survival)
- amount of FFP used annually (and hence average volume per transfusion, though more about distribution of volumes and repeat transfusions on the same person would be helpful)
- pool sizes used by different suppliers (although this is in principle a decision variable)

Your advice is not specifically sought on these process variables, but please feel free to comment as appropriate.

THANK YOU FOR YOUR HELP