

A comparison of the relative risk of vCJD transmission via single unit and pooled plasma from UK and non-UK sources

Sonya Crowe, Stephen Dobra and Jenny Ball, Health Protection Analytical Team, Department of Health
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PART I: BACKGROUND TO RISK ASSESSMENT

1. Introduction

This paper concerns the possible risk of person-to-person vCJD transmission via transfusion of Fresh Frozen Plasma (FFP). We propose a risk assessment methodology to assess such risks for pooled and imported FFP products relative to the baseline risk associated with UK sourced single unit FFP. We also assess the *implications* of different assumptions for the reduction in infectivity due to the manufacturing process. An assessment of the claimed reductions in infectivity through processing is outside the scope of this paper.

The risk assessment concentrates on four potential supply options of FFP:

1. UK-sourced single unit FFP (as a baseline)
2. Non-UK-sourced single unit FFP
3. Non-UK-sourced pooled FFP
4. Non-UK-sourced prion-reduced pooled FFP

The analysis presented in this paper is concerned only with vCJD transmission, but the sourcing of plasma has a wide range of other implications, from microbiological risk to clinical efficacy and safety.

1.1 Background to Part II: Risk assessment of single unit versus pooled plasma

SEAC have previously given advice on the pooling of blood in their Position Statement on TSE infectivity in Blood, July 2006, which stated:

“The implication of this relationship between dose and probability of infection for strategies to reduce the public health risks in relation to blood transfusion is that pooling blood to dilute infectivity does not decrease the risks to public health. Indeed, depending on the dose, pooling is likely to increase the risks to public health” (the full position statement is given in appendix A).

This paper puts forward a risk assessment methodology in which the risks to public health of pooled plasma are quantified under a number of different scenarios. We believe that this methodology is consistent with the SEAC statement, although some additional assumptions have been made in order to quantify the risk.

Firstly, we present a comparison of the risk of single unit plasma with respect to pooled plasma of various pool sizes from the *same source country*. We then compare the relative risk of single unit plasma to pooled plasma (for various pool sizes) from a *different source country*. We do this on a scenario

basis, using different *assumed* values for the risk reduction of sourcing from outside the UK; in part III of this paper we go on to present a methodology for estimating this risk reduction through sourcing. Finally, we compare the relative risk of single unit UK plasma to pooled plasma (for various pool sizes) that has been prion filtered.

Due to the uncertainty of a number of key parameters associated with vCJD, we use a scenario-based approach for two of the main parameters: vCJD prevalence in the UK donor population and the infectivity of blood. The selection of these parameter scenarios is discussed in section 2. Under different infectivity and prevalence scenarios, we assess risk of transmission of vCJD via plasma in a pooled product (UK or non-UK sourced, prion filtered or non-prion filtered) compared to the baseline risk of single unit UK plasma. We ask the committee to consider this general risk assessment methodology and whether it is consistent with their advice.

1.2 Background to Part III: Risk assessment of country sourcing

There remains considerable uncertainty about the underlying prevalence of vCJD in the UK population, and populations elsewhere in the world. However, it is important when considering the risk reduction of a policy such as importation of plasma that an estimate is made of the relative prevalence of the non-UK source country to that of the UK. This allows, as detailed in part II of this paper, an assessment of the risk reduction associated with sourcing single unit or pooled plasma from non-UK sources with respect to the baseline of single unit UK plasma.

We present a methodology for estimating the relative vCJD prevalence of a source country with respect to the UK, through comparisons of vCJD and BSE incidence, adjusted to take into account their relative degrees of active and passive surveillance. Again, we ask SEAC to assess the general methodology proposed.

2. Key Scientific Inputs

There are many unknown parameters involved in any assessment of potential vCJD transmission risks. The absolute scale of the risk is dependent primarily on the infectivity present in plasma, the effect of leucodepletion and the prevalence of vCJD in the donor population (either in the UK or elsewhere, depending on sourcing). There is also a question as to the susceptibility of different genotypes to developing clinical disease, and the possibility of a 'carrier-state'. Other relevant factors (e.g. the volumes of units transfused and donated, the number of FFP units per transfusion and the total number of transfusions) may also vary, although they are not subject to the same levels of uncertainty. In section 3, where the risk assessment methodology is presented, a summary of the chosen values for these parameters is given.

Rather than attempting to make predictions, we have used a scenario-based model that considers a wide range of assumptions to explore the relative risk of the four products outlined in section 1. In carrying out this risk assessment,

it has been necessary to make the following assumptions, based on the current body of research and evidence presented in this field.

2.1 Infectivity of whole blood

The levels of infectivity reported in rodent studies to examine the infectivity in blood of animals with TSEs vary widely, ranging from about 1 to 300 infectious doses (ID)/ml of blood. SEAC noted that the efficiency of transmission via the intravenous (i.v.) route is probably less efficient than the intracerebral (i.c.) route¹. A small number of studies using different animal models suggest that the efficiency of transmission by the i.v. route is between 10% and 100% of the efficiency of the i.c. route. We use two scenarios for blood infectivity:

- 1) a “high” scenario of 30 i.v. ID/ml, based on the upper value of 300 i.c. ID/ml from the hamster-scrapie model and a 10% efficiency of i.v. transmission relative to i.c. transmission.
- 2) a “low” scenario of 0.1 i.v. ID/ml, based on the lower value of 1 i.c. ID/ml from the hamster-scrapie model and a 10% efficiency of transmission of the i.v. route relative to the i.c. route. The argument for considering a “low” scenario is that transmission might be less efficient in an endogenous blood transfusion compared with experiments with spiked material whether by the i.c. or i.v. route and that the donation might not be very late in the incubation period.

Assumption: Two scenarios for the infectivity of whole blood for the purposes of this model: a 'low' scenario (0.1 ID/ml i.v. transmission) and a 'high' scenario (30 ID/ml i.v. transmission).

2.2 Distribution of infectivity in blood product and leucodepletion

The distribution of vCJD infectivity across different human blood components is another uncertainty, as is the effect of leucodepletion (which was implemented as a precaution against vCJD transmission in 1999 in the UK). However, published and unpublished data from studies of the infectivity in components of blood from hamsters with hamster scrapie show that around one half of the infectivity in blood can be removed by depleting blood of white blood cells² and that infectivity is not, or is minimally, associated with platelets³ or red blood cells⁴. These data suggest, at least in this model of TSE infection, that infectivity may be distributed equally between plasma and white blood cells but is weakly bound to white blood cells. For the purposes of this risk assessment, we therefore assume a model in which leucodepletion removes 50% of the infectivity of whole blood, and that the remaining 50% of

¹ TSE infectivity in Blood. SEAC Position Statement, published July 2006.

<http://www.seac.gov.uk/statements/statement0806.htm>

² Gregori et al. (2004) Effectiveness of leucodepletion for removal of infectivity of transmissible spongiform encephalopathies from blood. *Lancet*. 364, 529-531.

³ Holada et al. (2002) Scrapie infectivity in hamster blood is not associated with platelets. *J. Virol.* 76, 4649-4650.

⁴ Unpublished data from the VA Medical Center, University of Maryland, Baltimore, USA presented by Dr R Rohwer.

infectivity resides exclusively in the residual plasma (some of which goes into red cell and platelet products).

Assumption: 50% of the infectivity of whole blood is removed by leucodepletion and the remaining 50% of infectivity resides within the residual plasma.

2.3 vCJD prevalence in the UK

The current prevalence of vCJD amongst UK donors is essentially unknown. To indicate the *possible* scale of any secondary infection, we consider a range of scenarios, based on a retrospective study⁵ of stored appendix and tonsil tissue that found three positive appendix samples (based on the detection of the abnormal prion protein PrP^{Sc}) in a set of about 12,500, i.e. about 1 in 4,000. If the presence of PrP^{Sc} indicates infection, then the results suggest that infection is far more common than indicated by the small number of cases seen⁶, with a 95% Confidence Interval for prevalence ranging from roughly 1 in 20,000 to 1 in 1,400. It is worth noting that these figures apply to the age range tested in the study, which was probably biased towards the most at risk cohort.

Assumption: Two scenarios for prevalence of vCJD in the UK: a 'low' scenario (1 in 20,000) and a 'high' scenario (1 in 4,000). In the absence of any further evidence, these will also be used for the UK donor population and applied irrespective of age or genotype.

2.4 Dose-response model

Due to uncertainties, SEAC have not been able to recommend a particular dose-response model. For risk assessments purposes we have adopted a Poisson model. In this “*one-hit*” model, infection certainly occurs once some minimum dose (an Infectious Dose, or ID) is received. Infectious doses occur in a given material according to a Poisson distribution with a rate parameter defining the “functional infectivity level” of the material. From the Poisson distribution, the probability of infection is then $[1-\exp(-i)]$ where i is the expected number of functional IDs transfused given the amount of material to have come from an infected donor. The probability of finding an infectious dose in any given volume of the pooled material is independent of any other volume of the pooled material.

Assumption: The dose-response follows a Poisson distribution.

⁵ Hilton et al. (2004) J. Pathol. 203, 733-739

⁶ Note that secondary transmission risks are driven by the existing prevalence of infection within the population, not the current or predicted number of vCJD cases. This is a key distinction, given that many of those infected may die of other causes without ever developing vCJD, but may still have acted as sources of onward infection.

2.5 Susceptibility to infection and/or developing clinical symptoms of vCJD

It remains unclear whether the entire population is susceptible to infection and/or developing clinical symptoms of vCJD, and whether or not this is dependent on genotype. In this risk assessment we assume for simplicity that everyone is susceptible to both infection and clinical disease, independent of genotype. If we were to assume a lower given percentage of susceptibility, then the absolute expected numbers of infections would scale proportionately. However, in this risk assessment we present results that are referenced to a benchmark risk (for single unit UK plasma), and therefore the relative risks presented are independent of the susceptibility assumption.

