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CIRCULATION:

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70% of FFP goes to people over 50 years

MSBT 23/1A

POTENTIAL vCJD TRANSMISSION AND FRESH FROZEN PLASMA: ANALYSIS OF SOURCING OPTIONS

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Summary

This report analyses the potential risk of person-to-person vCJD transmission via Fresh Frozen Plasma sourced from UK donors. It also considers the possible reduction of that risk from sourcing elsewhere – specifically from the US. It should be stressed that *only* vCJD risks are covered here: other potential risks and benefits of alternative options are considered in a separate paper prepared by the National Blood Service (NBS).

The potential transmission of vCJD by this route is subject to large uncertainties, especially concerning the prevalence of the disease within the UK population, the infectivity of plasma from any individuals incubating the disease and the effectiveness of leucodepletion in reducing that infectivity. Rather than attempting a predictive exercise, a scenario-based approached is used to explore three main questions from the point of view of reducing the risks of vCJD transmission.

- How many infections *could* result from use of UK-derived FFP, given current knowledge?
- If vCJD prevalence in the US might not be zero, how much would this negate any benefit from switching to a US source?
- What are the relative merits of pooled and unpooled supplies? Specifically, if an unpooled US source were unavailable, under what circumstances would a pooled US source carry less vCJD risk than unpooled UK plasma?

Risk from UK-derived plasma

A risk to public health from this transmission route cannot at present be ruled out. Unless quite optimistic assumptions are made about the potential infectivity of leucodepleted blood, the *annual* number of new infections via FFP could run at up to about 1% of the presumed number of primary infections – e.g. about 85 per year for a primary outbreak of 10,000 people in the UK. The duration of such a risk would depend on the incubation period for the primary outbreak, which could well be of the order of 20 – 30 years.

In short, continuing the status quo could result in a significant number of secondary infections (though the total could be reduced by efforts to restrict the use of FFP).

Unpooled US plasma

Given plausible limits on the relative scale of US infection, use of unpooled US plasma would avoid all, or almost all, the above infections.

Pooled versus unpooled sources

Sourcing FFP – pooled or unpooled - from a population free of vCJD would of course remove any transmission risk altogether. However we also consider the possibility that vCJD prevalence amongst US donors might be non-zero - while still being much lower than in the UK. If so, results can be dependent on whether or not US plasma were to be pooled.

Implementing an *unpooled* option would achieve a risk reduction proportionate to relative vCJD prevalence. For example, if US prevalence were to be one-hundredth that of the UK, the number of infections would be reduced by the same factor. From the numerical starting point used above, the maximum number of infections caused would drop from about 85 to less than 1. Though the numbers vary greatly for other scenarios, the proportionate effect is robust.

If plasma is *pooled*, then a further uncertainty comes to the fore, in the shape of the dose-response curve. If a "threshold effect" exists, in which a significant dose is required to give *any* chance of infection, then pooling can actually reduce the number of onward infections. However with no (or a very low) threshold, pooling will significantly increase the number of infections.

Conclusion

If the potential vCJD risk from continued use of UK-derived FFP is considered unacceptable, the most reliable precautionary measure would be to find an alternative source of unpooled plasma. Should this be unavailable (or unaffordable) however, the analysis shows that in a wide range of scenarios any risk of vCJD transmission would be smaller even for pooled US-derived FFP than for unpooled UK plasma.

CONTENTS

1. INTRODUCTION

Background and Objective

1.1 This paper concerns the possible risk of person-to-person vCJD transmission via transfusion of Fresh Frozen Plasma (FFP), and options available to reduce any such risk. Potential transmission risks from various blood products have been studied in previous analyses. As a result, precautionary measures are already in place – the most relevant here being leucodepletion of plasma products. It is not clear that plasma from donors incubating vCJD contains *any* infectivity, though some animal models suggest so. In addition, the effectiveness of leucodepletion of FFP remains unproven: as noted later, some animal experiments suggest that it may have no practical effect. Even low levels of residual infectivity are of concern, given that individual patients typically receive a substantial quantity – several hundred ml - of FFP, and that about 100,000 transfusions take place each year. The question has therefore been raised as to whether further precautionary measures would be appropriate.

1.2 This analysis has a tight focus, concentrating on 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]

1.3 The present study is concerned *only* with vCJD transmission, but is one contribution to a broader risk analysis. The sourcing of plasma has a wide range of implications. Though all the options currently under consideration maintain the use of unpaid volunteer donors, alternative supplies may carry greater or lesser risks of containing viral agents, and be subject to different processes in the course of preparation. Cost implications and guarantees of adequate supplies must also be considered. Finally, any sourcing option can be combined with efforts to prevent excessive or unnecessary use of FFP (Contreras 1992). Such issues are being addressed in a parallel paper prepared by the National Blood Service.

Uncertainties and Outcome Measures

1.4 There are many unknowns involved in any assessment of potential vCJD transmission risks. The absolute scale of any risk is dependent primarily on the infectivity present in plasma, the effect of leucodepletion and of course the prevalence of vCJD in the donor population. It may not be safe to assume a zero prevalence of the disease in the US – or anywhere else - though the lack

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[1] Supply from the US is considered here as raising the most promising options (given the need for a large supply, use of volunteer donors and lack of recorded vCJD cases). However the same analysis can be applied to any other alternative source population.

of reported cases to date (and absence of a large historical BSE outbreak) suggests a prevalence substantially lower than in the UK. The potential effect of pooling plasma must therefore be taken into account in comparing the options. This is highly-dependent on the presumed dose-response relationship (discussed in paragraph 3.2) – and firm evidence to decide amongst alternative models is again lacking as yet.

1.5 Given these uncertainties, a scenario-based approach is used. The aim is not to attempt predictions, but rather to clarify:

- what scale of transmission risks *could* be associated with use of UK-sourced FFP, given different assumptions consistent with current knowledge
- the potential impact on those risks of substituting pooled or unpooled US plasma.

