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 Supply.

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 depend 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 100 to about 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 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. 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 remains unproven. 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. 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 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

[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.

options. This is highly-dependent on the presumed dose-response relationship – 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 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. (DN: we will have to see how much information we have in order to do this – i.e. survival rates etc)

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.

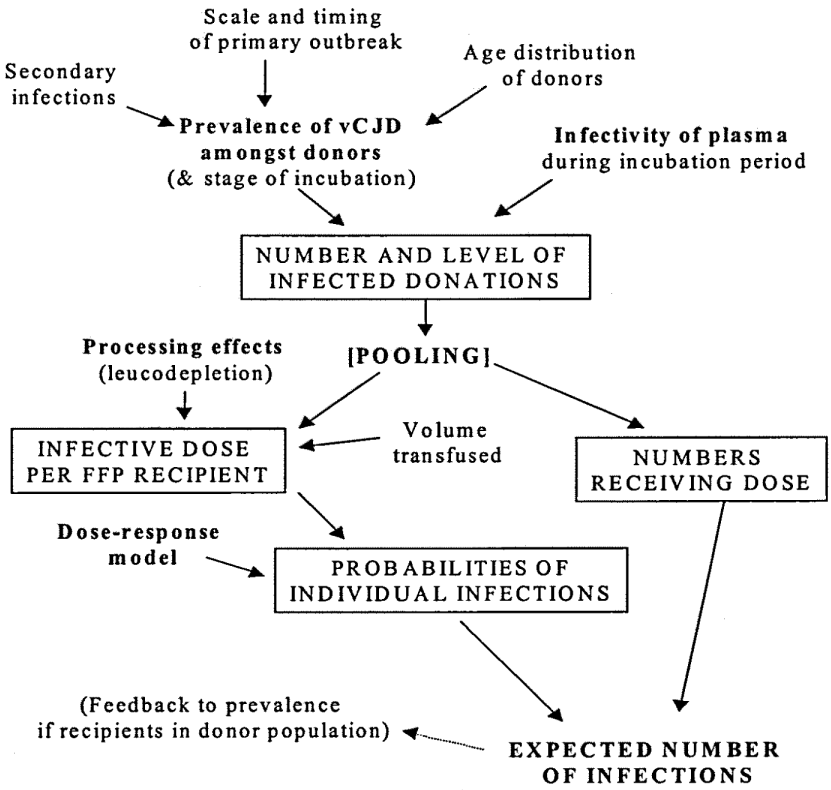
2. METHOD OF ANALYSIS

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.
- 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 will therefore 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 probabilities 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 shown 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 pools being of a fixed size. (If necessary, the model could be disaggregated to consider "mixed strategies" on pool size.)
- 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) 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 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. 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. 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 qualitatively-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 intercranial (i/c) route, absolute values remain subject to much uncertainty. The previous Risk Assessment carried out for DH by DNV Technica Ltd 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, Bruce suggests that infectivity is unlikely to be higher than 0.5 i/v ID_{50} / ml, but notes that null results from animal experiments reflect a bioassay sensitivity of up to 100. In mouse experiments using the Fukuoda-1 TSE, Brown observed levels of 20 IUs per ml of plasma *after* the onset of clinical signs (compared with 100 IUs per ml in buffy coat), this 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 intercranial route (see reference [5] in bibliography.)

3.7 We therefore use a wide range of values up to 1 i/v ID_{50}, , but with sensitivity analysis ranging up to 100 i/v ID_{50} / ml. (As will be seen, some key results are anyway insensitive to the level of infectivity once this reaches at least 0.01 ID_{50} / ml). 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.

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).

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.

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.

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	1,250	
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*.)

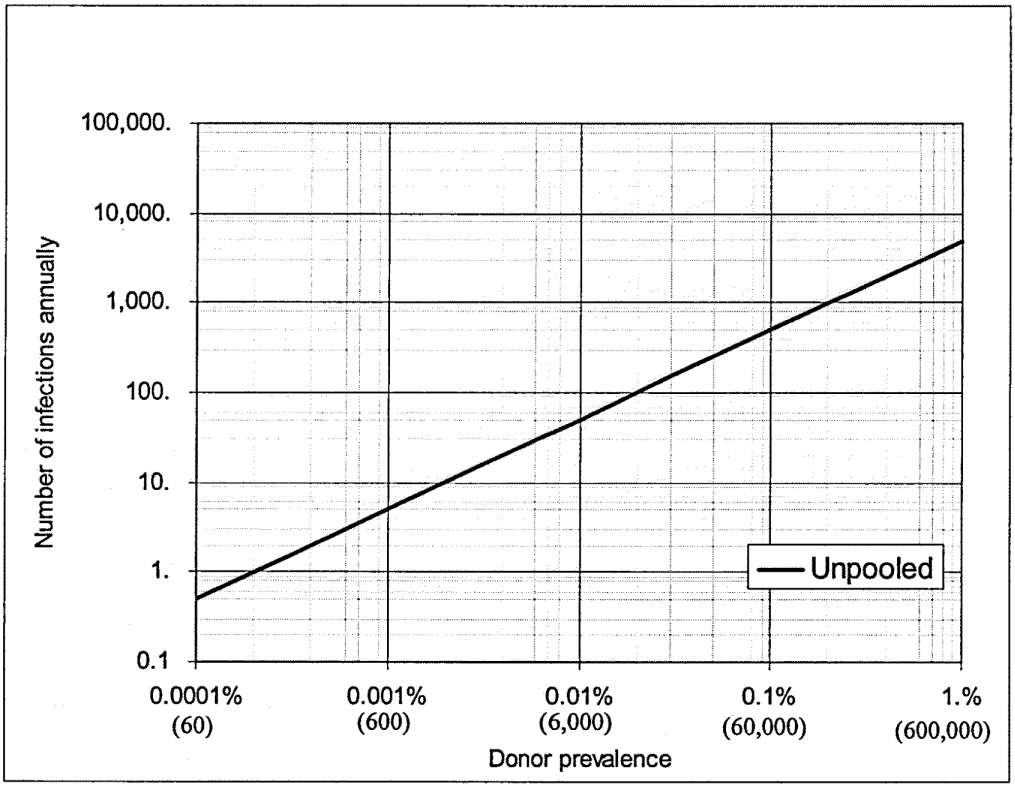
Table 2: Secondary vCJD infections caused annually by unpooled FFP in scenarios with varying infectivity and prevalence
[5 x 250ml units transfused]

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 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 will 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 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 vCJD, 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

- a long incubation period for blood-borne infection (e.g. the mean of 12 years considered as an upper bound for surgical transmission).

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 1995 data supplied by the Scottish National Blood Transfusion Service provides a breakdown of FFP recipients by age. This shows a concentration of usage amongst those aged 50-80, but with substantial quantities also going to neonates. The pattern of usage across the UK may be presumed to be similar, though some changes may have occurred in the intervening years. Advice to date does not suggest that much FFP is given to patients who will then have a much shorter than normal life-expectancy (neonates are generally premature babies, most of whom should survive to live a normal life span).

4.8 A very rough calculation therefore suggests that recipients of FFP should have a *mean* life-expectancy of the order of 20 years. If the mean incubation period for this transmission route were to be roughly 5 years, the number of symptom-free life years lost per infection would be of the order of 15.

4.9 Given the uncertainties involved, the above is clearly only an illustrative figure, but should be of the right order. 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. As a partial exception to this, more information about the use of FFP for treating neonates could be used to inform any targeting or 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 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. [2] 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 (e.g. 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 1000^{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 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 15 such years. The result is as shown in Table 3 below.

[2] Self-sustaining conditions occur if, on average, each person infected goes on to infect at least on 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.