Assumption: 100% of the population is susceptible to infection and developing clinical symptoms of vCJD.

PART II: RISK ASSESSMENT OF SINGLE UNIT VERSUS POOLED PLASMA

3. Methodology

3.1 Model overview

The model developed for the risk assessment methodology presented in this paper tracks potential infectivity through blood donation, processing and transfusion of FFP into individual recipients. This provides scenarios for the expected number of infections within the population *per 100,000 transfusion episodes*. Some of the main variables in the model are set out schematically in Figure 1. As discussed above, there are a number of uncertainties around many of the key parameters and so no attempt is made to reproduce every detail of the donation and transfusion process: the model is intended to produce approximate alternative scenarios that can distinguish the effects of the four products outlined above.

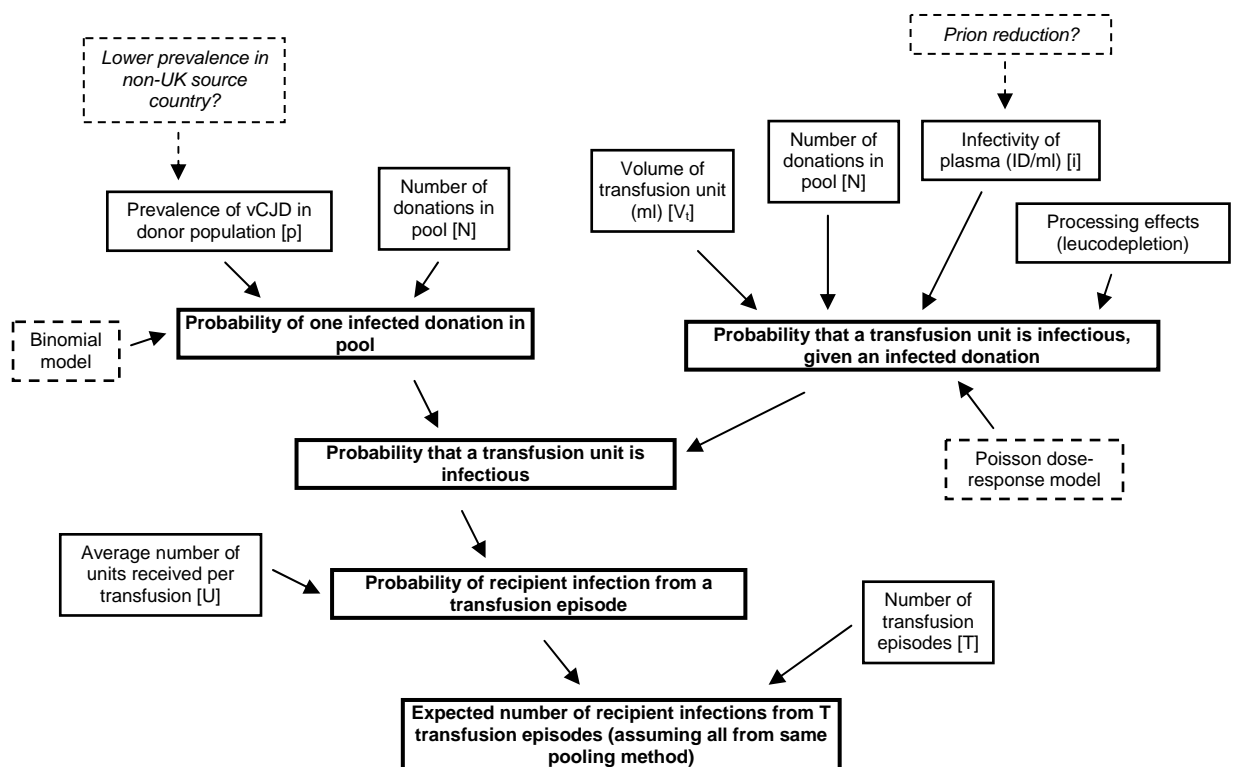


Figure 1: Schematic representation of the proposed risk assessment model

3.2 Simplifying assumptions

The methodology presented in this paper has been deliberately kept relatively simple. In particular:

- It is assumed that all plasma is either pooled or unpooled, with all pools being the same size, though this size is variable between scenarios (we present pool size scenarios of $n = 100, 500, 1000$ and 1500 , where n is the number of transfusion units derived from a pool). The model does not

consider “mixed strategies” on pool size. Each recipient is assumed to receive the same volume derived from a single pool.

- A single averaged infectivity density (titre) of infected plasma has been assumed. That is, the fact that the infectivity density might vary over the incubation period has not been taken into account.
- No allowance has been made for highly transfused patients (e.g. those with thrombotic thrombocytopenic purpura, TTP) who 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”, i.e. the model would count infection of the same individual twice over as two infections. However, this effect is in the same direction for any of the policy options (single unit, pooled, UK or non-UK sourced plasma) 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.
- We have assumed for the purposes of this analysis that the probability of more than three infected donations per pool is negligible (for an underlying prevalence of 1/4,000 the probability of more than three infected donations in a pool of 1,000 donations is approx. 0.01% and for a prevalence of 1/20,000 this probability is just 0.00002%).

3.3 Probability of a pool containing an infected donation

Firstly, we estimate the probability that a pool contains an infected donation, which is dependent upon the underlying prevalence of the donor population [p]. In the model this prevalence is adjusted for different scenarios, both for the UK prevalence (1/4,000 or 1/20,000) and for assumed log reductions achieved via sourcing outside of the UK. In general, the number of donations in a pool that are from infected donors is a random variable based on the donor prevalence [p] and number of donations in a pool [N], expressed in terms of the Binomial distribution (a donation is either infected or it isn't). The probability of x infected donations in a pool is given by:

$$P(\text{pool contains } x \text{ infected donations}) = P(\text{Binomial}(N, p)=x) \quad (1)$$

The probability of there being an infected donation in a pool (i.e. any number of donations greater than zero) is given by the sum of these,

$$\begin{aligned}
 P(\text{pool containing an infected donation}) &= \\
 &= \sum_{x=1}^N P(\text{Binomial}(N, p)=x) = 1 - P(\text{Binomial}(N, p)=0) = 1 - (1-p)^N \quad (2)
 \end{aligned}$$

For single unit plasma, each transfusion unit has been derived completely from one donor, and the prevalence amongst donors [p] gives the chance that a donated unit was derived from an infected donor. This is equivalent to setting N = 1 in equation (1) above.

3.4 Probability of a transfusion unit being infectious, given that there are x infected donations in the pool

In the following sections, we present a methodology for estimating the probability of a transfusion unit being infectious. Firstly, we estimate the probability of a transfusion unit being infectious, *given that there are x donations containing infectivity in the pool*. Note that, whilst it is assumed that there is at least one infected donated unit, the probability of the infected donation containing an infectious dose (i.e. an amount of infectivity that will cause infection) depends upon the infectivity density of plasma [i], the volume of an infected donation [V_d], the number of infected units [x] and the Poisson dose-response model. The probability of there being no infectious doses in the pool is equivalent to the probability that there are no infectious doses in the infected donations, which is given by;

$$P(\text{no IDs in the pool, given } x \text{ infected donations}) = \exp(-ixV_d) \quad (3)$$

This expression is derived from the Poisson distribution with an expected infectivity of ixV_d . It can be equated to the probability that there are no infectious doses in any of the transfusion units derived from the pool (because if there were an infectious dose in any transfusion unit, then this would imply that there was at least one infectious dose in the pool it was derived from). Therefore,

$$P(\text{no IDs in any transfusion unit, given } x \text{ infected donations}) = \exp(-ixV_d) \quad (4)$$

Let the probability that, given x infected donations, a transfusion unit is infectious (i.e. it contains one or more infectious doses) = p_i . Therefore, the probability that a transfusion unit does not contain an infectious dose = $(1 - p_i)$. The probability of all n transfusion units (where n is the total number of transfusion units derived from the pool, which we call the 'pool size') not containing an infectious dose is then given by:

$$P(\text{no IDs in any transfusion unit, given } x \text{ infected donations}) = (1 - p_i)^n \quad (5)$$

From equations (4) and (5), we have $(1 - p_i)^n = \exp(-ixV_d)$, which re-arranged gives:

$$P(\text{transfusion unit is infectious, given an infected donation}) \\ = p_i = 1 - \exp(-ixV_d/n) = 1 - \exp(-ixV_t/N) \quad (6)$$

where the latter has been derived from $n = NV_d / V_t$, where V_t is the volume of a transfusion unit derived from the pool (assuming that all transfusion units are of the same size, and that the volume of the infected donation is equal to the average volume of a donation).

It is useful to consider this in terms of two specific cases:

- (ii) High infectivity: When i is very large compared to N , i.e. i/N approaches infinity.

Using the approximation $e^{-z} \rightarrow 0$ as $z \rightarrow \infty$, with $z = \frac{ixV_t}{N}$, equation (6) can be approximated by:

$$p_i \sim 1 - \{0\} = 1 \quad \text{for } \frac{i}{N} \rightarrow \infty \quad (7)$$

So in the high infectivity limit, the probability that a transfusion unit is infectious (given that there are x infected donations in the pool) is 100%, and is *independent of the number of donations in the pool* (N). In other words, if infectivity is high then all of the transfusion units derived from a pool (of however many donations) will be infectious.

- (iii) Low infectivity: When i is very small compared to N , i.e. i/N approaches zero.