1.6 Specifically, we consider outcomes for different scenarios measured in terms of:

- how many secondary vCJD infections could result in a given year from use of FFP under each of the options considered
- roughly how these infections would translate into clinical cases of vCJD, and life-years lost or saved, though this is subject to further uncertainties about the life expectancy of recipients.

For ease of comparison across scenarios, results can be scaled to the size of the primary outbreak, i.e. measured relative to a given number of primary infections.

1.7 Though some information can be gleaned from published research, direct evidence regarding vCJD in human blood is sparse as yet. We have therefore been reliant on expert guidance from members of SEAC, MSBT and other recognised researchers in the field of TSEs. To provide a common structure for this advice, a brief questionnaire was circulated to key individuals (this is appended in Annex D, with a summary of responses to each question). A bibliography of relevant published research appears at the end of the main text.

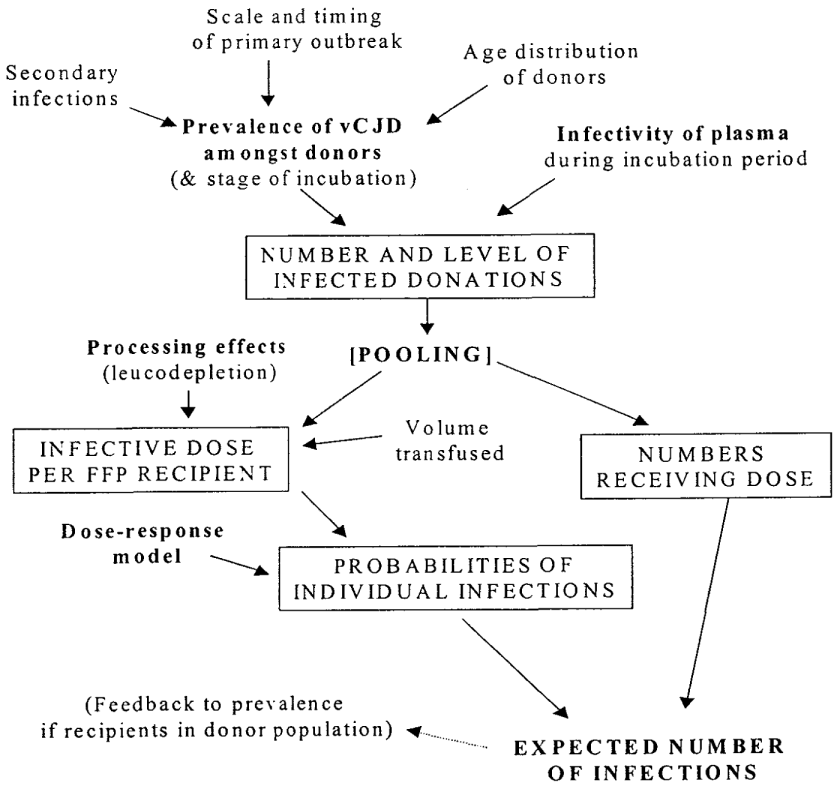
2. METHOD OF ANALYSIS

Overall structure of model

2.1 The model used here tracks potential infectivity through the donation and processing of blood and transfusion of FFP into individual recipients. Given a known number of transfusions taking place, this provides scenarios for the expected number of infections within the population *per year*. Some of the main variables at this stage are set out in Figure 1 below. Given further information about the most common recipients of FFP and their life-expectancies, the model can additionally calculate the expected number of clinical vCJD cases and life-years lost in each scenario.

2.2 Given the gross uncertainties attaching to key parameters, no attempt is made to reproduce every detail of the donation and transfusion process. Rather, the model is intended to produce rough alternative scenarios that will distinguish the effects of policy options.

Fig. 1: OUTLINE MODEL STRUCTURE:
Expected number of infections from donations used for FFP
[Key variables shown in **bold**]



Key variables

2.3 Given a certain demand for FFP, and consequently a given volume of donated blood used for this purpose, then as set out in Figure 1

- the number of infected donations, and the level of infection, will primarily depend on the **prevalence of vCJD** in the donor population and **infectivity** of plasma amongst those incubating the disease. The potential level of infectivity *may* depend on how far through the incubation period an individual is (see Brown 1999 and Questionnaire responses in Annex D).
- The donated blood may or may not be pooled. This is a decision variable rather than an unknown. A large pool will spread the material in any infected donation widely, so that many recipients would receive a small fraction of it.
- Whether pooled or not, we presume that processing will involve **leucodepletion**, which may have a significant effect on vCJD infectivity. The residual infectivity, together with the volume transfused, will determine the dose received by any given recipient of FFP.
- Transfusions normally involve several (typically 3-5) units of FFP. Even if each unit is unpooled, recipients are likely to receive plasma from several different donors. The model takes this into account.
- Given a particular dose, an individual's chance of becoming infected will be determined by the **dose-response** relationship. Several alternative models are discussed below. In particular, the dose-response relationship is the key to whether it is more damaging to spread a given dose amongst many recipients.
- The probability of individual infection, multiplied by the numbers receiving the estimated dose, determines the expected number of secondary vCJD infections. Finally, however, if the recipient and donor populations overlap substantially, these secondary infections will increase the prevalence of the disease amongst donors. This "feedback" amplifies the effect of the transmission route. However these longer-term dynamics are not analysed in the present model.

2.4 Many variables, especially those referred to in bold, are subject to great scientific uncertainty. These play a key role in defining the scenarios that *could occur* given different policy options. Each is discussed in turn below. In addition, the model in spreadsheet form (see Annex A) allows several other parameters to be varied, including:

- unit volumes for donation and transfusions
- the mean number of units per FFP transfusion and
- the total number of transfusions given per year (with a baseline of 100,000), any increase or decrease in usage having a proportionate impact on the expected number of infections.