Table 3: Symptom-free life-years saved *per year* by switching to unpooled US plasma: rough calculations for scenarios with US prevalence 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	126	1,260	12,600
0.1	126	1,260	12,600
0.01	126 (97)	1,260 (965)	12,600 (9,650)
0.001	16 (0)	165 (0)	1,650 (0)
0.0001	0	16 (0)	165 (0)

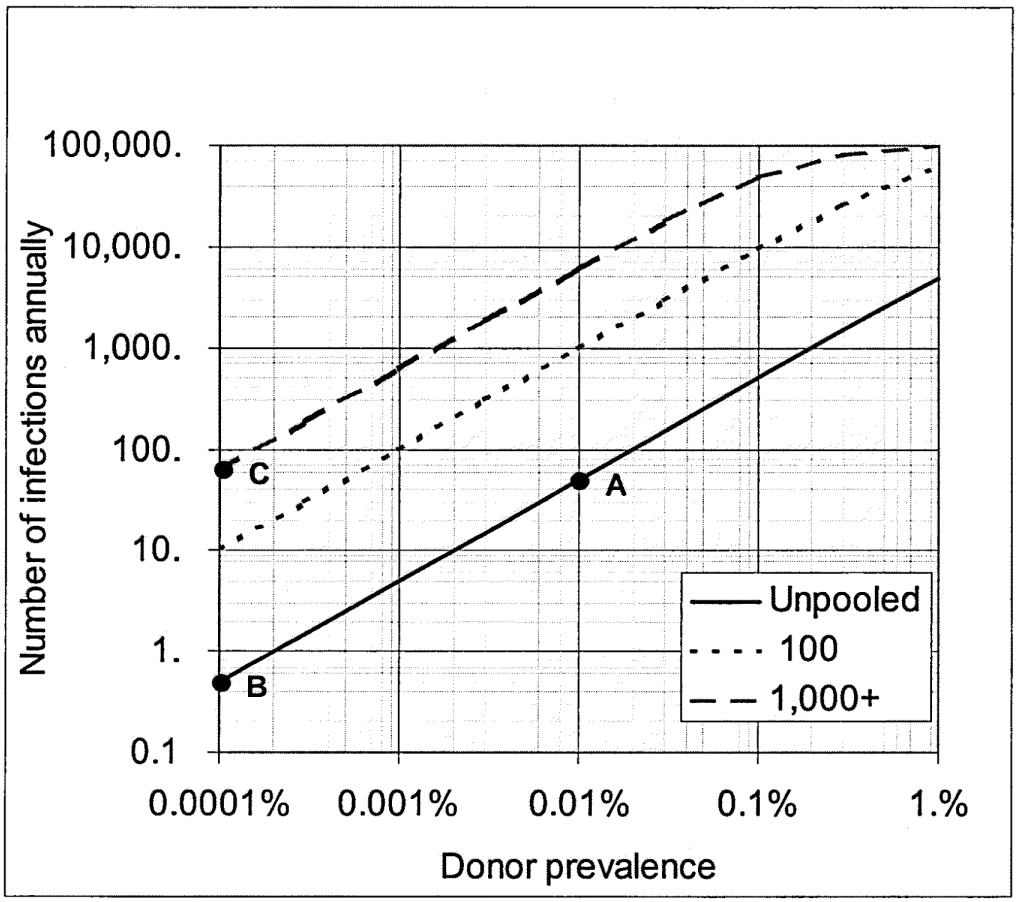
Based on linear dose-response model: figures in brackets show results for "statistical threshold" model, where different.

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

5.6 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 transfer of IDs would cause many more infections (rather than a few recipients getting a far greater dose than is needed for certain infection).

5.7 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 for four pooling options: 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.)

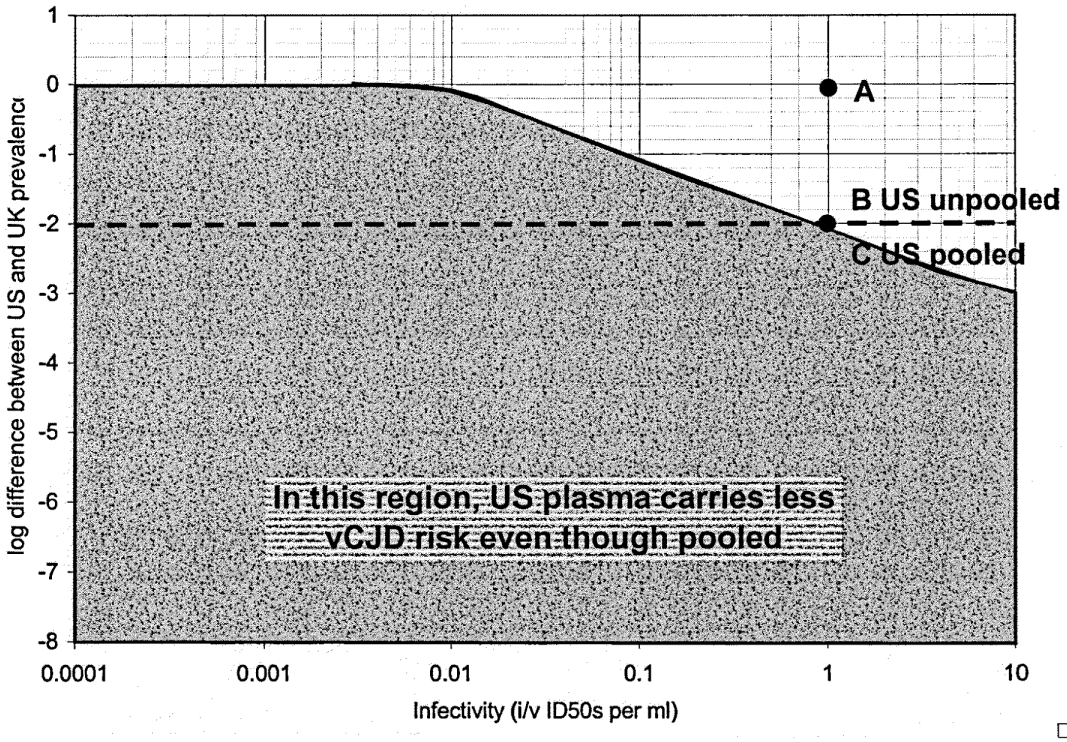
Graph 2: Annual Number of infections versus donor prevalence: pooled and unpooled options (Infectivity density of 1 ID_{50}/ml; Linear Dose-Response)



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[3] 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 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 ponits 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.