Using the series expansion $e^y = \sum_{n=0}^{\infty} \frac{y^n}{n!} \approx 1 + y + \frac{y^2}{2} + \frac{y^3}{6} + \dots \approx 1 + y$, as

$y \rightarrow 0$. With $y = -\frac{ixV_t}{N}$, equation (6) can be approximated by:

$$p_i \sim 1 - \{1 + (-ixV_t/N)\} = ixV_t/N \quad \text{For } \frac{i}{N} \rightarrow 0 \quad (8)$$

So in the low infectivity limit, the probability that a transfusion unit is infectious (given that there are x infected donations in the pool) is *inversely proportional to the number of donations in the pool* (N), i.e. the more donations in a pool, the smaller the chance that any one of the transfusion units is infectious.

3.5 Expected number of infectious transfusion units, given that there are x infected donations in the pool

It is worth considering at this point the expected number of infectious units in a pool consisting of N donations, given that there are x infected donations in the pool (E_i). This is equal simply to the probability that, given x infected donations, a transfusion unit is infectious (p_i) multiplied by the number of transfusion units derived from the pool (n), i.e.,

$$E_i = p_i * n = [1 - \exp(-ixV_d/n)] * n = [1 - \exp(-ixV_t/N)] * NV_d/V_t \quad (9)$$

Again, it is useful to consider two specific cases:

- (i) High infectivity: When i is very large compared to N , i.e. i/N approaches infinity.

Using equation (7), equation (9) can be approximated by:

$$E_i \sim 1 * NV_d/V_t = NV_d/V_t \quad \text{for } \frac{i}{N} \rightarrow \infty \quad (10)$$

So in the high infectivity limit, the expected number of infectious transfusion units derived from a pool (given that there are x infected donations in the pool) is equal to the number of donations in the pool multiplied by the ratio of the donation and transfusion volumes.

- (ii) Low infectivity: When i is very small compared to N , i.e. i/N approaches zero.

Using equation (8), equation (9) can be approximated by:

$$E_i \sim ixV_t/N * NV_d/V_t = ixV_d \quad \text{For } \frac{i}{N} \rightarrow 0 \quad (11)$$

So in the low infectivity limit, the expected number of infectious transfusion units derived from a pool (given that there are x infected donations in the pool) is *independent of the number of donations in the pool* (N) and is equal to the expected infectivity entering the pool.

These results demonstrate that for a given number (x) of infected donations entering a pool, the number of expected infectious transfusion units resulting from that particular pool:

- increases as the pool size increases, except in the very low infectivity region where all pool sizes tend to the same value of ixV_d , and
- is never less than for a single unit donation (or for a pool of smaller pool size).

3.6 Probability of a transfusion unit being infectious

Finally, we estimate the probability that a transfusion unit is infectious (P_t) by multiplying the probability of obtaining x infected donations in the pool by the probability that a transfusion unit is infectious, given x infected donations, and summing over all x , i.e.

$$P(\text{transfusion unit is infectious}) = P_t = \sum_{x=1}^N P(\text{pool containing } x \text{ infected donations}) * P(\text{transfusion unit is infectious, given } x \text{ infected donations}) \quad (12)$$

Substituting equations (1) and (5) into equation (10) gives:

$$P(\text{transfusion unit is infectious}) = P_t = \sum_{x=1}^N [P(\text{Binomial}(N, p)=x)].[1 - \exp(-ixV_t/N)] \quad (13)$$

3.7 Estimated number of infections due to a given number of transfusion episodes

In a single transfusion episode, a recipient typically receives a number of transfusion units (U), each of which is assumed to have the same overall

likelihood of causing infection as derived above. The probability of any given transfusion episode causing infection may then be expressed as:

$$P(\text{infection from transfusion episode}) = 1 - \{1 - P(\text{transfusion unit is infectious})\}^U$$

Finally, the estimated number of infections due to T transfusion episodes of FFP (assuming all of them from the same type of product, i.e. the same pooling size and source country), is given by E_t :

$$\text{Expected number of infections from T transfusion episodes} = E_t = T [1 - \{1 - P(\text{transfusion unit is infectious})\}^U],$$

Combining this with equation (13) gives:

$$\begin{aligned} \text{Expected number of infections from T transfusion episodes} &= E_t = \\ &= T [1 - \{1 - \sum_{x=1}^N [P(\text{Binomial}(N, p)=x)].[1 - \exp(-ixV_t/N)]\}^U] \end{aligned} \quad (14)$$

where

T = Number of transfusion episodes
 N = Number of donations in the pool
 p = vCJD prevalence of donor population
 i = Infectivity density of plasma (ID/ml)
 V_t = Average volume of transfusion unit (ml)
 U = Average number of transfusion units per transfusion episode

3.8 Number of infected donations per pool

We have assumed for the purposes of this analysis, that the probability of more than three infected donations per pool is negligible (for an underlying prevalence of 1/4,000 the probability of more than three infected donations in a pool of 1,500 is approx. 0.06%). In other words, we approximate the probability of a pool containing an infected donation by setting equation (1) equal to zero for $x > 3$. This allows us to approximate equation (14), giving:

$$\begin{aligned} \text{Expected number of infections from T transfusion episodes} &= E_t = \\ &= T [1 - \{1 - ([P(\text{Binomial}(N, p)=1)].[1 - \exp(-iV_t/N)] + [P(\text{Binomial}(N, p)=2)].[1 - \exp(-2iV_t/N)] + [P(\text{Binomial}(N, p)=3)].[1 - \exp(-3iV_t/N)])\}^U] \end{aligned} \quad (15)$$

3.9 Summary of Inputs

We have chosen baseline working values (or ranges) for the relevant inputs, which are summarised in Table 1 below. To illustrate a range of possible pool sizes (n), we have used four scenarios: n = 100, 500, 1000 and 1500. From provisional data from the Epidemiology and Survival of Transfusion Recipients

(EASTR) Study⁷, it has been estimated that the average number of transfusion units per plasma transfusion episode [U] is 3. Note that whilst subsequent calculations are based on an average of three units being given per transfusion episode, should this prove to be an overestimate then all infection scenarios would be affected proportionately. In order to make comparisons across the different products (single unit as well as different pool sizes), 100,000 transfusion episodes [T] are considered in each case. The average volume of a transfusion unit [V_t] is taken to be 220ml for the single-unit product, based on NHSBT issue data. For all of the pooled products, the average volume of a transfusion unit is assumed to be 200ml, based on the actual volume of a currently licensed pooled FFP product. Similarly, the average volume of a donation [V_d] is assumed to be 400ml for the pooled products, based on the range of donation volumes used in the same licensed pooled product. For single unit plasma, the donation volume is taken to be 220 ml (from NHSBT issue data).

Table 1: Input parameters for modelling

Parameter	Single unit FFP	Pooled FFP			
		Pool 1	Pool 2	Pool 3	Pool 4
Pool size: Number of transfusion units derived from the pool [n]	-	100	500	1,000	1,500
Average volume of transfusion unit [V _t]	220	200	200	200	200
Average volume of donation [V _d]	220	400	400	400	400
Average number of transfusion units received per transfusion episode [U]	3	3	3	3	3
Number of transfusion episodes [T]	100,000	100,000	100,000	100,000	100,000

3.10 Reducing infectivity via the pooling process

The effect of pooling could potentially be counter-balanced by reducing the infectivity of donations in a pooled product through specific steps in the manufacturing process. In this paper, we investigate the effect of an *assumed* 2.5 log reduction in the infectivity of blood that comprises a pooled product. Note that we do not attempt to say whether or not any given products *do* achieve this log reduction, rather we present a methodology for modelling this outcome should it be the case. A 2.5 log reduction in the infectivity of plasma can be taken into account directly in equation (15) by adjusting the infectivity density of plasma [i], to the assumed reduced infectivity density [i']. For the case of a 2.5 log reduction in infectivity, this corresponds to the substitution:

$$i \rightarrow i' = i / (10^{2.5}) \quad (16)$$

⁷ "The EASTR study is the only national survey of transfusion epidemiology in England, and includes details of over 14000 transfusion recipients treated at 29 hospitals. The study team hope that the first papers from the study will be published later this year and have provided interim results to inform this paper. Some of the analysis methods used are still being refined and the collection of survival data are ongoing. Although there will be some change in the results by the time of publication, these are unlikely to be major and their central message will be unchanged." Angus Wells, April 2008.