Simplifying assumptions

2.5 The model has deliberately been kept simple. In particular:

- It is assumed that all plasma is either pooled or unpooled, with all pools being of the same size, though this size is variable between scenarios and if necessary, the model could be disaggregated to consider "mixed strategies" on pool size.
- A single averaged infectivity density of infected plasma has been assumed. As already discussed, the infectivity density might vary over the incubation period. The model can accept different levels of infectivity, each occurring with a different prevalence in the population. However, given the huge uncertainties surrounding the level of infectivity anyway, this is currently thought to be unnecessarily complex.
- At present, no allowance has been made for the point that some classes of patient (e.g. those with the condition thrombotic thrombocytopenic purpura, TTP) may receive many transfusions of FFP. In principle, this will lead the model to overstate the expected number of infections due to the "double-counting". That is, the model would count infection of the same individual twice over as two infections. However this effect is in the same direction for any policy option and is also small unless the chance of being infected by a single random transfusion is at least 5-10%, well above the range of scenarios considered here.

2.6 A further key working assumption (supported by expert advice as in the responses to the Questionnaire in Annex D) is that the any level of infectivity present in FFP is constant during storage, neither growing by continued prion conversion nor decaying significantly.

3. KEY SCIENTIFIC INPUTS

Introduction

3.1 We now comment briefly in turn on factors identified in the previous section, starting with the Dose Response model, then moving on to individual variables.

Dose-Response Models

3.2 The analysis allows a choice between several different models linking the infective dose received by an individual and the probability of infection. In the present context, the dose-response model assumed is key in determining the effect of pooling infective plasma on the expected number of infections amongst recipients.

3.3 As detailed in Annex B, four alternative models have been considered, corresponding to those used in similar studies and/or appearing in the literature.

- *Linear* models treat the probability of infection as proportionate to the dose received, as measured in ID_{50}s – one ID_{50} being the dose required to infect 50% of those receiving it. In the simplest ("piecewise linear") version of the model, infection is regarded as certain once a dose of at least $2ID_{50}$s are received. This is the working model accepted by SEAC in the context of vCJD transmission risks via surgery. An "asymptotic" model is similar except that the probability of infection gradually approaches 1 as the dose increases
- In a "*one-hit*" model, infection certainly occurs once some minimum dose – an Infectious Unit, or IU – reaches the brain (Brown 1999). Two variants of this approach are outlined in the Annex.

3.4 For present purposes, it is not necessary to use results from all four models. The asymptotic and one of the "one-hit" models consistently give results less pessimistic than (but of similar order to) the basic linear model. However, the other "one-hit" model gives significantly different results. It is the least pessimistic model, in the sense of predicting a smaller chance of infection from a given dose. More importantly, its statistical linkage between intravenous infection and the chance of an Infectious Unit reaching the brain results in a significant threshold effect. That is, the chance of infection from a modest intravenous dose becomes vanishingly small. As a result, pooled FFP could have a lower risk of transmitting vCJD than unpooled - in contradiction to the other three models. In what follows, results are therefore given firstly for the basic linear model and secondly for this "statistical threshold" model

Infectivity of donated Blood Plasma

3.5 As already noted, plasma from humans incubating vCJD has not been proven to contain *any* infectivity, while results of animal experiments appear mixed so far. Though it is widely accepted that transmission via intravenous (i/v) transfusion is less efficient by a factor of at least 5-10 than the intracranial (i/c) route, absolute values remain subject to much uncertainty. The previous Risk Assessment carried out for DH by DNV Technica Ltd[2] used a baseline estimate of 10 i/c ID_{50} (or 1 i/v ID_{50}) per ml of plasma.

3.6 Responses to the expert questionnaire reflect the current uncertainty. For example, based on a study in a mouse model of BSE, Dr. Bruce has suggested (personal communication) that infectivity could be of the order of 0.5 i/v IUs / ml. However she notes that current mouse bioassays of vCJD plasma have an estimated limit of detection of about 100 human i.v. IUs/ml. In mouse experiments using the Fukuoka-1 TSE, Brown (1999) observed levels of 20 i.c. IUs per ml of plasma *after* the onset of clinical signs (compared with 100 i.c. IUs per ml in buffy coat), which was not removed by leucodepletion. He also noted that about 7 times more plasma was needed to transmit the disease by the intravenous rather than intracranial route.

3.7 We therefore use a wide range of values up to 1 i/v ID_{50} per ml, but with sensitivity analysis ranging up to 100 i/v ID_{50}s / ml (or 350 i/c IUs per ml for the "one-hit" models[3]). (As will be seen, some key results are anyway insensitive to the level of infectivity once this reaches at least 0.01 ID_{50}s / ml). As already discussed, we take the chosen value to apply throughout the incubation period.

Effect of Leucodepletion

3.8 Based on evidence of PrP^{Sc} association with white cells, leucodepletion of non-pooled products has already been introduced as a precaution against vCJD transmission. However there are doubts as to its effectiveness in this context, though research is ongoing. Results obtained by Brown (1999) with classical CJD in rodents show leucodepletion having no significant effect on plasma infectivity in contrast to labile blood components. Some recent evidence of PrP^{Sc} association with plasminogen (Fischer et al, 2000), would also imply non-removal of infectivity with white cells. We therefore consider a *worst case* in which leucodepletion has no effect. It should also be noted that substantial quantities of FFP are transfused. Therefore if its initial infectivity is high, even a large reduction through leucodepletion could leave the infection risk essentially unchanged. This is illustrated in Section 4 below.

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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. February 1999, *DNV*

[3] In comparing these two model types, we assume an equivalence between 2 i/v ID_{50} of the linear models and 7 i/c IUs of the "one-hit" models.

Prevalence of vCJD in donor populations

3.9 The current prevalence of vCJD amongst UK donors is essentially unknown. To indicate the *possible* scale of any secondary infection, we consider a wide range of scenarios, with prevalence from 1 in 100 down to 1 in 100,000. (If typical of the population as a whole, these figures would imply a total number of UK infections ranging from about 600,000 to 600. This range of scenarios is consistent with that used in the Surgical Transmission Risk Assessment, as endorsed by SEAC.)