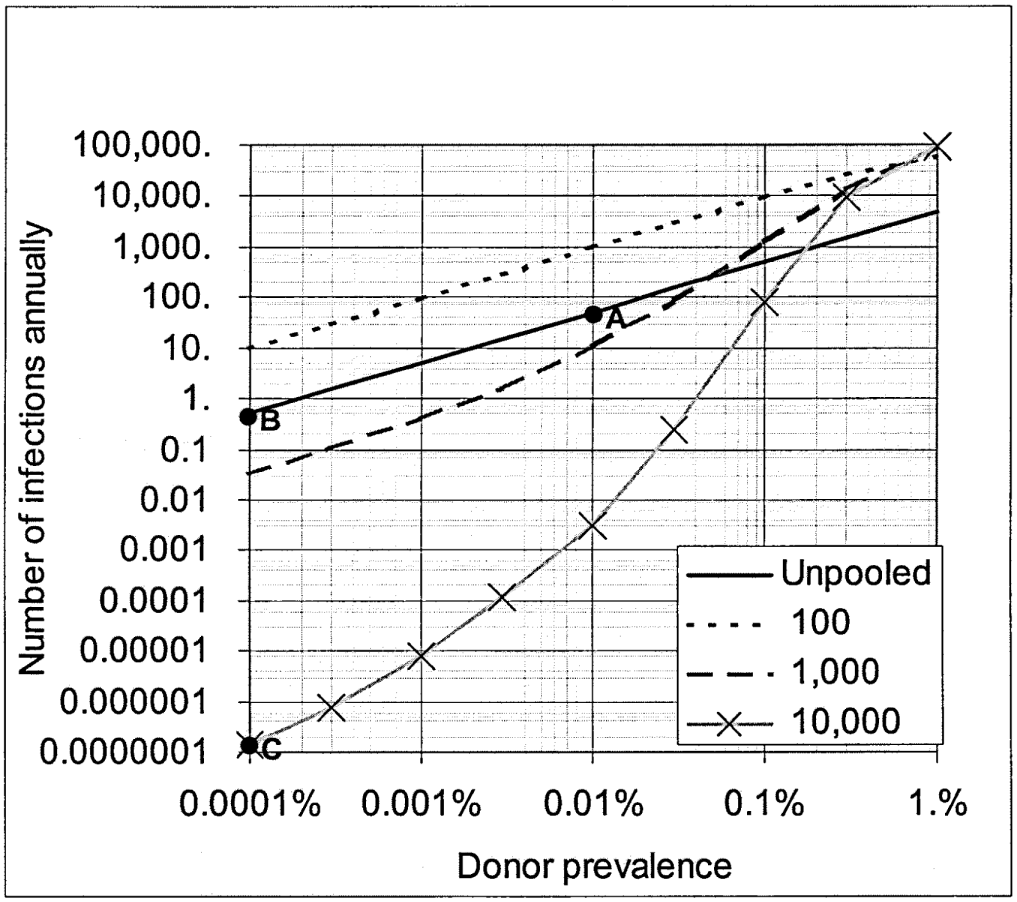
5.11 In summary then, even pooled US FFP would almost always be preferable to unpooled UK in terms of reducing risks from vCJD – though of course this analysis takes no account of other possible reasons for preferring an unpooled product.

[3] 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.

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 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 neonoates. These benefits could be further quantified given more information on current usage. With this partial exception, however, we do not believe that a more complex or detailed analysis would throw further light on decisions between the policy options under consideration.

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Potential vCJD transmission and Fresh Frozen Plasma: Analysis of Sourcing Options

EOR4 of Department of Health

DRAFT December 22nd 2000

ANNEXES

ANNEX A: FULL STRUCTURE OF MODEL

A1: Derivation of the annual number of infections due to FFP

A.1 To obtain this, it is necessary to obtain the expected number of i/v ID_{50}s or i/c IUs received by each recipient together with an assumed relationship between dose and response.

Pooled Plasma

A.2 The *expected* dose (number of i/v ID_{50}s or i/c IUs) in a given pool is simply the product of the number of donations in the pool which are from infected donors (a random variable, **X**, based on the donor prevalence and pool size) with the volume of plasma from each of these donors (**a**) and its infectivity density (**i**). That is, the expected dose in a given pool is given by **X.i.a**.

A.3 Each recipient will receive just a fraction of a given pool and may receive plasma from different pools. Plasma is normally transfused in predefined quantities – a transfusion unit with volume **v**. The *expected* dose in a given transfusion unit is the expected number in a given pool (derived above) reduced in proportion to the fraction of the pool represented by the transfusion unit $\left(\frac{\mathbf{v}}{\mathbf{n.a}}\right)$.

Unpooled Plasma

A.4 With unpooled plasma, each transfusion unit will have been derived completely from one donor. The prevalence amongst donors (**p**) gives the chance that a given unit was derived entirely from an infected donor, all other units have zero risk from vCJD. The expected dose of infectivity in any given transfusion unit is derived by multiplying the prevalence amongst donors by the volume of a transfusion unit and the infectivity density (**p.v.i**).

Pooled or Unpooled

A.5 The expected dose of infectivity in a transfusion unit (whether from pooled or unpooled plasma) can be transformed into a probability of infection using the dose-response relationship. For pooled plasma, all possible values for the number of infected donations in the pool need to be accounted for (weighted according to their likelihood of occurrence).

A.6 In a single transfusion, a recipient typically receives a number (**u**) of transfusion units. It is assumed that each unit has the same overall likelihood of causing infection (or not), as derived above. The probability of any given transfusion causing infection is multiplied by the annual number of transfusions (**t**) to give the expected annual number of infections due to FFP.

A2: Algebraic representation of the same derivation

Definitions:

Prevalence amongst donors = **p**

Infectivity density (in i/v ID_{50}s per ml for Linear dose - response, i/c IUs per ml for "Poisson") = **i**

Number of donations in pool = **n** (**n** = 1 for unpooled plasma)

Volume (ml) of plasma from each donor = **a**

Volume (ml) of each transfusion unit = **v**

Number of units in each transfusion = **u**

Annual number of FFP transfusions = **t**

Dose response relationship (i.e. probability of infection after receiving **z** i/v ID_{50}s or i/c IUs) = g(**z**)

Number of *infected* donations in any given pool = **X**

X ~ Binomial(**n**, **p**) (since there are **n** donations in each pool and each one can be from an infected or an uninfected donor, one of two possibilities)

f(**x**) = **P**(**X** = **x**)

Calculations:

Number of i/v ID_{50}s OR i/c IUs in a given pool = **X.i.a**

Fraction of pool used to make each transfusion unit = $\frac{\mathbf{v}}{\mathbf{n.a}}$

Number of i/v ID_{50}s OR i/c IUs in a given transfusion unit = $(\mathbf{X.i.a}).\left(\frac{\mathbf{v}}{\mathbf{n.a}}\right) = \frac{\mathbf{X.i.v}}{\mathbf{n}}$

$\mathbf{P}(\text{infection from one transfusion unit} \mid \text{i/v } ID_{50}\text{s OR i/c IUs in transfusion unit}) = g\left(\frac{\mathbf{X.i.v}}{\mathbf{n}}\right)$

$\mathbf{P}(\text{infection from one transfusion unit}) = \sum_{x=0}^{n} f(x).g\left(\frac{\mathbf{x.i.v}}{\mathbf{n}}\right)$

$\mathbf{P}(\text{infection from one transfusion}) = 1 - \left[1 - \sum_{x=0}^{n} f(x).g\left(\frac{\mathbf{x.i.v}}{\mathbf{n}}\right)\right]^{u}$

$\text{Annual number of infections due to FFP} = \mathbf{t}.\left\{1 - \left[1 - \sum_{x=0}^{n} f(x).g\left(\frac{\mathbf{x.i.v}}{\mathbf{n}}\right)\right]^{u}\right\}$

Dose-Response Relationships:

Linear (z in i/v ID_{50}s):

$$g(\mathbf{z}) = \begin{cases} \mathbf{z}/2, \text{for } \mathbf{z} < 2 \\ 1, \text{otherwise} \end{cases}$$