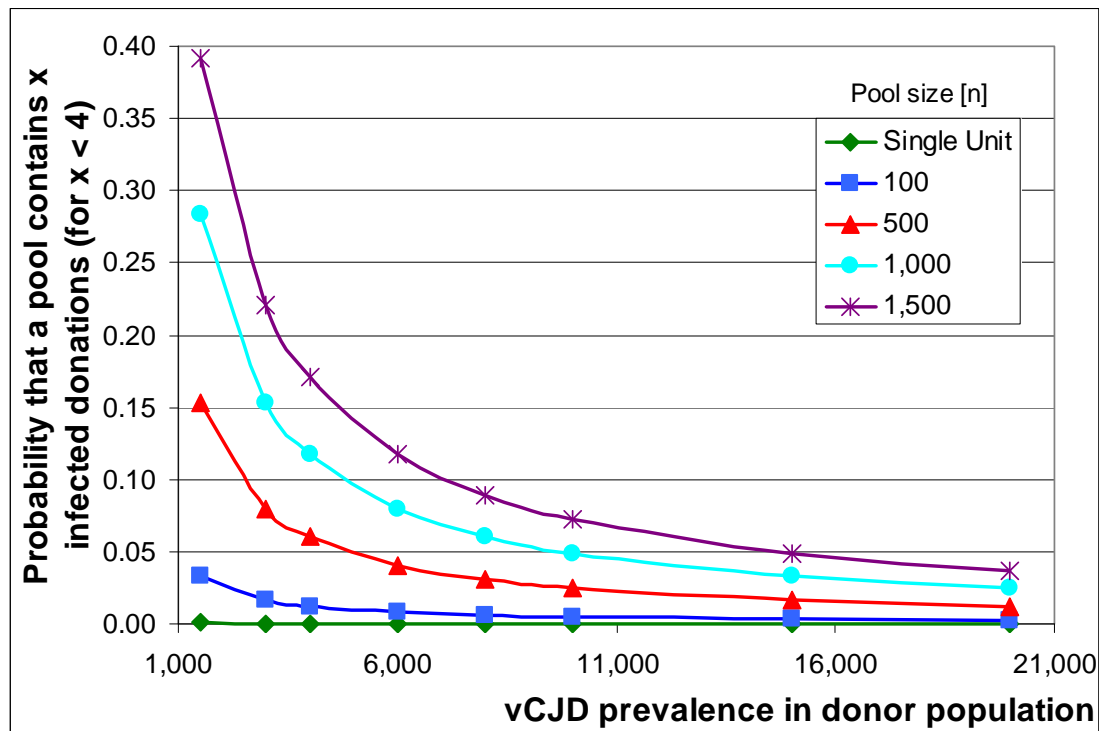
4. Results

Whilst choosing specific model inputs allows us to calculate the potential outcomes of policy options for any given scenario, some more general results follow from the structure of the model itself - in particular, relationships between pool size, infectivity, prevalence of vCJD amongst donors and average donation volume. These relationships are discussed briefly in sections 4.1 to 4.5, whilst the main results of the scenario-based analysis are presented in sections 4.6, 4.7 and 4.8. In section 4.9 we present the results of an alternative 'worst case' scenario, in which a very regular plasmapheresis donor is infected.

4.1 Probability that a pool contains an infected donation

From equation 2, we can see that the probability of a pool containing an infected donation is dependent only on the prevalence and the number of donations in a pool: in particular, it is independent of infectivity. Graph 1 illustrates the relationship between this probability and the underlying prevalence of the donor population, for a number of different pool sizes (where 'pool size' is defined as the number of transfusion units derived from the pool). We have used the approximation that a pool will contain no more than 3 infectious donations (i.e. $x < 4$), as discussed in section 3.8. As one would expect, for all pool sizes the probability of a pool containing an infected donation falls as the prevalence falls from 1 in 1,500 to 1 in 20,000. As one would also expect, the probability increases as the size of the pool increases; the more donations there are in a pool, the more likely that one of them will be infected.

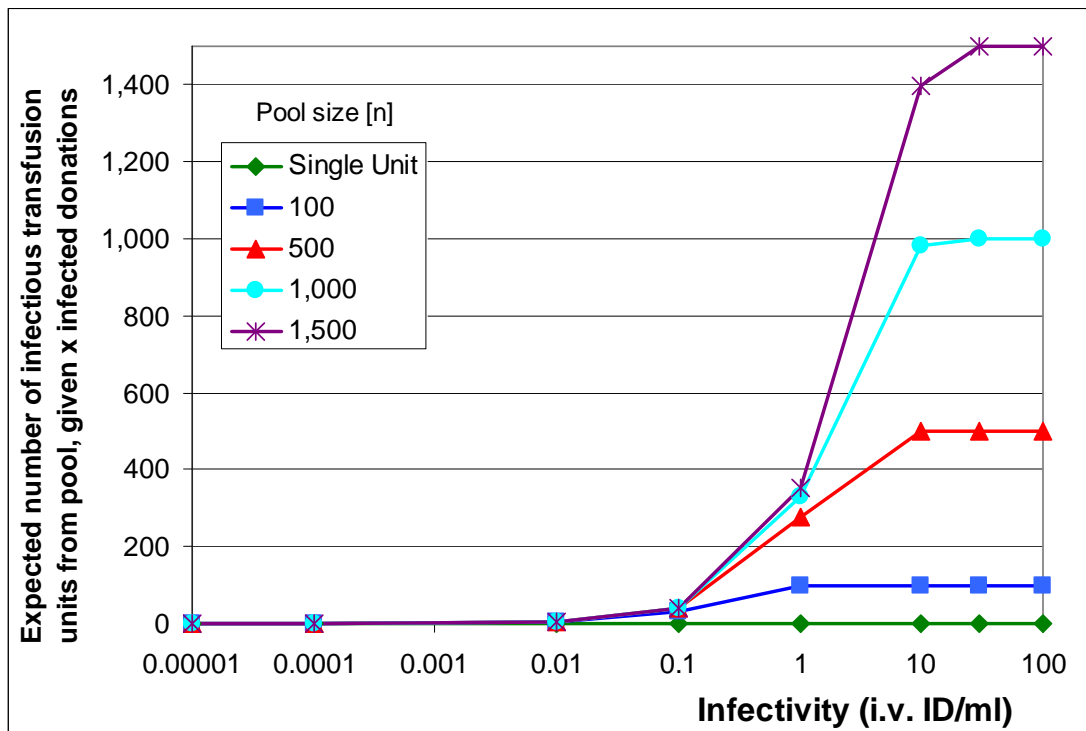
Graph 1: Probability that a pool contains an infected donation (using the approximation $x < 4$). Pool size refers to the number of transfusion units derived from the pool [n].



4.2 Expected number of infectious transfusion units, given that the pool contains x infected donations

Graph 2 shows the expected number of infectious transfusion units per pool, given that a pool contains x infected donations (E_i), as a function of infectivity. At the saturation infectivity level, all of the transfusion units derived from the pool will be infectious, as discussed in section 3.5 and expressed specifically by equation (10). Note that we have assumed the average volume donated to a pool from a given donor is 400ml, whilst the average size of a transfusion unit derived from a pool is 200ml, therefore at saturation a pool of 750 donations gives rise to 1,500 infectious units. In contrast, for single unit plasma we have assumed an equal donation volume and transfusion unit volume of 220 ml, therefore the maximum number of infectious units from an infected single unit donation is 1. However, at low levels of infectivity below this 'saturation' level, E_i approaches the value ixV_d , irrespective of the pool size: this is graphical illustration of the phenomenon described by equation (11) in section 3.5.

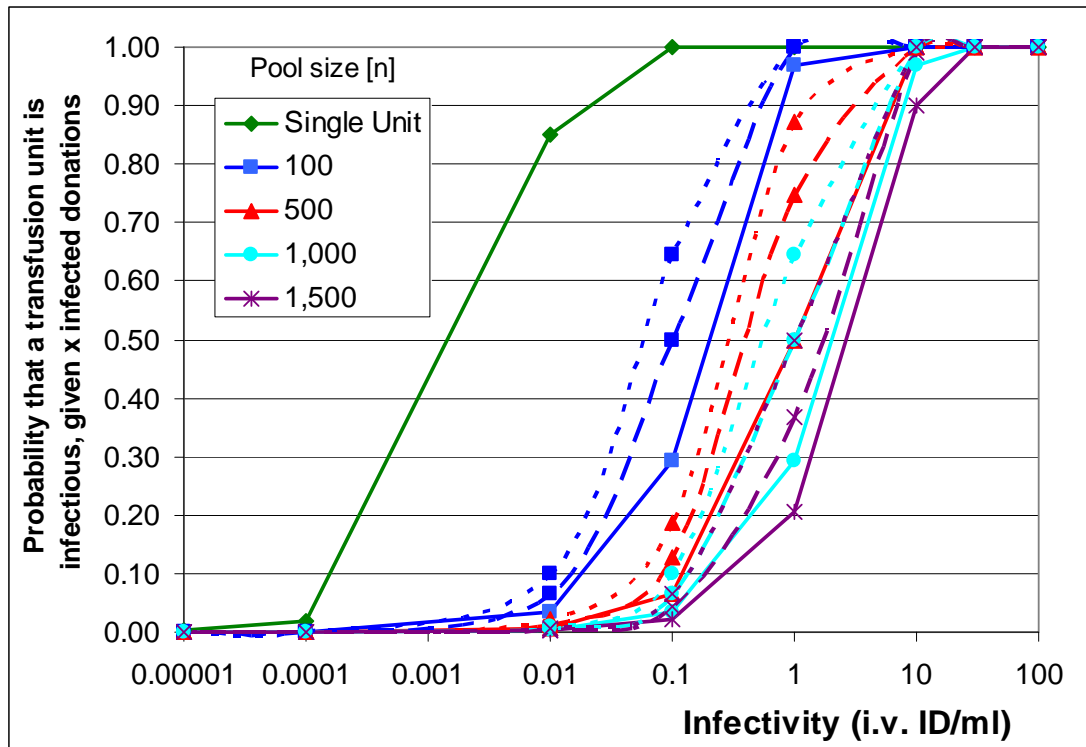
Graph 2: Expected number of infectious transfusion units, given that the pool contains x infected donations. Pool size refers to the number of transfusion units derived from the pool $[n]$.