3.10 The US population will have had some exposure to potential sources of TSE infection, but substantially less than that represented by the large BSE outbreak in the UK. Prevalence amongst US donors should be substantially less than for the UK, and may well be negligible. However it may not be safe to assume zero prevalence. In general, our approach will be to vary possible (relative) US prevalence as a form of sensitivity analysis, to determine at what level this would start to have a bearing on policy options. (Expert guidance, given in responses to the Questionnaire, Annex D, suggests that a figure for US prevalence of up to a hundredth that of UK prevalence would be sufficient to be precautionary whilst retaining some plausibility.)

Summary of Inputs

3.11 Other relevant factors (e.g. the number of FFP transfusions, and volumes transfused) appear not to be subject to the same levels of uncertainty. A summary of all relevant inputs, showing either baseline working values or ranges, is shown in Table 1 below. Note that subsequent calculations are based on 5 units typically being used per transfusion: should this prove to be an overestimate, all infection scenarios would be affected proportionately.

Table 1: Summary of baseline inputs

Variable	Units	Value/range	Comments
Infectivity of plasma	i/v ID_{50}	Up to 1 (100 in sensitivity analysis)	From pre-clinical donors, throughout incubation period
Effect of leucodepletion	log reduction in infectivity	0 minimum	
Volume of donation	ml	250	
Volume of transfusion unit	ml	250	
Units per transfusion	Number (mean)	3 - 5	
Number of FFP transfusions	Number per year	100,000 approx	Subject to possible reduction
vCJD prevalence in UK	% of donors incubating	0.0001 – 0.1	If typical of whole population, would imply outbreak of 600 – 600,000 infections
Relative vCJD prevalence in US	% donors incubating as proportion of UK prevalence	1/100 maximum	Implies US prevalence at 100-fold less than UK: may be zero.

4. ANALYSIS OF THE CURRENT SITUATION

Possible scale of vCJD transmission

4.1 The first aim of analysis is to investigate the *possible* scale of any transmission risks from use of UK-derived FFP. Table 2 summarises scenarios for various combinations of primary outbreak and infectivity of leucodepleted FFP. It shows the annual number of secondary infections expected in each scenario, initially using the linear dose–response model, but with figures in brackets showing results from the "statistical threshold" model *where these are different* (taking 2 i/v. ID50s to be equivalent to 7 i/c IUs).

Table 2: Secondary vCJD infections caused annually by unpooled UK-derived FFP in scenarios with varying infectivity and prevalence [5 x 250ml units transfused]

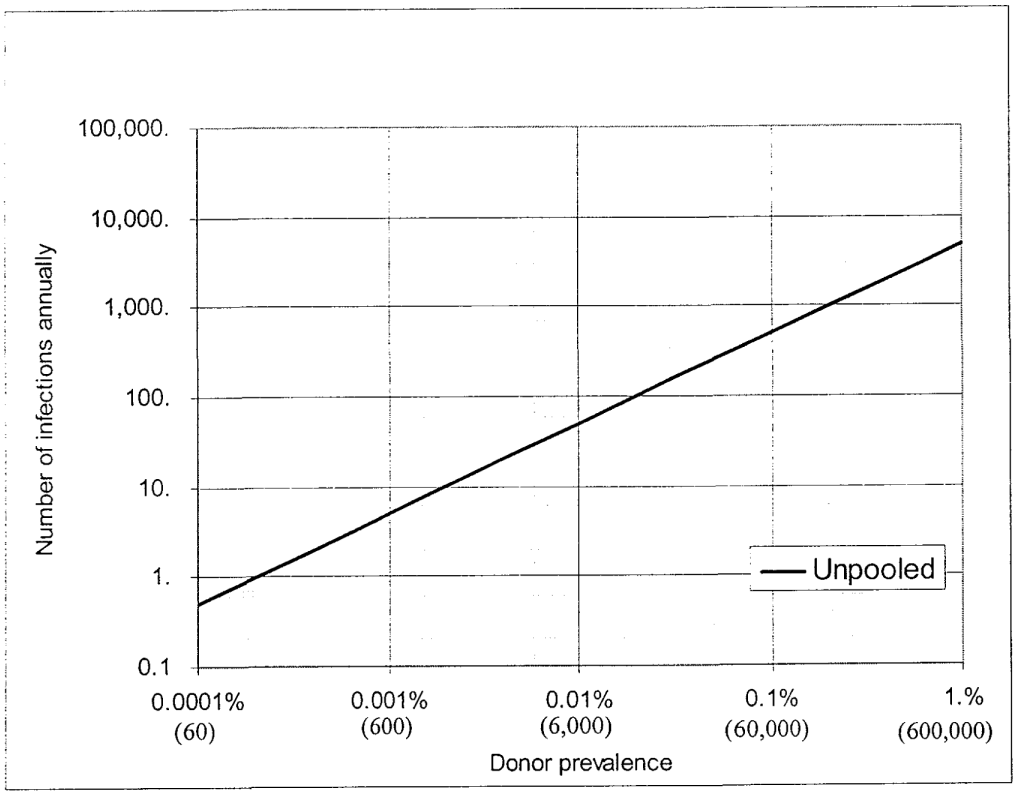
Infectivity [ID_{50} per ml], leucodepleted FFP	**Primary vCJD outbreak:** number of infections & corresponding prevalence for UK population		
	1,000	**10,000**	**100,000**
	(0.0017%)	**(0.017%)**	**(0.17%)**
1	8	85	850
0.1	8	85	850
0.01	8 (7)	85 (65)	850 (650)
0.001	1 (0)	11 (0)	110 (0)
0.0001	0	1 (0)	11 (0)

4.2 Note that rows refer to infectivity of FFP after leucodepletion: for example, if initial infectivity is 1 ID_{50} per ml, and leucodepletion were to have a 100-fold effect, then the third row (0.01 ID_{50} per ml would apply). However with the linear dose-response model, the same results appear for *any* level of FFP infectivity from 0.01 ID_{50} / ml upward. This is because transmission via unpooled donations is effectively from individual to individual and involves a substantial volume of material. Unless infectivity is very low, anyone receiving a unit of FFP from an infective donor would receive a greater dose than needed for certain infection. Even with the "statistical threshold" model, the same results hold almost to the same boundary.