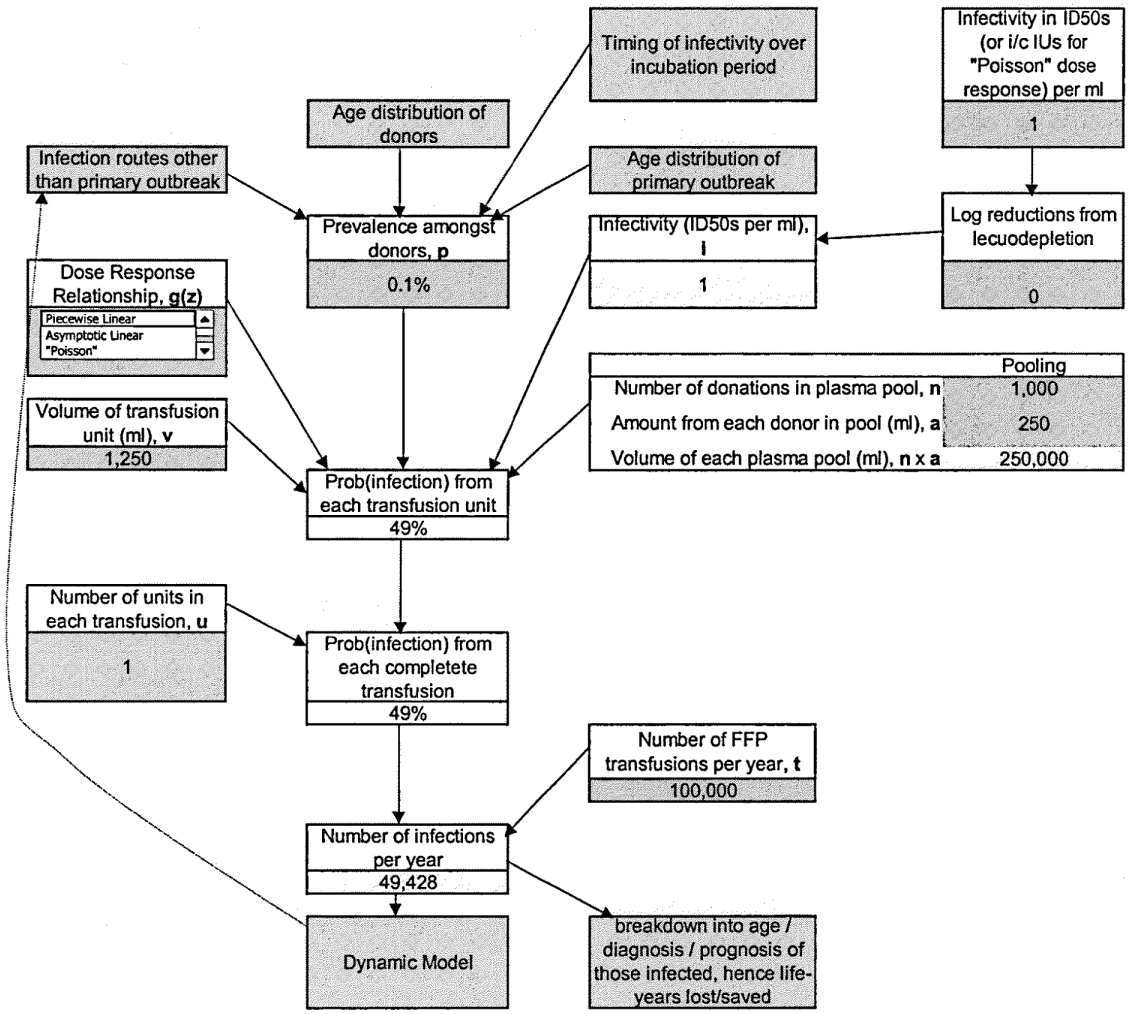
"Poisson" – statistical threshold model (z in i/c IUs):

$g(\mathbf{z}) = 1 - F(6)$

where $F(\mathbf{y}) = \mathbf{P}(\mathbf{Y} \leq \mathbf{y})$ and $\mathbf{Y} \sim \text{Poisson}(\mathbf{z})$

A3: Spreadsheet Model

A.7 The diagram below is a screen-shot from the spreadsheet used to carry out the above calculations. Blue boxes represent input values, yellow represents boxes containing calculations and grey boxes represent possible extensions to the model (i.e. issues which need to be borne in mind but which are not yet implemented within the model). Variables are denoted by bold letters to correspond with those used in the calculations above.



ANNEX B: DOSE-RESPONSE MODELS

B.1 The models considered here fall into two categories – *linear* and *one-hit* - with two specific models being considered in each.

Linear models

B.2 Linear models (whether exact or approximate) are based on a continuous relationship between infective dose and probability of infection. The basic measure of infectivity is that of an ID_{50}, defined as the dose required to give a 50% chance of infecting an individual recipient. In the simple forms considered here, no lower threshold is assumed: any dose, no matter how small, will lead to some non-zero chance of infection.

B.3 As the dose received increases however, the linear relationship will break down as infection becomes virtually certain.

- The *piecewise linear* model takes the probability of infection to be proportional to the dose received, up to a limit of 2 ID_{50}s, at which point infection is regarded as certain. This was used in EOR's Risk Assessment for vCJD transmission on surgical instruments, and endorsed by SEAC as a simple working model in that context. However the sharp change in the dose-response curve at exactly 2 ID_{50}s may be seen as implausible.
- The *asymptotic* linear model is a slightly more complex variant of the above, in which a linear relationship holds for doses up to 1 ID_{50} (50% chance of infection) but the probability of infection thereafter approaches 1 asymptotically. Such a model has been used in previous EOR analyses of transmission via blood products (**DN** refer also to being more in line with statistical models of accumulating hazards).

B.4 In either case, any difference in efficiency between different infection routes is modelled simply by defining ID_{50}s relative to route – e.g. for intravenous (i/v) transfusion versus intercranial (i/c) innoculation of the same material.

"One-hit" (Poisson) models

B.5 The general *one-hit* model of infection (Peto: Biometrics 1953) assumes that some minimum infectious dose – defined as one Infectious Unit (IU) – is required to transmit the disease in question. If at least one IU is received, infection is certain: otherwise it has zero probability. Infectious units occur in a given material according to a Poisson distribution with rate parameter k, defining the "functional infectivity level" of the material.

B.6 In the context of CJD, Brown (Transfusion 1999) uses this approach to consider infectivity levels for blood in animal studies – specifically mouse experiments using platelet-poor plasma. He develops two different variants of the model when relating intravenous to intercranial innoculation. Having determined that infection by the former route requires about seven times more plasma, he discusses two possible explanations:

(1) that although each i/c IU is capable of transmitting disease, only 1 in 7 of those transfused intravenously reaches the brain and so actually triggers the disease.

(2) that 7 i/c IUs are required to transmit the disease intravenously

We have constructed models to reflect each of these hypotheses (which reproduce the results in Brown's paper, given the same inputs).

B.7 These models have very different implications for the probability of infection from a transfusion liable to contain relatively few i/c IUs. In model (1), infection requires just one functional infectious unit, but only one in seven i/c IUs form such a unit for intravenous transmission. From the Poisson distribution, the probability of infection is then $[1-\exp(-i')]$ where i' is the expected number of functional i/c IUs transfused given the amount of material to have come from infectious donors.

B.8 In model (2), i/v transfusion recipients are infected if and only if they receive *more than 7* i/c IUs. The number *actually* received will be approximately Poisson distributed with a mean given by the density of i/c IUs in plasma from infected donors multiplied by the volume of such material transfused into each recipient. For small expected numbers of i/c IUs, 7 will lie well toward the right-hand tail of this distribution. We refer to this as a "statistical threshold" model. For small doses, it can be seen intuitively that it is more optimistic, in the sense of predicting a smaller chance of infection from i/v transfusion of blood with a given infectivity in terms of IUs.

Comparison of models

B.9 All the above models are consistent with Brown's earlier assumption (Transfusion 1998) that infectivity is never "diluted out" by being received at the same time as non-infective material. That is, an IU (or a given number of ID_{50}s) would retain the same capability of transmitting infection whether contained in the plasma from a pool of 10 or 10 million donations.

B.10 Though infectivity of material may be expressed in terms of ID_{50}s or IUs, in principle the choice of "currency" matters little provided that the dose-response relationship is specified so that receipt of infectious material can be translated into probability of infection.

B.11 Nevertheless, it is helpful to be able to compare all four models to each other more formally. This requires some assumption as to how ID_{50}s and IUs relate to each other. One assumption – though by no means the only possible one – would be to equate 1 i/c IU to 2 i/c ID_{50}s, so that the models will roughly agree as to the dosage at which infection via the intercranial route becomes highly-likely.