4.3 Probability that a transfusion unit is infectious, given that the pool contains x infected donations

Rather than simply considering E_i , it is instructive to look at one of its component factors, that is, the probability that a transfusion unit is infectious given that the pool contains x infected donations (p_i). From equation 6, the probability that a transfusion unit is infectious, given that the pool contains x infected donations (p_i), is dependent only on x , the infectivity and the number of donations in a pool (we are assuming a fixed size for the transfusion unit): in particular, it is independent of the prevalence. Graph 3 illustrates the relationship between p_i and the infectivity density of blood, for a number of different pool sizes (for $x=1$ (solid), $x=2$ (dashed) and $x=3$ (dotted)). As one would expect, for all pool sizes the probability increases as the infectivity density increases and all approach 1 as the infectivity reaches between 1 and 10 ID/ml. However, at low levels of infectivity below this 'saturation' infectivity, there remains a finite probability that, given a pool containing an infected donation, a transfusion unit derived from the pool is not infectious. In this region of low infectivity, the probability is dependent on pool size, with the probability *decreasing* as the pool size *increases*.

Graph 3: Probability that a transfusion unit is infectious, given that the pool contains an infected donation (for $x=1$ (solid), $x=2$ (dashed) and $x=3$ (dotted)). Pool size refers to the number of transfusion units derived from the pool $[n]$.



4.4 Expected number of infections from 100,000 transfusion episodes

From equation 11, one can see that the expected number of infections is determined by a combination of the two probabilities investigated in sections 4.1 and 4.3.

Firstly, for a given donor prevalence (in this case, 1 in 4,000), table 2 shows the number of expected infections as a function of the infectivity. Graph 4 illustrates this graphically. For UK-sourced single unit FFP, an estimated 75 infections result from 100,000 transfusion episodes both for the low and high infectivity scenario (the corresponding figure drops to 15 for a donor prevalence of 1 in 20,000). As expected, with increasing infectivity, the estimated number of infections increases up to a saturation infectivity of between approximately 1 and 10 ID/ml. Moreover, in this saturated region, the number of expected infections increases as the pooling size increases. In the low infectivity region below approximately 0.1 ID/ml, the number of expected infections also increases as the pooling size increases, but as the infectivity becomes smaller the number of expected infections tends towards the same value for any pool size.

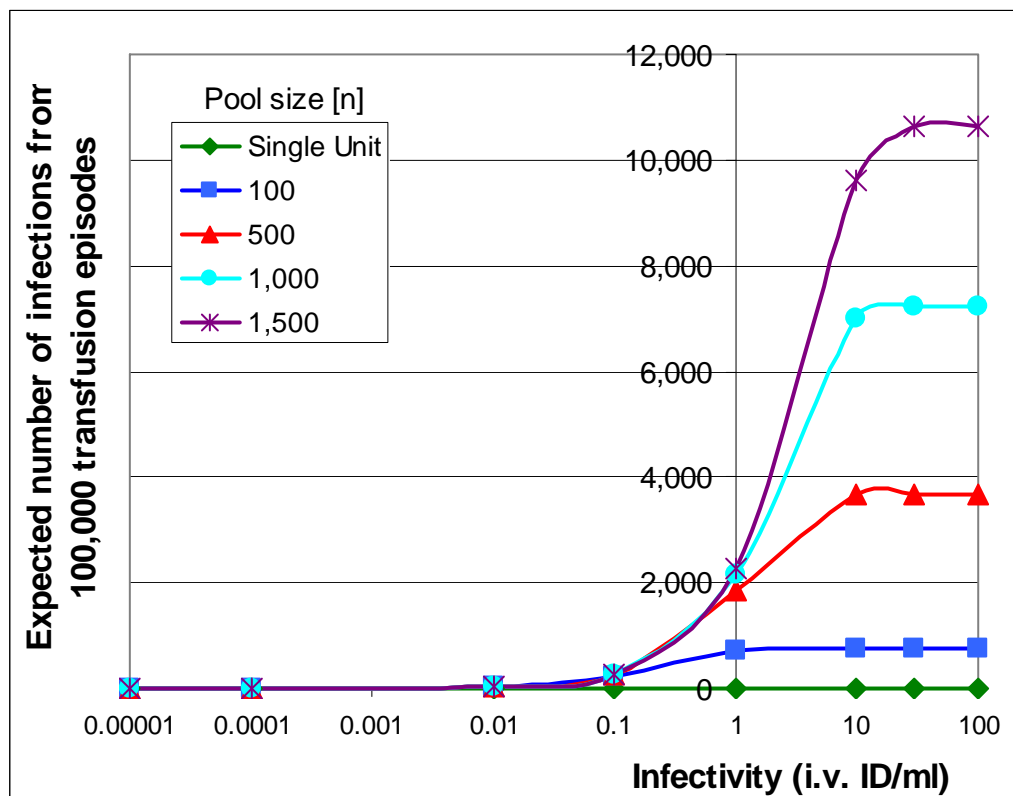
Secondly, the effect of donor prevalence is illustrated in graphs 5a and 5b, which show the expected number of infections from 100,000 transfusion episodes under an infectivity assumption of 30 and 0.1 ID/ml respectively. In both examples, the expected number of infections falls with decreasing prevalence for any pool size. Under the assumption of 30 ID/ml (which lies in the 'saturated' region), the expected number of infections increases with increasing pool size. For the 0.1 ID/ml assumption, the number of expected infections also increases as the pooling size increases, but by a much smaller amount; the values all tend to the same limit.

It is important to note that, for any infectivity and prevalence, the number of expected infections in a given scenario is never greater than that of the equivalent scenario with a larger pool size. This appears to be in line with the SEAC statement on pooling that “pooling blood to dilute infectivity does not decrease the risks to public health. Indeed, depending on the dose, pooling is likely to increase the risks to public health”.

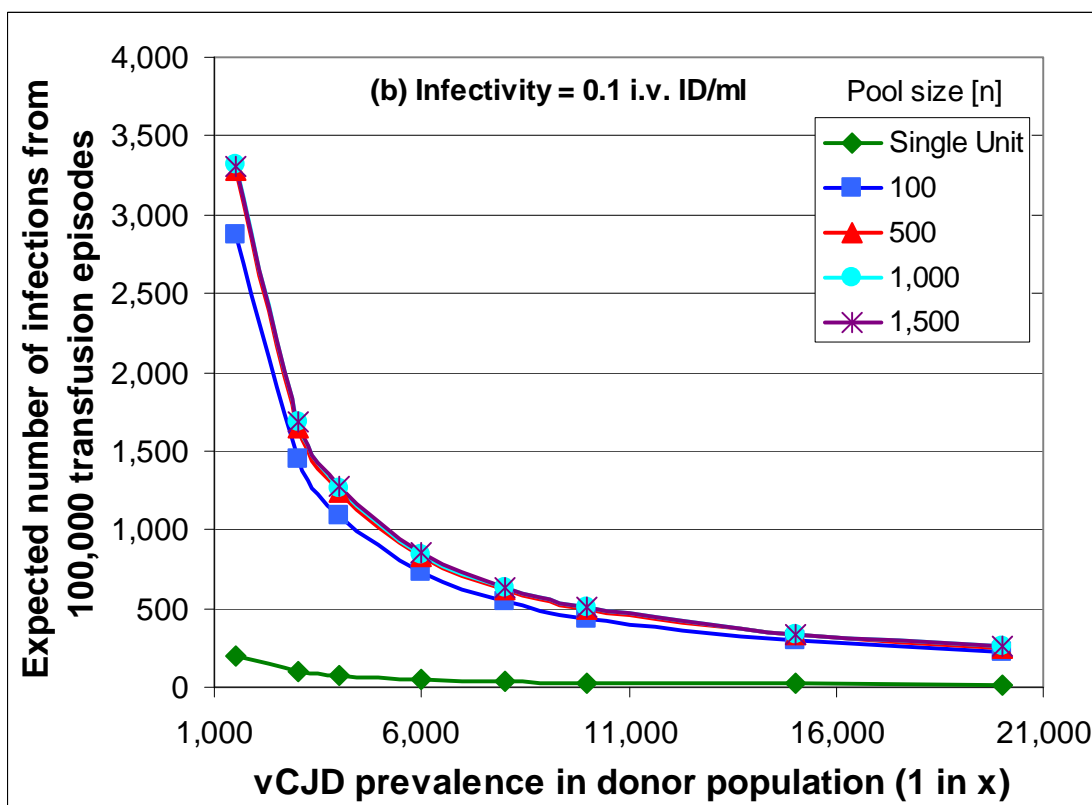
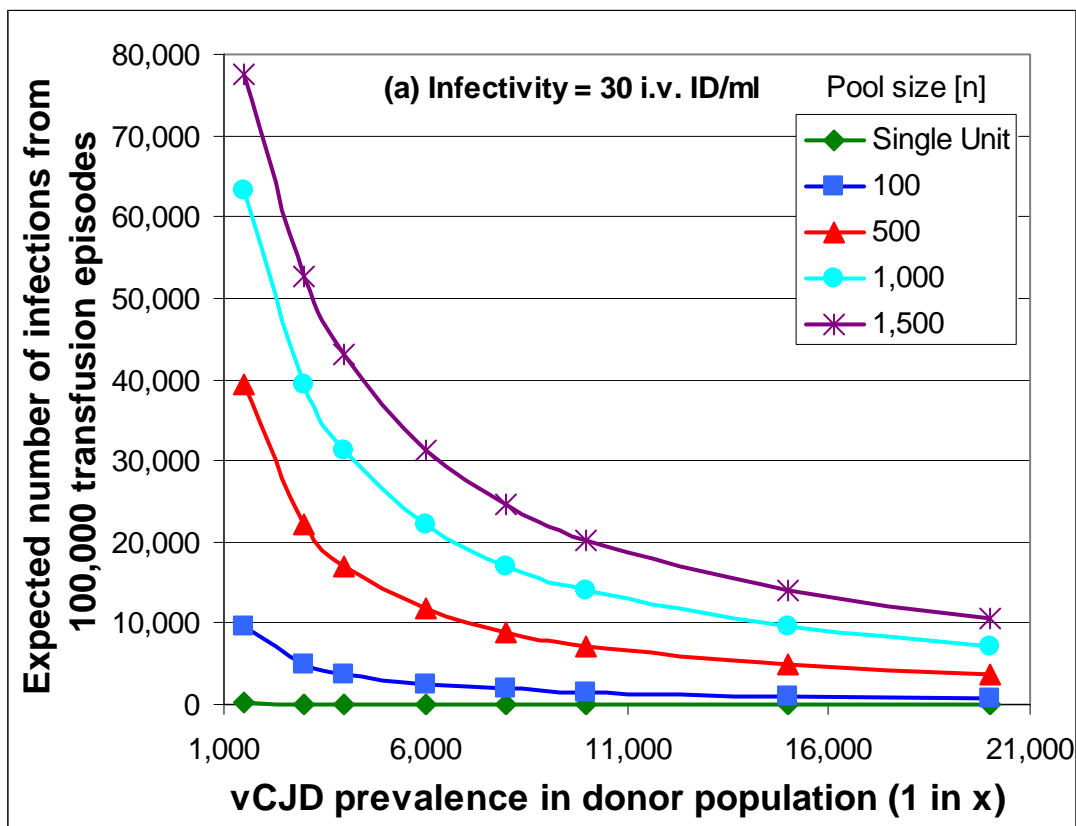
Table 2: Expected number of infections from 100,000 transfusion episodes