4.3 Graph 1 shows similar information to the upper part of Table 1, for a wider range of prevalence. The straight line reflects the point that in these scenarios, infections caused *annually* by FFP would run at a fixed proportion (just under 1%) of the primary outbreak. It may be noted this is comparable to figures in the Surgical Risk Assessment calculated for all surgery in fairly pessimistic

(though not worst case) scenarios – a route involving millions of operations rather than just 100,000 transfusions.

Graph 1: Annual number of infections versus donor prevalence: unpooled FFP
[Infectivity at least 0.01 ID_{50} per ml; Linear Dose-Response]



Note: numbers in brackets indicate the number of infections in the UK, assuming the donor prevalence is typical of the population in general

Plausibility of pessimistic scenarios

4.4 It may be objected that such scenarios are implausible from an epidemiological point of view, implying more infections than is possible given the number of cases observed. In particular, we note Brown's (1999) study of classical CJD. This investigates why blood-related transmissions have not showed up in appreciable numbers (and proposes the "statistical threshold" dose-response model as one possible explanation). Without disputing Brown's analysis, it may be considered less compelling for variant than for classical CJD, incidence of which has long been in a rough steady state.

4.5 Specifically absence of blood-related vCJD cases to date may reflect

- small infectivity, perhaps combined with some threshold effect
- small prevalence amongst donors

- infectivity only appearing in the latter stages of the primary incubation period, which in itself may be long
- a long incubation period for blood-borne infection (e.g. the mean of 12 years considered as an upper bound for the Risk Assessment for surgical transmission which has been endorsed by SEAC).

All the above may apply in some combination. The last two suggest the need for caution in ruling out pessimistic scenarios, implying (respectively) that the risk of transmission might be rising as the primary outbreak develops and/or that substantial blood-related infection might already have occurred without yet impacting on figures for clinical cases.

Clinical Cases and Life-Years lost

4.6 For any given number of vCJD infections, the number of recipients surviving to develop vCJD symptoms, and the number of life-years they would lose, will depend on:

- the incubation period (from infection to onset of symptoms) by this route, and
- the existing life-expectancy of recipients, dependent both on age and diagnosis.

Loss of *symptom-free* life-years may be regarded as an appropriate rough measure of impact on health, given that quality of life once symptomatic will be extremely poor. (This measure has already been used in assessing the cost-effectiveness of measures to reduce surgical transmission of vCJD.)

4.7 In calculating life-years lost through infection, a key question is obviously the "normal" life-expectancy of FFP recipients. Firstly, this will be dependent upon age: the most useful data on this is supplied for 1995 by the Scottish National Blood Transfusion Service. This shows a concentration of usage amongst those aged 50 upwards, but with a significant proportion (approaching 10%) going to neonates. The pattern across the UK is presumed to be roughly similar, though some changes may have occurred in the intervening years.

4.8 As regards life-expectancy, the neonates are generally premature babies, most of whom can expect an essentially normal life-span. Of the rest, at least some will have underlying conditions that are life-threatening. There is some uncertainty as to how much allowance should be made for this. However calculations are presented in Annex E, making use of US research on blood product recipients. These suggest a mean life expectancy of FFP recipients (including neonates) of *around* 12 - 15 years. If the mean vCJD incubation period for this route were to be 3 – 5 years, a figure of the order of 10 for symptom-free life-years would be lost per infection.

4.9 Given the uncertainties involved, this is clearly only an illustrative figure. More detailed calculations would be possible given a further breakdown of FFP usage by age and prognosis. However the incubation period would remain uncertain, and more detailed modelling is not required to discriminate

between the broad policy options under consideration. However more information about use on neonates could helpfully inform any prioritisation of precautionary measures.

5. POOLED AND UNPOOLED ALTERNATIVES

Introduction

5.1 This section sets out the potential consequences of switching supply to a different donor population. An important preliminary point is that any such option cuts the feedback from new infections to donor prevalence which would otherwise occur, as anyone infected in turn becomes a potential source of further onward transmission. The amplifying effect of such feedback is not very great when considering FFP on its own. However, it should be seen in the context of a more general concern - that the combined effect of all secondary transmission routes could lead to vCJD becoming self-sustaining within the UK population.[4] EOR's previous risk assessment for surgical transmission suggested that such scenarios (while pessimistic) are not beyond the bounds of possibility given present knowledge.

5.2 Any option that reduces the amount of feedback is therefore beneficial in principle. (Where there is continued use of UK products, an alternative way of cutting feedback would be to bar recipients from subsequently donating: a separate study of this is being prepared, considering blood products in general rather than just FFP.) The rest of this paper, however, considers only the direct effects of transmission, in terms of immediate infections caused per year.

5.3 If US donor prevalence is zero, switching to this source – pooled or unpooled – would prevent *all* the infections set out in the previous section (Table 2). It can be argued that zero prevalence is likely to be the case. Because this cannot be guaranteed, however, the rest of this section considers scenarios in which a very small proportion of US donors might be incubating the disease.

Unpooled US Plasma

5.4 If US-derived plasma is used unpooled, the same model applies as for UK plasma. As in Table 2 and Graph 1 above, the annual number of expected infections caused simply remains proportionate to donor prevalence. So for example, if US donors have 100^{th} (or $1,000^{th}$) the UK prevalence the expected number of infections is cut by a factor of 100 or 1,000. ***This result is highly-robust, and guarantees that a large proportion of any risk can be removed if this option is available.***

5.5 For example, suppose (pessimistically) that US donor prevalence were to be 1% of UK. A switch to unpooled US plasma would then prevent 99% of the

[4] Self-sustaining conditions occur if, on average, each person infected goes on to infect at least one other individual. In examining this possibility, the key point is to consider the combined effect of all secondary (person-to-person) transmission routes – e.g. through different blood products, surgery etc.

infections shown for each scenario in Table 2. This can be roughly translated into a saving of symptom-free life years using the suggestion in para 4.8 that each infection prevented would save about 10 such years. The result is as shown in Table 3a below.