B.12 Figure B-1(a) and (b) below show how the two linear and two Poisson models relate the chance of infection by i/v transfusion to the infectivity of the material expressed in i/c units. The x-axes show the expected amount of infectivity contained in a transfusion, given the amount of material coming from infected donors - measured, respectively, in i/v ID_{50}s (with equivalent i/c

ID_{50}s given for comparison) and i/c IUs. The y-axis in both cases represents the chance of an individual being infected by the transfusion, when the infectivity is transferred intravenously. Both diagrams take i/v transmission to be 7 times less efficient than i/c, in the sense implied by the model in question. The x-axes of the two diagrams are co-ordinated by taking 1 i/c IU to be equivalent to 2 i/c ID_{50}s as discussed above: varying this would allow the two x-scales to vary against each other.

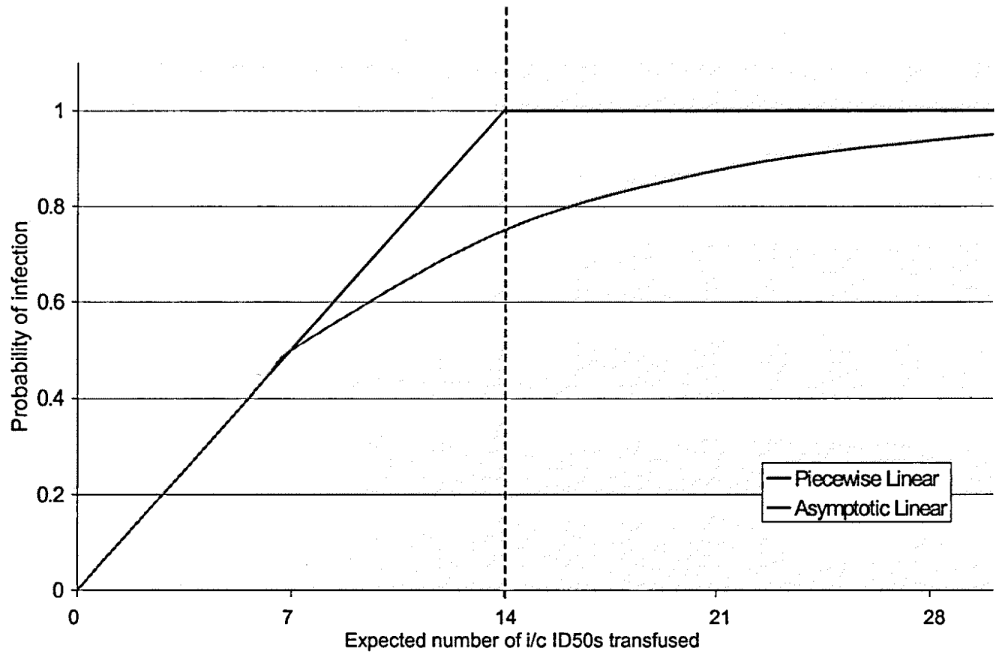
Commentary

B.13 The two linear models are broadly similar to each other, the Piecewise Linear being the more pessimistic (predicting a greater chance of infection for a given dose) - most significantly around the 2 ID_{50}s region,.

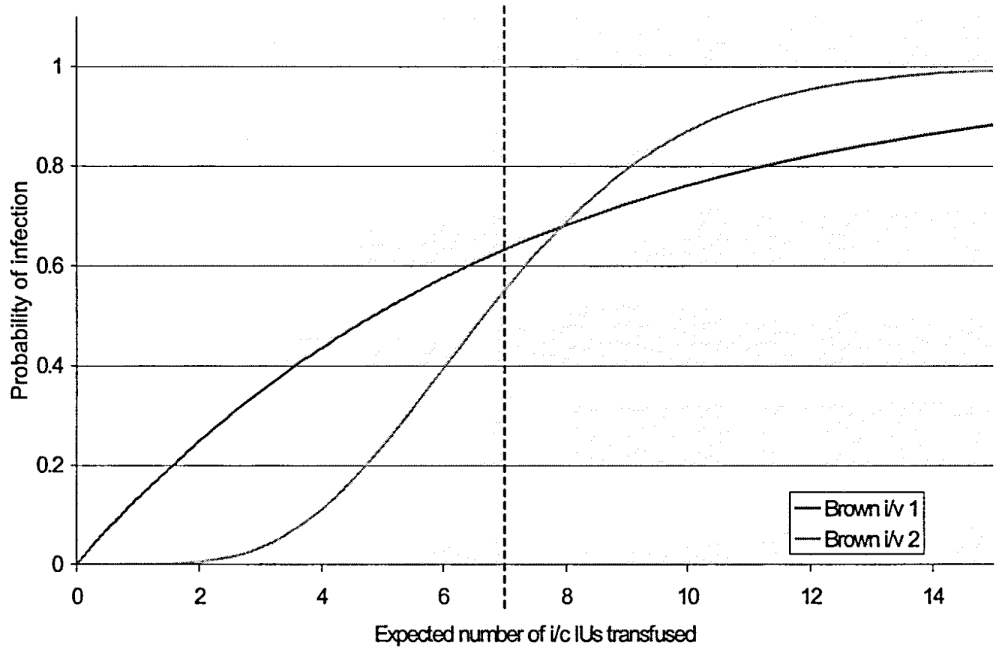
B.14 Given the assumptions made here, both the Poisson models are more optimistic than both linear models. In particular, the "Brown (2)" model is significantly more optimistic for low doses than any of the other three. In effect, a lower threshold appears: as the expected number of i/c IUs transfused decreases, i/v infection of the recipient becomes *extremely* unlikely – in fact vanishingly small below about 0.5 i/c IUs. If considered plausible, this has important implications in suggesting that in some circumstances large enough pools of donated blood could actually decrease the expected risks of onward infection. With all the other models by contrast, pooling can only increase the risks of transmission – in many circumstances dramatically.

Figure B-1: Comparison of four dose-response curves

(a – upper graph) Piecewise Linear and asymptotic – relates i/c **ID_{50}s** to probability of transfusion



(b – lower graph) Poisson (Brown i\v models 1 and 2) – relates i/c **IUs** to probability of infection



ANNEX C: IMPLICATIONS OF MODEL STRUCTURE

Purpose

C.1 While choosing specific model inputs allows us to calculate the potential outcomes of policy options any given scenario, some more general results follow from the structure of the model itself - in particular relationships between pool size, infectivity and prevalence of vCJD amongst donors. The key examples noted briefly in the main text (paragraphs 5.7 and 5.12), are illustrated more fully here.

C.2 Three pairs of graphs follow. Each considers one of the dose-response models discussed in Annex B: Piecewise Linear (results for the asymptotic model being very similar); "Brown 1" and "Brown 2 (statistical threshold)". In each case the first graph shows how the annual number of infections varies against infectivity of FFP (after leucodepletion), whilst the second plots infections against donor prevalence. Each shows results for different pool sizes. The vertical dotted line on the upper graph of each set represents the hypothesised comparability between the linear and Poisson models discussed in Annex B (i.e. that 2 i/v ID_{50}s per ml are equivalent to 7 i/c IUs per ml).

C.3 Assumptions made throughout are of 250 ml of FFP being obtained from each donor, 1250 ml being used in each transfusion and 100,000 FFP transfusions annually. Transfusions of unpooled plasma are taken to comprise 5 units from separate donors: for pooled plasma, each recipient is assumed to receive the same volume derived from a single pool.