Infectivity (i.v. ID/ml)	Expected number of infections from 100,000 transfusion episodes (for UK prevalence = 1/4,000, susceptibility = 100%)				
	Single Unit	Number of transfusion units derived from pool [n]			
		100	500	1,000	1,500
100	75	3,681	17,099	31,272	43,017
30	75	3,681	17,099	31,271	42,984
10	75	3,681	17,083	30,449	39,710
1	75	3,566	8,922	10,362	10,907
0.1	75	1,088	1,242	1,263	1,270
0.01	64	127	129	129	129
0.0001	1.4	1.29	1.29	1.29	1.29
0.00001	0.142	0.129	0.129	0.129	0.129

Graph 4: Expected number of infections from 100,000 transfusion episodes as a function of infectivity. Pool size refers to the number of transfusion units derived from the pool [n].



Graphs 5a and 5b: Expected number of infections from 100,000 transfusion episodes for an infectivity of (a) 30 ID/ml and (b) 0.1 ID/ml. Pool size refers to the number of transfusion units derived from the pool [n].

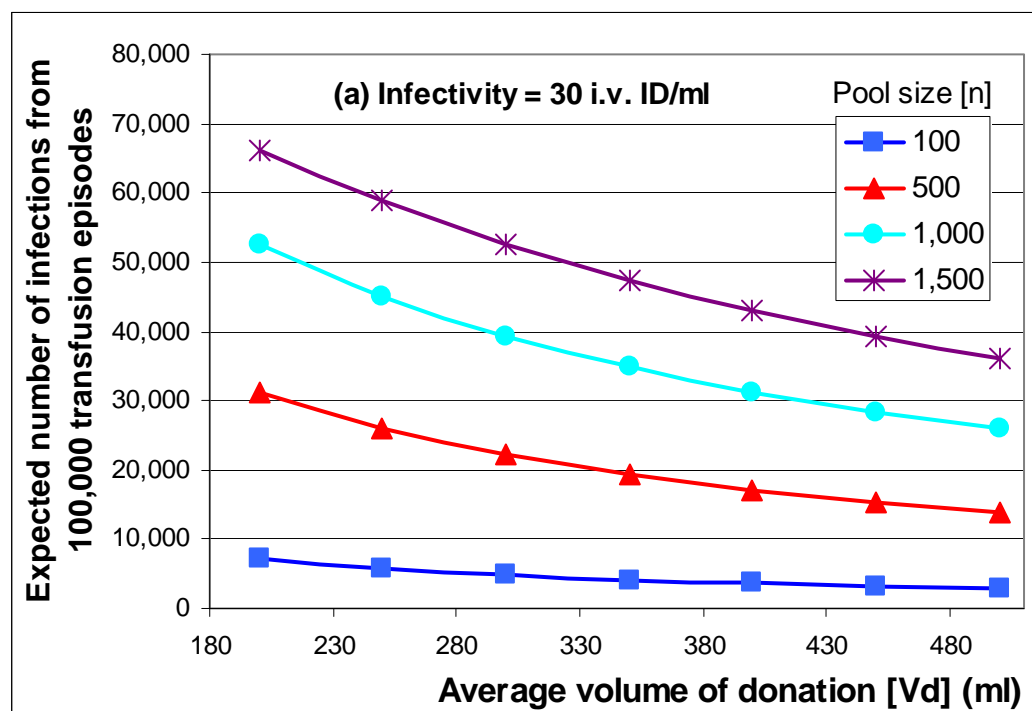


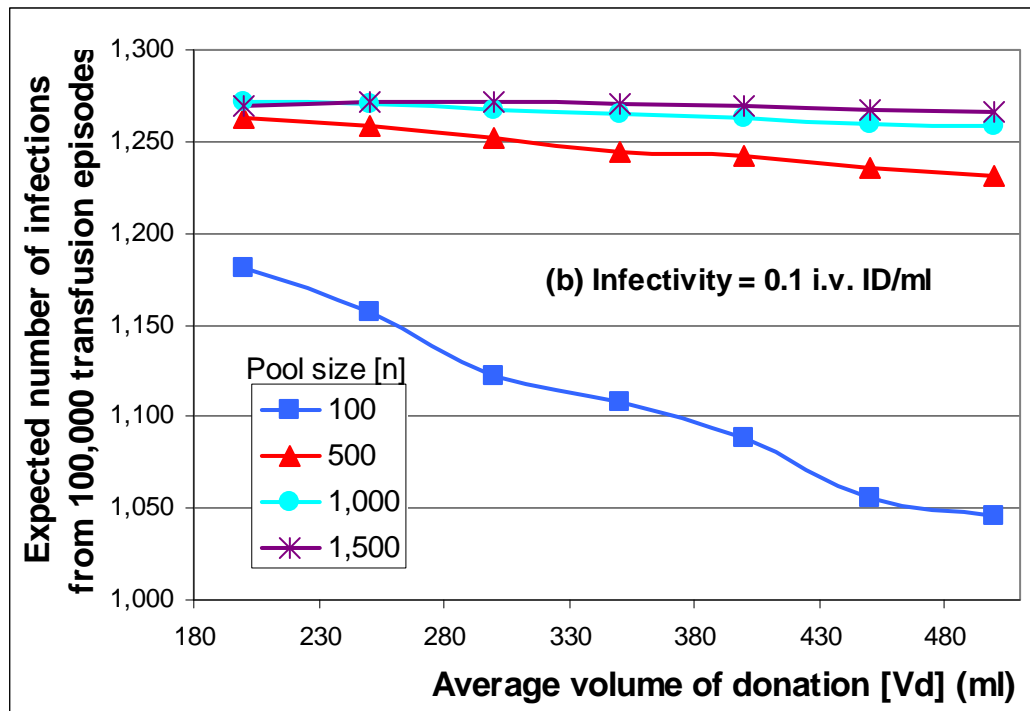
4.5 The effect of varying the average donation volume

In sections 4.1 to 4.4 (and again in sections 4.6 and 4.7), we have used an input value of 400ml for the average donation volume, V_d (as discussed in section 3.9). Whilst the expression for the expected number of infections given in equation 9 does not explicitly include V_d as a parameter, it does depend on this variable via the term N (number of donations in a pool) and the relationship $N = nV_t/V_d$. We have assumed a value of 200ml for the volume of a transfusion unit [V_t], and we are investigating the pool sizes (number of transfusion units derived from the pool) $n = 100, 500, 1000$ and 1500 . Therefore, for a given pool size, the average donation volume is directly proportional to the number of donations in the pool (and vice versa).

Graphs 6a and 6b show the expected number of infections from 100,000 transfusion episodes as a function of donation volume, for 30 ID/ml and 0.1 ID/ml respectively. For the higher infectivity scenario, the expected number of infections decreases with increasing donation volume: for larger donation volumes, each pool contains fewer donations and hence there is a lower donor exposure. In the (unrealistic) limit of a donation volume equal to the total volume of the pool, there would only be exposure to one donor and therefore the expected number of infections is the same as for the single unit product. For the low infectivity scenario, we see similar behaviour but less pronounced (particularly in the case of large pool sizes).

Graphs 6a and 6b: Expected number of infections from 100,000 transfusion episodes as a function of donation volume, for an infectivity of (a) 30 ID/ml and (b) 0.1 ID/ml. Pool size refers to the number of transfusion units derived from the pool [n].





4.6 The effect of reducing donor prevalence via importation

The effect of reducing the expected number of infections via importation of plasma (single unit or pooled) has been investigated by *assuming* a range of different possible reductions of prevalence in the source country with respect to UK-sourced plasma. Table 3 shows the percentage of expected infections relative to UK single unit plasma for a number of different pool sizes and a range of assumed log reductions in prevalence (due to sourcing). The results in Tables 3a and 3b are based on an assumption of 0.1 and 30 ID/ml infectivity respectively. In both cases, a UK prevalence of 1 in 4,000 is assumed.

Table 3: The percentage of expected infections resulting from imported pooled FFP, relative to UK single unit plasma. This assumes a UK donor prevalence of 1 in 4,000.