Cost-Effectiveness

5.6 Table 3b shows the corresponding cost per symptom-free life year saved under such a policy, assuming an additional cost in the order of £30m per year as estimated by NBS (as of April 2001, communicated via HSD). In this context, symptom-free life-years approximate closely to QALYs (Quality-Adjusted Life Years) used in other cost-effectiveness calculations, for example, by the National Institute for Clinical Excellence (NICE). Though such calculations only form part of the basis for any such recommendation, £20,000 - 30,000 per QALY has come to be regarded as a normal upper bound for affordability[5]. (However this is primarily in the context of introduction of new treatments rather than prevention of iatrogenic diseases.)

5.7 Figures given in Table 3(b) can be compared with this. Costs in "pessimistic" scenarios (with a primary outbreak of 100,000 infections and high enough infectivity) are clearly below the NICE limit, those in scenarios with an outbreak of 1,000 clearly above it. Results for 10,000 infections (the middle column) may be considered as borderline, given the uncertainties in this analysis. Note that these calculations are done simply on the basis of purchase costs and vCJD risk reduction benefits. Other costs and benefits of options are considered in a separate paper prepared by the NBS. However it may be assumed that the costs cited include those of ensuring that other risks are kept to an acceptable levels (e.g. by introducing additional steps to guard against viral infections).

5.8 The figures given can also be adapted to show the cost-effectiveness of a selective policy covering only FFP given to neonates. If it is assumed that the cost per unit of US plasma would be roughly the same regardless of the amount purchased, the cost per infection prevented would remain as before. However each infection prevented would entail a far greater saving in symptom-free life-years. Assuming that neonates given FFP would otherwise have a normal life-expectancy of the order of 80 years, each infection would entail a loss of about 75 symptom-free life-years, rather than the 10 assumed in Table 3. **For a policy covering only neonates, then, costs per symptom-free life-year saved would be much smaller – i.e. by a factor of about 7.5.**

[5] For example, NICE recommended use of taxanes for treatment of cancers of the ovary and breast with estimated costs of £6,500 - £10,000 per life-year saved, and for cancer of the breast at an estimated £15,000 - £20,000 per life year.

Table 3a: Symptom-free life-years saved *per year* by switching to unpooled US plasma: rough calculations for scenarios with US prevalence no more than 1% of UK

Infectivity [ID_{50} per ml], leucodepleted FFP	**Primary vCJD outbreak in UK:** number of infections & corresponding prevalence		
	1,000	**10,000**	**100,000**
	(0.0017%)	**(0.017%)**	**(0.17%)**
1	85	850	8,500
0.1	85	850	8,500
0.01	85 (65)	850 (650)	8,500 (6,500)
0.001	11 (0)	110 (0)	1,100 (0)
0.0001	1	11 (0)	110 (0)

Based on linear dose-response model: figures in brackets show results for "statistical threshold" model, where different.

Table 3b: Cost (£ thousands) per symptom-free life year saved by switching to unpooled US plasma (assuming additional cost of £30m per year)

Infectivity [ID_{50} per ml], leucodepleted FFP	**Primary vCJD outbreak in UK:** number of infections & corresponding prevalence		
	1,000	**10,000**	**100,000**
	(0.0017%)	**(0.017%)**	**(0.17%)**
1	360	36	3.6
0.1	360	36	3.6
0.01	360 (470)	36 (47)	3.6 (4.7)
0.001	2,700 (HIGH*)	270 (HIGH*)	27 (HIGH*)
0.0001	27,000 (HIGH*)	2,700 (HIGH*)	270 (HIGH*)

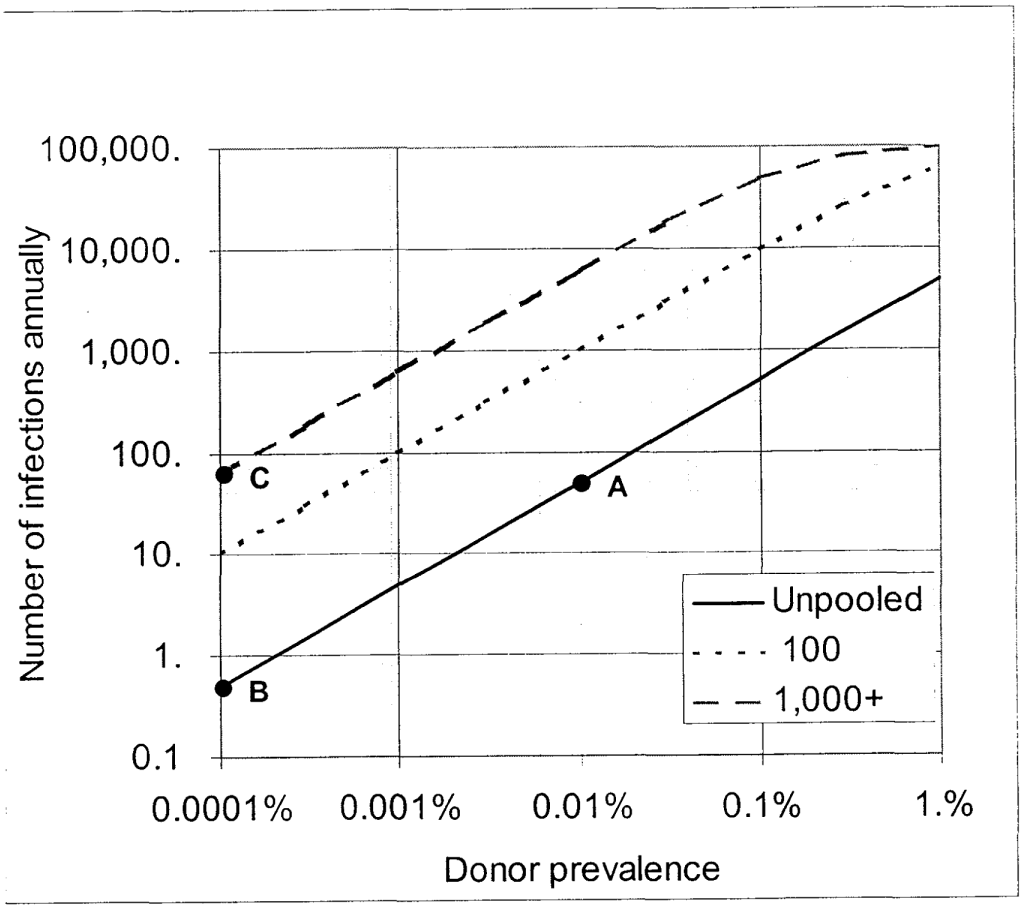
In scenarios marked (HIGH*), the chance of preventing any infections in the statistical threshold model would be remote, so the cost per life-year saved would be very high.