Commentary

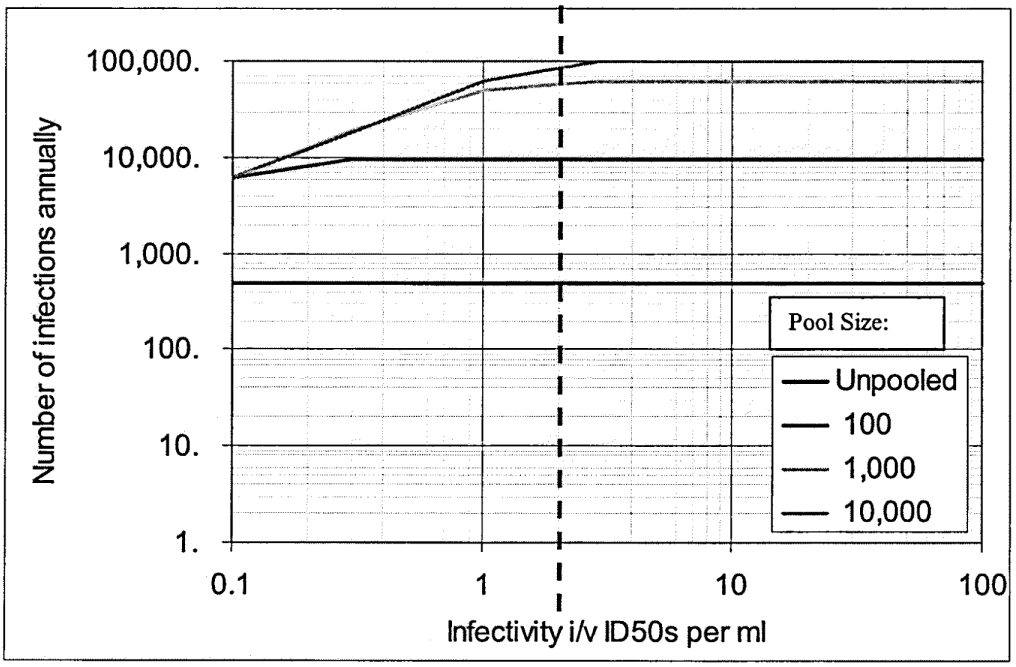
C.4 The graphs in Figure C-1 show that if the Piecewise Linear model is adopted:

- Unless the pool size is large, varying FFP infectivity between 0.1 and 100 i/v ID_{50} per ml has no effect on the expected number of infections. (Essentially, all those unlucky enough to receive a transfusion including blood from an infected donor would be infected for certain in such scenarios.) Given the current uncertainty about vCJD infectivity in blood components, the robustness of this result is significant.
- The pool size (up to about 1,000) and donor prevalence (up to at least 0.1%) both have a roughly linear impact on the number of secondary infections. Above these limits, both have a less than proportionate impact: increasing pool size always increases the number of infections, but the difference between a pool of 1,000 and one of 10,000 is marginal.

C.5 As shown in Figure C-2, the Brown (1) model produces results very similar to the Piecewise Linear model. However the "Brown (2)" model is markedly different, reflecting its greater optimism regarding the chance of infection given small intravenous doses. As shown in Figure C-3, the "threshold effect" means that for low infectivity and/or donor prevalence, *larger* donor pools may give rise to *fewer* infections, as there would now be very little chance of anyone receiving the minimum dose needed for infection.

Figure C-1: Indicative results for Piecewise Linear dose-response model (assumes 250 ml from each donor in the pool, 1,250 ml used in each transfusion, 100,000 transfusions annually)

(a): Number of infections annually for varying infectivity and pool sizes with 0.1% donor prevalence



(b): As above, varying donor prevalence (infectivity now fixed at 1 ID_{50} per ml)

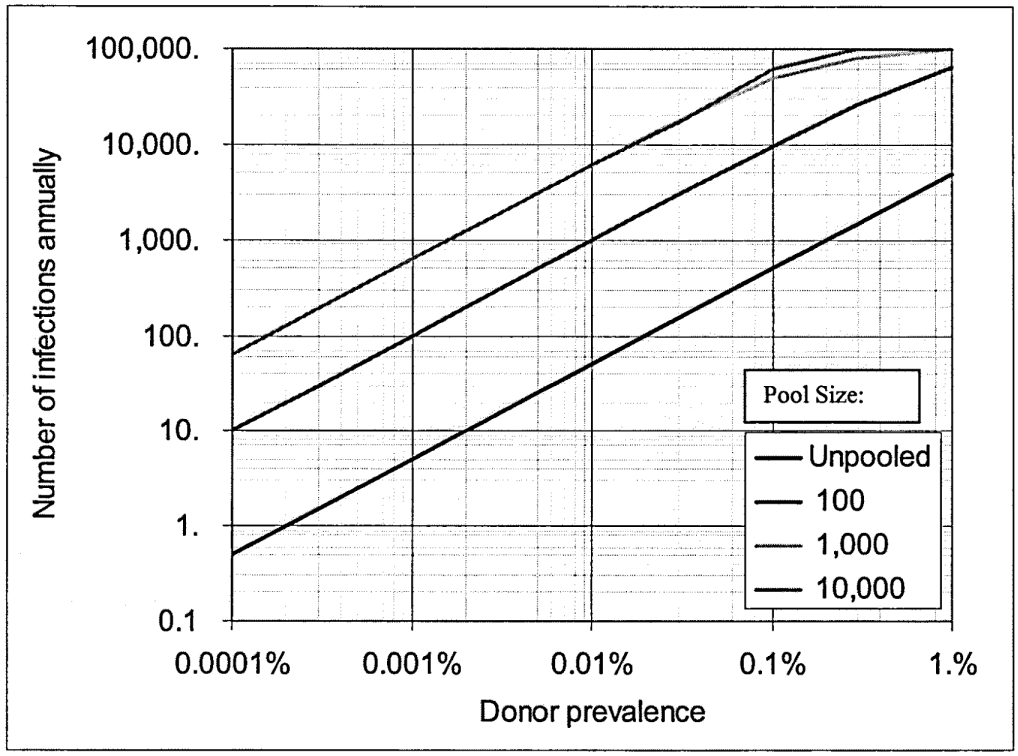
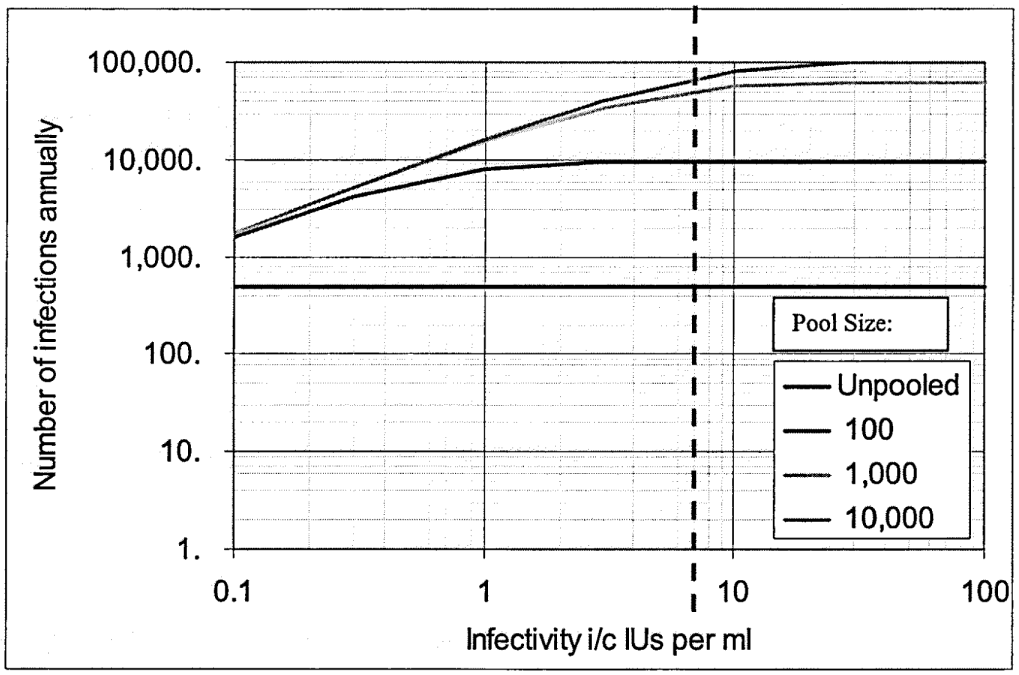