(a) Infectivity = 0.1 ID/ml

Source prevalence relative to UK (log ₁₀ reduction)	Relative risk of non-UK-sourced (single unit and pooled) products against UK-sourced single unit FFP. UK prevalence = 1/4,000. Infectivity = 0.1 ID/ml				
	Single Unit	Pool size: Number of transfusion units derived from pool [n]			
		100	500	1,000	1,500
0	100%	1450%	1660%	1690%	1690%
1	10%	146%	167%	169%	170%
2	1%	15%	17%	17%	17%
3	0.1%	1.5%	1.7%	1.7%	1.7%
5	0.001%	0.01%	0.02%	0.02%	0.02%

(b) Infectivity = 30 ID/ml

Source prevalence relative to UK (log10 reduction)	Relative risk of non-UK-sourced (single unit and pooled) products against UK-sourced single unit FFP. UK prevalence = 1/4,000. Infectivity = 30 ID/ml				
	Single Unit	Pool size: Number of transfusion units derived from pool [n]			
		100	500	1,000	1,500
0	100%	4,910%	22,800%	41,700%	57,300%
1	10%	499%	2,480%	4,910%	7,290%
2	1%	50%	250%	499%	747%
3	0.1%	5%	25%	50%	75%
5	0.001%	0.1%	0.3%	0.5%	0.7%

Firstly, consider the highlighted first rows in Tables 3a and 3b, which correspond to UK-sourced plasma (the log reduction in source prevalence relative to the UK is 0). Under all scenarios, the UK pooled plasma of all pool sizes is expected to cause significantly more infections than the benchmark single unit UK plasma. In the worst-case scenario investigated, for which the infectivity and pool size are large, the expected number of infections is over 50,000% that of the UK single unit plasma, and for all of the cases investigated this figure is above 1,400%. It is worth noting the effect discussed in section 4.4 whereby the relative expected number of infections increases with increasing pool size for both infectivity scenarios (0.1 and 30 ID/ml), but that this is much less pronounced in the low infectivity scenario.

Now consider the effect of importation. For single unit plasma, the results show a proportionate fall in the expected number of infections with the log reduction of the source prevalence. So even with a source country prevalence that is 1% that of the UK's, we see a significant reduction in risk equivalent to 1% of the current risk from UK sourced single unit plasma. Similarly, for the pooled plasma options, an approximately proportionate relationship between relative number of infections and log reduction in source prevalence is observed for log reductions of two or greater.

The blue highlighted cells show the scenario options for which there is expected to be a risk reduction with respect to UK-sourced single unit plasma (i.e. <100%). For the low infectivity scenario (Table 3a), this corresponds to a two log or greater source prevalence reduction with respect to the UK, for any pool size. For a source country with 1% of the UK's prevalence, or less, there is expected to be *at least* an 80% reduction in risk through importation (i.e. <20% relative risk), for any of the pool sizes investigated. In the high infectivity scenario (Table 3b), a reduction in the risk through importation is observed only in the cases where the source country prevalence is 0.1% of the UK's prevalence, or less. However, for a source country prevalence of 0.001% (a log reduction of five with respect to the UK), there is a significant reduction in risk for *all* scenarios – low or high infectivity, small or large pool sizes – of at least 99% (in most cases > 99.9%). However, it is important to note that, whilst there are a number of scenarios in which pooled imported plasma would give significant risk reduction over the UK single unit plasma, there are also scenarios under which it would represent a huge *increase* in risk. For

example, under a high infectivity scenario, a log reduction in prevalence of only one is expected to give rise to enhanced risks above UK-sourced single unit plasma of up to nearly 7,500% in the case of large pooling. Even for a log reduction of two, enhanced expected risks of nearly 750% are observed for this large pooling size. Given the uncertainty associated with scenario parameters, this large variation between significant risk reduction and significant risk enhancement presents a challenge for risk management.

4.7 The effect of reducing infectivity via the manufacturing process

The effect of reducing the expected number of infections via specific steps in the processing of pooled plasma has been investigated by *assuming* a certain log reduction in the infectivity (note that we do not attempt to say whether or not any given products *do* achieve a certain log reduction, but look at the implications of assuming such a reduction). Tables 4a and 4b show the equivalent results to Tables 3a and 3b, but with prion reduction assumed to reduce infectivity (in pooled plasma) by 2.5 log.

Table 4: The percentage of expected infections resulting from imported pooled FFP with a 2.5 log reduction in infectivity, relative to UK single unit plasma. This assumes a UK donor prevalence of 1 in 4,000.

(a) Infectivity = 0.1 ID/ml

Source prevalence relative to UK (log ₁₀ reduction)	Relative risk of non-UK-sourced (single unit and pooled) products against UK-sourced single unit FFP. UK prevalence = 1/4,000. Infectivity = 0.1 ID/ml [REDUCED INFECTIVITY (2.5 log reduction)]				
	Single Unit	Pool size: Number of transfusion units derived from pool [n]			
		100	500	1,000	1,500
0	100%	5%	5%	5%	5%
1	10%	1%	1%	1%	1%
2	1%	0.05%	0.05%	0.05%	0.05%
3	0.1%	0.005%	0.005%	0.005%	0.005%
5	0.001%	0.0001%	0.0001%	0.0001%	0.0001%

(b) Infectivity = 30 ID/ml

Source prevalence relative to UK (log ₁₀ reduction)	Relative risk of non-UK-sourced (single unit and pooled) products against UK-sourced single unit FFP. UK prevalence = 1/4,000. Infectivity = 30 ID/ml [REDUCED INFECTIVITY (2.5 log reduction)]				
	Single Unit	Pool size: Number of transfusion units derived from pool [n]			
		100	500	1,000	1,500
0	100%	1,390%	1,580%	1,600%	1,610%
1	10%	140%	158%	161%	162%
2	1%	14%	16%	16%	16%
3	0.1%	1%	2%	2%	2%
5	0.001%	0.01%	0.02%	0.02%	0.02%

For the low infectivity scenario, prion reduction (assuming a 2.5 log reduction in infectivity) offers a significant risk reduction with respect to UK-sourced

single unit plasma for all scenarios investigated. Even if sourced from the UK, prion reduced pooled plasma gives an expected relative risk of approximately 5% of UK-sourced single unit plasma, for all pool sizes. Further expected risk reduction is observed through importation; when combined with log 2.5 infectivity reduction, sourcing from a country with as much as 10% of the UK's prevalence still gives an expected risk of just 1% that of the UK-sourced single unit plasma.

For the high infectivity scenario however, there remains circumstances in which prion-reduced pooled plasma could still pose a higher risk of infection with respect to single-unit UK plasma; for UK-sourced pooled plasma or imported pooled plasma from a source with >1% of the UK's prevalence.

Nevertheless, an assumed source prevalence of 1% of the UK's (or less) combined with log 2.5 prion filtration gives a significant risk reduction for *all* of the scenarios – low or high infectivity, low or high prevalence, small or large pool sizes – considered in this paper.

Tables 5a and 5b below show the equivalent results to Tables 4a and 4b, but with prion reduction assumed to reduce infectivity (in pooled plasma) by 1 log.

Table 5: The percentage of expected infections resulting from imported pooled FFP with a 1 log *reduction in infectivity*, relative to UK single unit plasma. This assumes a UK donor prevalence of 1 in 4,000.

(a) Infectivity = 0.1 ID/ml

Source prevalence relative to UK (log10 reduction)	Relative Risk of non-UK sourced (single unit and pooled) products against UK-sourced single unit FFP. UK prevalence = 1/4,000. Infectivity = 0.1 ID/ml [REDUCED INFECTIVITY (1 log)]				
	Single Unit	Pool size: Number of transfusion units derived from pool [n]			
		100	500	1,000	1,500
0	100%	169%	172%	172%	172%
1	10%	17%	17%	17%	17%
2	1%	1.70%	1.72%	1.72%	1.72%
3	0.1%	0.170%	0.172%	0.172%	0.172%
5	0.001%	0.0017%	0.0017%	0.0017%	0.0017%

(b) Infectivity = 30 ID/ml

Source prevalence relative to UK (log10 reduction)	Relative Risk of non-UK sourced (single unit and pooled) products against UK-sourced single unit FFP. UK prevalence = 1/4,000. Infectivity = 30 ID/ml [REDUCED INFECTIVITY (1 log)]				
	Single Unit	Pool size: Number of transfusion units derived from pool [n]			
		100	500	1,000	1,500
0	100%	4909%	20156%	28643%	32594%
1	10%	499%	2167%	3186%	3687%
2	1%	50%	218%	322%	373%
3	0.1%	5%	22%	32%	37%
5	0.001%	0.05%	0.22%	0.32%	0.37%

For the low infectivity scenario, prion reduction (assuming a 1 log reduction in infectivity) offers a significant risk reduction with respect to UK-sourced single unit plasma for imported plasma where the source prevalence is 10% of the UK or less. However, UK-sourced pooled plasma with prion reduction (assuming a 1 log reduction in infectivity) still poses a higher risk of infection with respect to single-unit UK plasma.

For the high infectivity scenario, prion reduction (assuming a 1 log reduction in infectivity) only offers a significant risk reduction, with respect to UK-sourced single unit plasma, for imported plasma where the source prevalence is 0.1% of the UK or less (except for small pool sizes ($n=100$) where a source prevalence of 1% that of the UK offers a risk reduction with respect to UK-sourced single unit plasma).

4.8 Comparison of overall risk reduction achieved through reduction in source prevalence versus infectivity

This section provides a comparison of the risk reduction achieved through a reduction in source prevalence (due to importation) with that achieved through a reduction in infectivity via the manufacturing process.