Pooled US Plasma: (a) Linear-no-threshold model

5.7 For pooled plasma, results (for non-zero US prevalence) are highly-dependent on the dose-response model chosen. With a no (or very low) threshold for infection pooling is highly undesirable. By spreading the infectivity amongst recipients, a given total amount of infectivity within the pool would cause many more infections than for unpooled plasma(where a few recipients get a far greater dose than is needed for certain infection).

5.8 For example, Graph 2 below uses the linear model to show, for an infectivity density of 1 ID_{50}/ml (graphs exploring a wide range of infectivity densities are given in Annex C), how expected numbers of infections vary with donor prevalence. Three pooling options are considered: unpooled (as in Graph 1), and with pool sizes of 100 or 1,000+. (A pool of 10,000 gives identical results except for very high donor prevalence.)

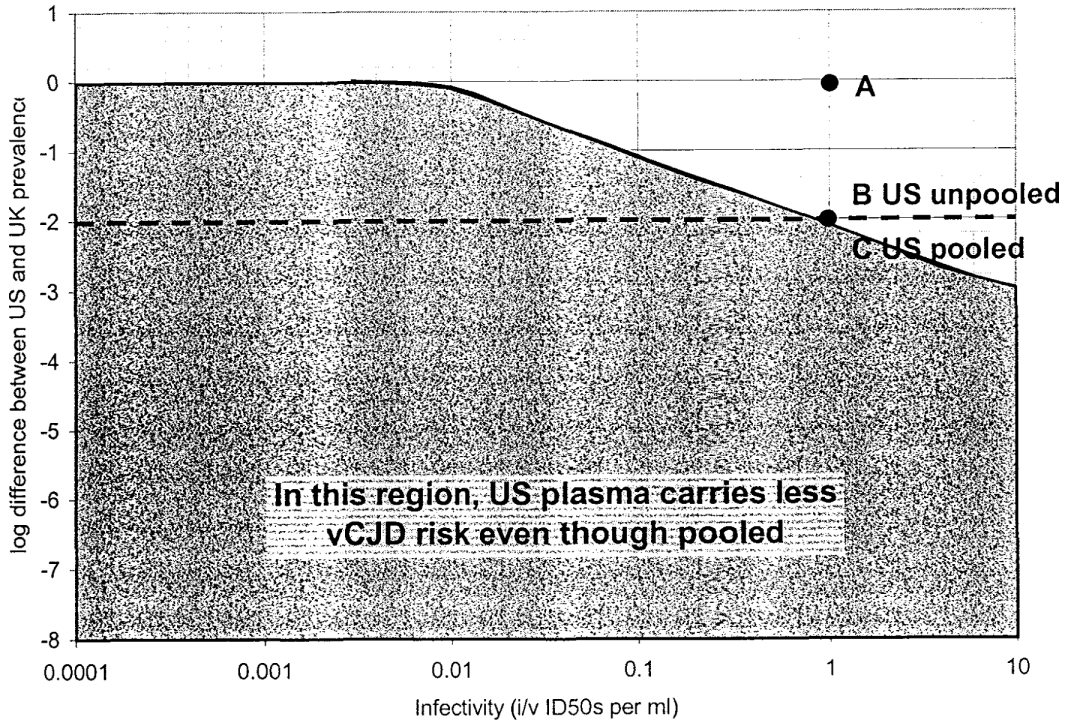
Graph 2: Annual Number of infections versus donor prevalence: pooled and unpooled options (Infectivity density of 1 ID_{50}/ml; Linear Dose-Response)



5.8 It can be seen that pooling greatly increases the expected number of infections. Indeed, it is even possible for pooling to offset the risk reduction achieved by a significantly lower prevalence of the disease. To give a numerical example, suppose that UK and US donor prevalence was 0.01% and 0.0001% respectively. A switch from UK to US sources (both *unpooled*) would reduce the number of infections from around 50 (point A on the graph) to around 0.5 annually (point B). However use of US plasma with a pool size of 100 would raise the number of infections to 10, and a pool size of 1,000 upwards to about 60 (point C).

5.9 In the example just given, use of US plasma from large pools slightly raises vCJD transmission risks above their starting-point with unpooled UK plasma. The question arises of how exceptional such an outcome would be. Sensitivity analysis shows that in fact, it requires an extreme combination of assumptions, as indicated in the graph below.

Graph 3: Region in which US plasma has smaller vCJD transmission risk, even if pooled in 1,000 units



5.10 The graph varies both relative donor prevalence (US as compared with UK) and infectivity of FFP. In the shaded region, the pooled product[6] would cause fewer infections given any of the dose-response models considered here. Above and to the right of this, the unpooled UK product *might* cause fewer (and then only given a no-threshold dose-response). The horizontal dashed

[6] As already noted, unpooled US FFP would always cause fewer infections than UK provided US prevalence is lower – i.e. in any scenario below the "0 log difference" line.