Figure C-2: Indicative results for "Brown 1" model

(a): Number of infections annually for varying infectivity and pool sizes with 0.1% donor prevalence,



(b): As above, varying donor prevalence (infectivity fixed at 1 i/c IU per ml)

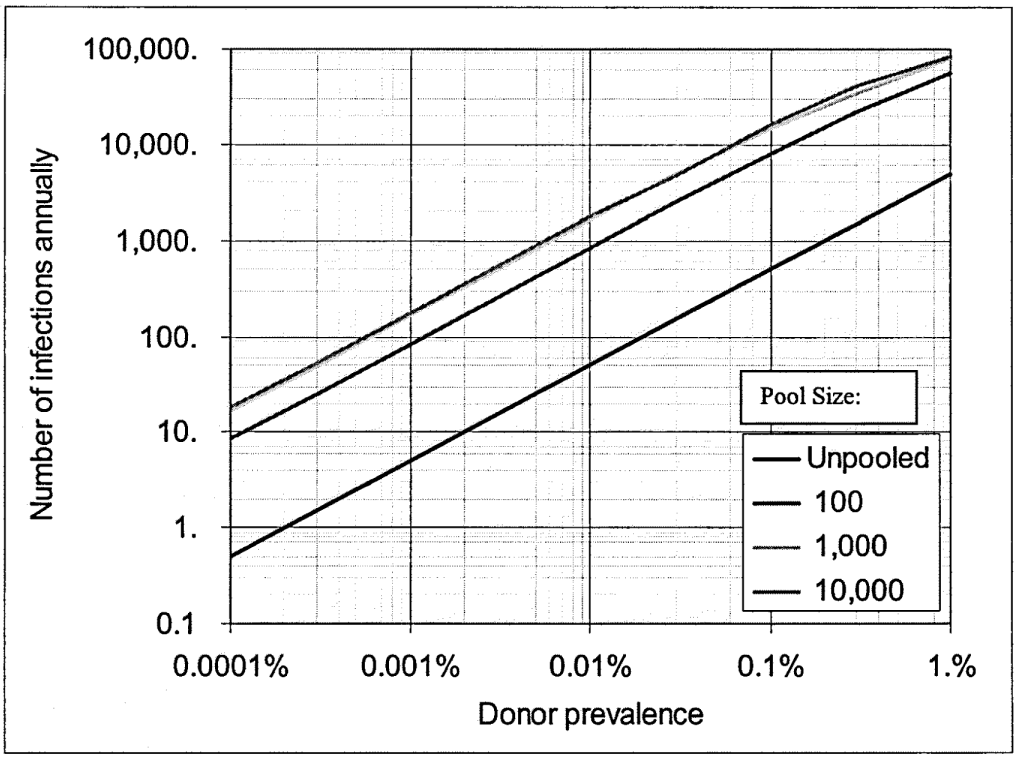
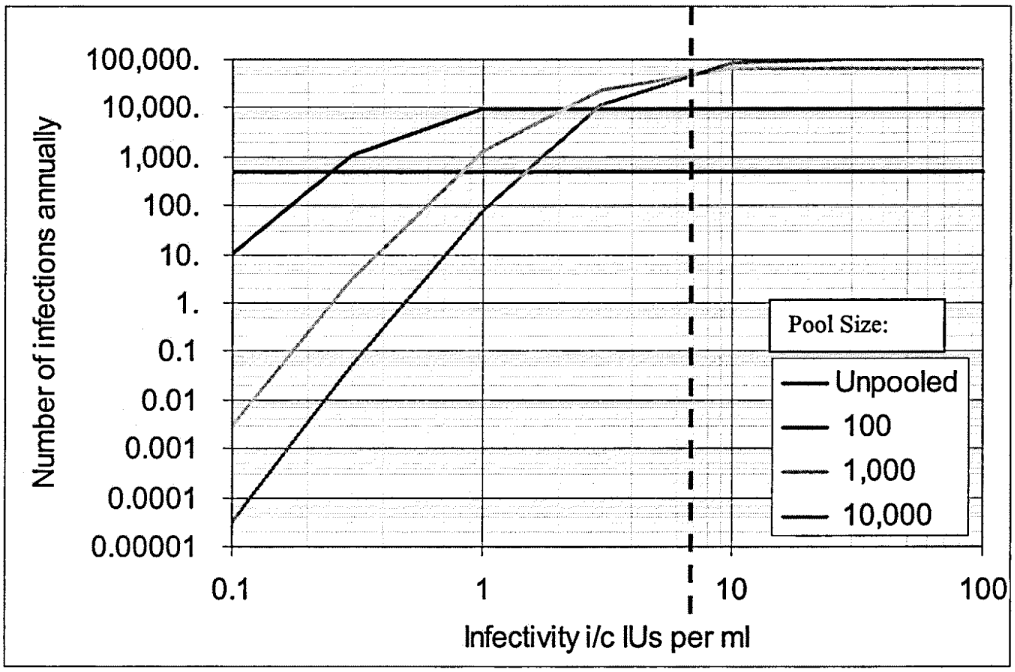
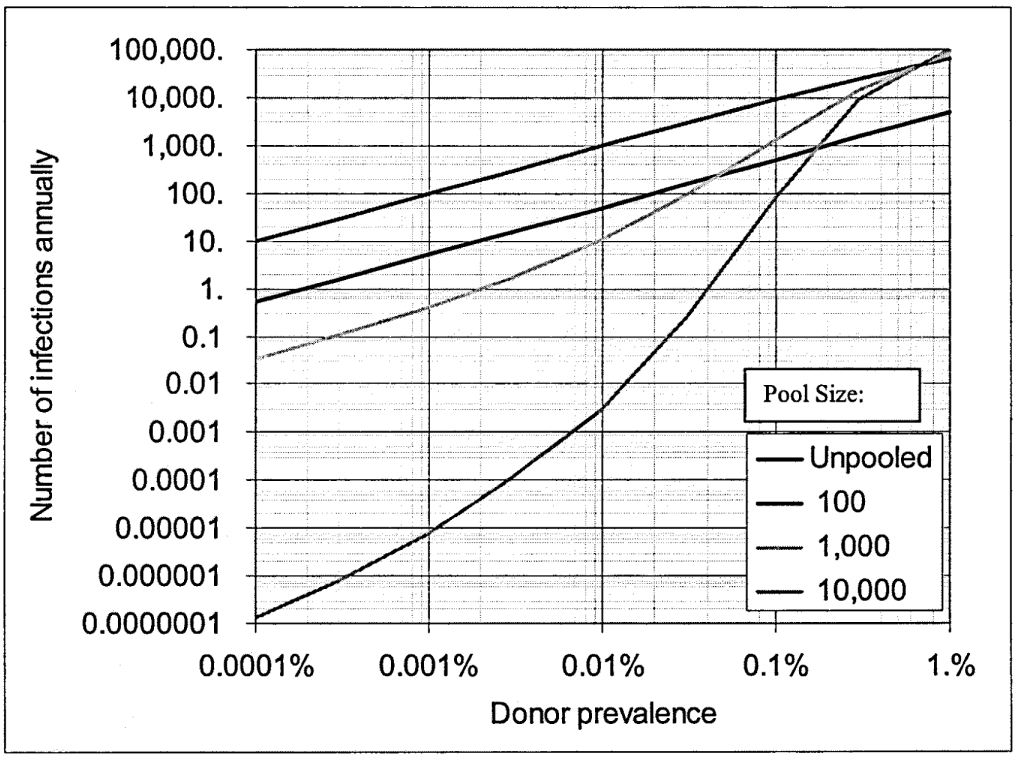


Figure C-3: Indicative results for "Brown 2" model

(a): Number of infections annually for varying infectivity and pool sizes with 0.1% donor prevalence,



(b): As above, varying donor prevalence (infectivity fixed at 1 i/c IU per ml)



ANNEX D

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

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

Sent: 4th December, 2000

Shown with principal responses in italics

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

[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.

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 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]

Taylor et al. 2000 estimated about 5 i.c. ID_{50} per ml in plasma of mice with a mouse-passaged BSE strain at the end-point of the disease.

[Moira Bruce]

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?)

Based on rodent models of non-vCJD, about 5-20 IU per ml

[Paul Brown]

[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

For our direct testing of vCJD plasma by i.c. bioassay in mice the limit of detection is approx 2 mouse IUs per ml. For human infectious doses this has to be multiplied by a factor to take into account the species barrier. The cow/mouse factor for BSE is said by MAFF to be 500 and it would be reasonable to assume that this is the same for human/mouse, given that the dose-response characteristics of BSE and vCJD in mice are similar.

[Moira Bruce]

10-100 *[Colin Masters]*

I know of no work other than that published by Paul Brown and his colleagues and I am sure he will give the clearest answers to your questions. The DNV estimates, of course, came before the work published in the 1999 paper and that no doubt would have influenced them. An important new observation published in 1999 is that infectivity in blood during the pre-clinical phase of the disease in the mouse model is relatively low and occurred in the buffy coat, but infectivity rises sharply at the onset of clinical signs when plasma shows very significant levels of infection. This, as I am sure you understand, is not a good model for the likely human situation but it perhaps might be taken to indicate that the risk of transmission of vCJD by plasma harvested in the UK is increasing as the group of putatively infected donors get further and further into their incubation period. The other indication from this work is that the intravenous route is considerably less efficient for infection by these agents than the intracerebral.

[Tim Wallington]

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

Based on the same models, incubation period infectivity in plasma should be at or very near zero

[Paul Brown]

There is some suggestion from rodent studies that infectivity in blood is higher towards the end point of disease, but really, we do not know. We do not know where the infectivity is coming from – CNS or lymphoid tissues or elsewhere. In Hueston et al. transfusion was from a donor sheep half way through the incubation period after oral exposure to BSE, at a time when there is likely to be widespread involvement of lymphoid, but not nervous tissues.

[Moira Bruce]

Maybe, but impossible to predict

[Colin Masters]

Presumably, infectivity increases the nearer to the point of clinical manifestation of the disease.

[Tim Wyatt]

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

This question depends entirely on whether or not blood in vCJD patients is significantly more infectious than in non-vCJD patients, and there is no direct information about this point. There are, however, some hints that vCJD may not be much different with respect to blood: notably, 4 sets of experiments currently in progress (two in primates, and two in rodent adapted vCJD), in which no transmissions have yet been recorded. Also, brain levels of infectivity are virtually identical in rodents infected with human vCJD, mouse-adapted vCJD, and human non-vCJD. Blood may follow suit, or it may not (e.g., lymphoreticular tissues appear to have more infectivity in vCJD, but this is not yet prove[n).]

[Paul Brown]

Limited data but iv route probably about tenfold less effective than ic route.

[Moira Bruce]

Moderate *[Colin Masters]*

It would be similar *[Tim Wyatt]*

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?

Once again, based on rodent models of non-vCJD, leukodepletion is a very good strategy for reducing infectivity in labile blood components, but it is not effective in reducing infectivity in plasma. The experiments by us that are quoted in this report did not 'seem' to show no significant effect – they documented no significant effect. The fact that infectivity rose, was stable, or declined in each of the three assays is irrelevant: NONE of them showed any significant PRACTICAL changes

[Paul Brown]

Evidence from P. Brown's work in mice model that leucodepletion does not significantly reduce infectivity of plasma. May be result of fragmentation of cells.

[Roger Eglin and John Barbara]

[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.

0-50% *[Colin Masters]*

As you point out there is little direct evidence on the effectiveness of leucodepletion. However, based on the likely pathophysiology of vCJD as caused by prion infectious by the oral route, it makes sense that leucocytes and antigen presenting cell, particularly follicular dendritic cells carry the main concentration of any infectious prion in blood. They are long lived cells, they have the time to accumulate PrP^{Sc}. If that is the case then leucodepletion should be particularly effective. Clearly, if the leucodepletion process fragments the cells or produces new micro vesicles derived from those cells then it could increase infectivity or more likely simply not be as effective as it should be in reducing it. The data available suggests that this is not a problem. Detail is available from Dr Lorna Williamson NBS Cambridge. The plasminogen data is most interesting but if I understand it correctly as yet there is no direct evidence that PrPSc is actual bound to plasminogen in vivo.

[Tim Wallington]

Leucodepletion only reduces the number of white cells by several logs. There are thus quite a large number remaining. I have concerns about the effectiveness of this process.

[Tim Wyatt]

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?

So far as I know, nothing in the history of TSE indicates that anything happens to the agents in the frozen state.

[Paul Brown]

No, this is a very far-fetched idea. All of our experience is that, if levels of infectivity change at all in frozen samples, they decrease.

[Moira Bruce]

Constant *[Colin Masters]*

Some [and I can't remember the guys name] that conversion as in a chemical reaction would occur i.e. it is a chemical reaction rather than an infectious process.

[Tim Wyatt]

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?

Far less *[Paul Brown]*

I am not sure how far –40C could slow a chemical reaction. Not much I suspect.

[Tim Wyatt]

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?

Whether you are speaking about blood or plasma, there is no direct evidence bearing on vCJD, and the evidence from rodent models of non-vCJD must vastly overestimate the potential for infectivity in the blood of humans with non-vCJD, or we would long since have identified cases due to blood or blood products.

[Paul Brown]

I would have thought the lower figure is zero, but the top end of the range is a guess. Based on the animal work it seems very unlikely that there would be more than about .5 human i.v. IUs per ml, and this maximum is probably a pessimistic figure.

[Moira Bruce]

From mouse models infectivity i/v is 1:5 to 1:7 LESS than infectivity i/c. Leucodepleted blood is not significantly reduced in infectivity at least in mouse models.

[Roger Eglin and John Barbara]

Less than 10% *[Colin Masters]*

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.)

I would be astonished if there were even a handful of cases of vCJD that turn up eventually in the US. If they do, they would certainly be in long-term residents to the UK, who have already been excluded as blood donors. Thus, the risk of a vCJD-contaminated plasma pool in the US is zero.

[Paul Brown]

Again, I know of no data. If exposure to infective material of bovine origin is the critical factor, then the bans on donation that have now been put in place in the US should be covering that. In that case a single log reduction in likely US prevalence seems far too little.

[Tim Wallington]

Would that not be a bit high given the low number of [?any] cases occurring in the US even with those who have travelled etc. Would 1/100 or 1/1000 be more realistic and still retain the precautionary element?

[Tim Wyatt]

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.

IUs do not dilute out but stay detectable – probably particulate in nature. Do not forget – current assays all based on IU detection only and cannot quantitate subclinical carriage.

Plasma fractionation processes remove 3-4 logs of infectivity by the cumulative process.

[Roger Eglin and John Barbara]

I would simply comment that you cannot simply extrapolate from the number of transfusions of FFP given and the amount of FFP used annually to the average volume for transfusion. As you point out particularly repeat transfusions on the same person will influence this. This is particularly the case as large quantities of FFP (an/or a derivative called cryosupernatant) are used in the treatment of individual patients with a condition called TTP.

[Tim Wallington]

THANK YOU FOR YOUR HELP