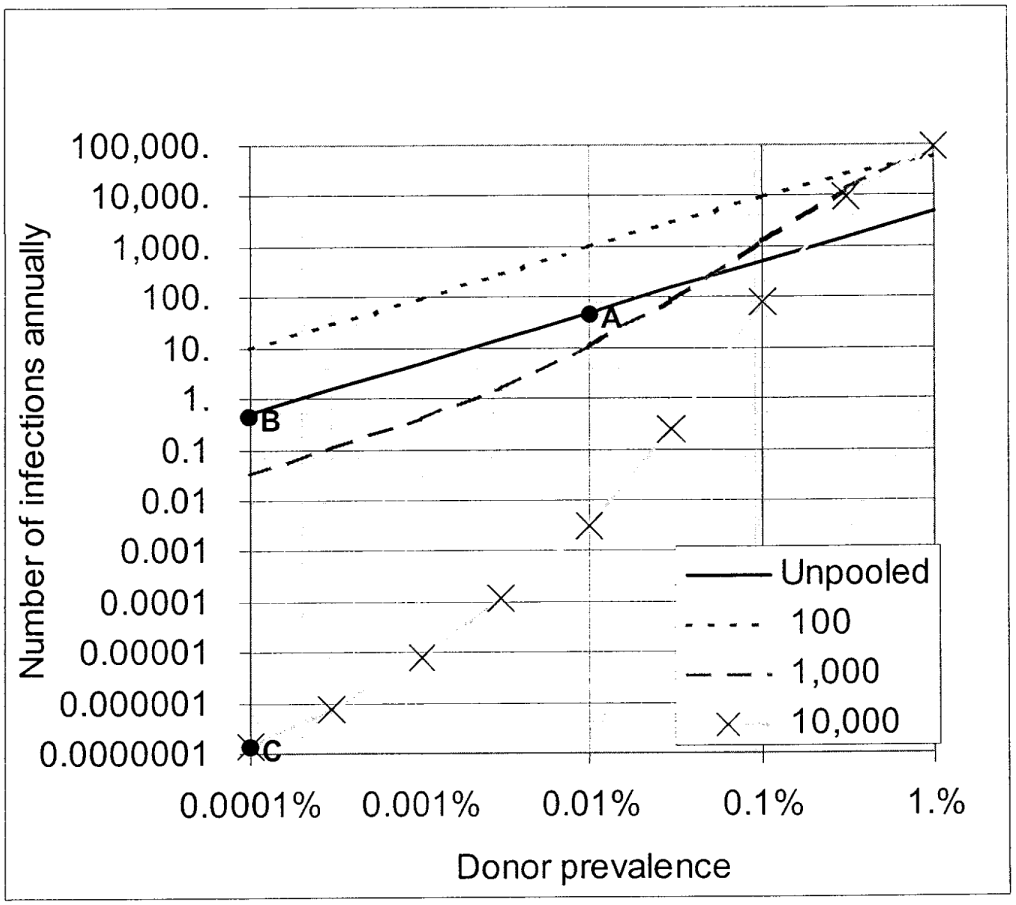
line (log difference = 2) indicates the minimum differential suggested as having any plausibility – i.e. a 100-fold smaller prevalence in the US. Even with this minimum differential, the risks from UK-derived plasma are smaller only given very high infectivity and a no-threshold model. The points marked A, B and C are equivalent to the points marked on Graph 2 (on this graph points B and C are the same). Point C is marginally above the shaded region since, as discussed in paragraph 5.8, with plasma in pools of 1,000 and with 1 ID_{50}/ml, the US option would cause a slightly greater number of infections.

5.11 In summary then, even pooled US FFP would almost always be preferable to unpooled UK in terms of reducing risks from vCJD – though of course this analysis takes no account of other possible reasons for preferring an unpooled product.

Pooled US plasma (b): "Statistical Threshold" Model

5.12 As already noted, this dose-response model gives a contrary result for the effect of pooling. As illustrated in Graph 4 for 1 ID_{50}/ml (again graphs with a wider range of infectivity are shown in Annex C), in many scenarios pooling can reduce the number of infections, because no individual gets the "threshold" dose.

Graph 4: Annual Number of infections versus donor prevalence: pooled and unpooled options ("Statistical Threshold" Dose-Response)



5.13 With this model a pool size of 100 still produces more infections than unpooled. For donor prevalences of less than about 0.1% however, using pools of 1,000 or 10,000 would reduce the number of infections expected. With a donor prevalence of 0.0001% for example, use of the largest pool would reduce expected infections from about 0.5 (point B, as on graph 2) to a vanishingly small number (point C).

6: SUMMARY AND CONCLUSIONS

6.1 Having shown that the continued use of UK-derived FFP *may* pose appreciable risks of vCJD transmission – risks quantified relative to a range of scenarios – we have considered the possible risk reductions achievable by using alternative, US-derived sources.

6.2 Clearly, if there is negligible prevalence of vCJD amongst US donors, all risk of transmission from this route would be eliminated. On the basis that zero prevalence cannot be guaranteed, however, we have investigated scenarios with some US prevalence, though at least 100-fold less than in the UK.

6.3 In such scenarios, pooling donations may increase or decrease transmission risks. This depends on the dose-response model relationship, and at present there is no direct evidence as to which model is the most appropriate. However, the implications of the analysis for practical policy are less ambiguous.

- Given that vCJD prevalence amongst US donors is much less than the UK, a substantial risk reduction can be guaranteed by using unpooled US plasma. The cost effectiveness of such a measure falls within the NICE criteria of affordability for the more pessimistic scenarios regarding the UK prevalence of vCJD and plasma infectivity.
- The use of pooled US plasma could in theory reduce the risk further, or increase it. However any further risk reduction could only be small, while (if no threshold dose exists), pooling could increase the risk substantially. Unless strong evidence for a threshold emerges from new research, use of unpooled plasma represents the better precautionary measure.
- Should US plasma not be available unpooled, even a pooled product would carry less vCJD transmission risk than UK-sourced FFP in almost all scenarios. However we note that pooled products may be undesirable for reasons unrelated to vCJD and not covered in this analysis.

6.4 Should a targeted or prioritised measure be required in the first instance, the greatest proportionate benefits – in terms of life-years potentially saved – would come from alternative sourcing of FFP for neonates. Initial analysis suggests that the cost effectiveness of such a policy could be 7 – 8 times greater than that of an untargeted policy. This point might warrant further exploration using more detailed information on current usage. With this partial exception, however, more complex analysis would be unlikely to throw further light on decisions between the options being considered.

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