Tables 6(a) and (b) demonstrate, for a particular log reduction in source prevalence with respect to the UK, the equivalent log reduction in infectivity required to achieve the same overall risk reduction, for various pool sizes. For example, for the low infectivity scenario and a pool size of $n=500$, table 6(a) demonstrates that, for UK sourced plasma, in order to achieve the risk reduction equivalent to that achieved by importing plasma from a source country with a prevalence of 1% that of the UK (i.e. a 2 log reduction) it would be necessary to achieve a 2.015 log reduction in infectivity via the manufacturing process. Similarly, for the high infectivity scenario a 3.314 log reduction in infectivity would be required (see table 6(b)).

These comparisons allow the identification of the cross-over points where reductions in infectivity and reductions in prevalence (due to importation) result in equivalent overall risk reductions. However, it should be noted that prion-reduced pooled UK sourced FFP is not being suggested as a supply option.

Table 6: Log reductions in infectivity that are required in order to achieve the same overall risk reduction as that achieved through reductions in donor prevalence relative to the UK. Both tables assume a UK donor prevalence of 1 in 4,000.

(a) Infectivity = 0.1 ID/ml

Source prevalence relative to UK (log ₁₀ reduction)	Equivalent log reduction in infectivity. (I.e. the log reduction in infectivity required to achieve the same overall risk reduction as that achieved through a reduction in source prevalence.) UK prevalence = 1/4,000. Infectivity = 0.1 ID/ml				
	Single Unit	Pool size, n =			
		100	500	1,000	1,500
0	n/a	n/a	n/a	n/a	n/a
1	n/a	1.066	1.013	1.007	1.004
2	n/a	2.072	2.015	2.007	2.005
3	n/a	3.073	3.015	3.007	3.005
5	n/a	5.085	5.018	5.007	5.006

(b) Infectivity = 30 ID/ml

Source prevalence relative to UK (log ₁₀ reduction)	Equivalent log reduction in infectivity. (I.e. the log reduction in infectivity required to achieve the same overall risk reduction as that achieved through a reduction in source prevalence.) UK prevalence = 1/4,000. Infectivity = 30 ID/ml				
	Single Unit	Pool size, n =			
		100	500	1,000	1,500
0	n/a	n/a	n/a	n/a	n/a
1	n/a	2.992	2.293	1.992	1.816
2	n/a	4.031	3.314	3.013	2.837
3	n/a	5.041	4.316	4.015	3.838
5	n/a	7.014	6.316	6.015	5.834

For the low infectivity scenario, table 6(a) demonstrates that similar sized reductions in source prevalence and infectivity have a similar effect on overall risk reduction.

However, table 6(b) demonstrates that, for the high infectivity scenario, a reduction in source prevalence has a stronger risk reduction effect compared to a similar sized reduction in infectivity.

4.9 Plasmapheresis: a ‘worst case’ case scenario

In the preceding analysis, we have considered the donation patterns to be independent of whether donors are contributing to a single unit or pooled product. However, in reality donation patterns tend to be rather different for the two types of product. For single unit plasma derived from whole blood, the minimum time allowed between donations from a given donor is 12 weeks, which corresponds to a maximum of 4.3 donations per year. However, for pooled products donors can donate by plasmapheresis, which has a limit of two donations per week, i.e. a maximum of 104 donations per year. Although this maximum frequency would be highly unlikely, plasmapheresis donors do tend to donate much more frequently than whole blood donors. One can therefore imagine a ‘worst case’ scenario in which an infected donor donates at this maximum frequency, thereby causing a significant impact on the expected number of infections.

In the preceding analysis, we have assumed that, in both the pooled and single unit cases, the vCJD prevalence is equal to the underlying prevalence of the UK population (or non-UK source country prevalence in the case of importation). Table 7 shows the expected number of infected donations per year based on a vCJD prevalence of 1 in 4,000 for a) single unit, whole blood donations (with a donation frequency of 4.3 donations per year); b) pooled plasmapheresis donations (with a donation frequency of 104 donations per year); c) pooled plasmapheresis donations (with a donation frequency of 12 donations per year). For plasmapheresis, the pool of donors is smaller than for whole blood donors and so less donors are expected to be infected. However, they donate more frequently and therefore the overall expected number of infected donations per year is the same for both cases (and equal to the prevalence multiplied by the number of units donated per year).

Table 7: Expected number of infected donations per year, based on a vCJD prevalence in the UK donor population of 1 in 4,000.

	(a) Single unit plasma (from whole blood donations)	(b) Pooled plasma (from apheresis donors)	(c) Pooled plasma (from apheresis donors)
Donation frequency (number per year)	4.3	104	12
Number of units donated per year	100,000	100,000	100,000
Number of donors	23,077	962	8,333
Expected number of infected donors	5.8	0.2	2.1
Expected number of infected donations per year	25	25	25
Probability of an infected donation	0.025%	0.025%	0.025%

Consider case (b), which has a very high (maximum) donor frequency for plasmapheresis. The number of donors required to supply 100,000 units at this frequency is under 1,000, and the expected number of infected donors is only 0.2. However, in reality a donor is either infected or not, and in this case the probability of having one infected donor is found (from equation 1) to be 18.9%; whilst it is significantly more likely that none of the donors will be infected, there is a substantial chance that one of them is. The implications of

one high-frequency plasmapheresis donor being infected in this scenario are severe. The donor will donate an expected 104 infected units per year, which gives an overall probability of an infected donation of 0.1%, i.e. four times that of the whole blood donation regime.

Similarly, for a prevalence of 1 in 20,000, the overall probability of an infected donation is also 0.1%, but the chance of having an infected donor in the high-frequency plasmapheresis scenario drops to 4.6%.

If we assume that one high-frequency plasmapheresis donor is infected, and that their infectious donations are randomly distributed amongst the plasma pools, then we can derive the following results for the expected number of transfusion recipient infections per year (which can be directly compared with tables 3a and b).

Table 8: The percentage of expected infections resulting from imported pooled FFP relative to UK-sourced single unit plasma, given the assumption that a high frequency plasmapheresis donor is infected. This assumes a UK donor prevalence of 1 in 4,000.

(a) Infectivity = 0.1 ID/ml

Source prevalence relative to UK (log10 reduction)	Relative risk of non-UK-sourced (single unit and pooled) products against UK-sourced single unit FFP. UK prevalence = 1/4,000. Infectivity = 0.1 ID/ml [High frequency plasmapheresis donation scenario]				
	Single Unit	Pool size: Number of transfusion units derived from pool [n]			
		100	500	1,000	1,500
0	100%	5,940%	6,740%	6,770%	6,620%
1	10%	606%	692%	704%	708%
2	1%	61%	69%	71%	71%
3	0.1%	6.1%	6.9%	7.1%	7.1%
5	0.001%	0.06%	0.07%	0.07%	0.07%

(b) Infectivity = 30 ID/ml

Source prevalence relative to UK (log10 reduction)	Relative risk of non-UK-sourced (single unit and pooled) products against UK-sourced single unit FFP. UK prevalence = 1/4,000. Infectivity = 30 ID/ml [High frequency plasmapheresis donation scenario]				
	Single Unit	Pool size: Number of transfusion units derived from pool [n]			
		100	500	1,000	1,500
0	100%	19,300%	72,200%	105,100%	119,800%
1	10%	2,060%	10,000%	19,300%	27,800%
2	1%	208%	1,040%	2,060%	3,080%
3	0.1%	21%	104%	208%	311%
5	0.001%	0.2%	1.0%	2.1%	3.1%

It is important to note that in this 'worst case' scenario, an extra log reduction in the source prevalence with respect to the UK is required in order to achieve a risk reduction compared to the results in Table 3.

PART III: RISK ASSESSMENT OF COUNTRY SOURCING

5. Methodology

5.1 Model overview

The risk assessment model presented in this paper offers a mechanism by which to estimate the log reduction in vCJD prevalence for a given country with respect to the UK. This can be used alongside the analysis presented in part II of this paper in order to assess the risk reduction achieved through sourcing a plasma product from a non-UK country, with respect to UK plasma.

A number of possible methodologies are presented, which can be split broadly into two categories; methodologies based on vCJD incidence and methodologies based on BSE incidence. Within each of these categories, different approaches are discussed with reference, where relevant, to scientific literature. As discussed in part I of this paper, there are a number of uncertainties around many of the key parameters associated with vCJD and so it is not possible to construct a highly accurate model for calculating the risk of a country relative to the UK: this model is intended to give an *approximate* indication of the risk levels.

In section 5.2 we discuss the Geographical BSE Risk (GBR) rating system, which is a qualitative indicator of the likelihood of BSE-infected cattle in a given country and can be used to qualitatively rank order the relative BSE/vCJD risk for different countries. However, many countries fall within the same GBR rating category, and so this currently offers an imprecise measure of the relative BSE/vCJD risk of different countries. In order to distinguish better the relative risk of these countries, we propose a model for modifying the GBR rating and therefore creating a system by which to qualitatively rank country risk more sensitively.

We then go on to propose methodologies for quantitative estimates of vCJD prevalence in a given country relative to the UK: in section 5.3 we present the vCJD incidence based method and in section 5.4 we propose two different methodologies based on BSE incidence rates.

In section 5.5 we discuss methods by which to adjust the methodologies based on BSE incidence to take into account under-ascertainment of BSE cases in the estimates and in section 5.6 we propose an adjustment factor, again for those methodologies based on BSE incidence, to account for imports of UK beef to the country being risk assessed

5.2 Assessment of the geographical risk of BSE (GBR)

The European Food Standard agency have produced an assessment of the risk of BSE in different countries, which take into account a number of factors in addition to recorded BSE incidence. The Geographical BSE-Risk (GBR) is a qualitative indicator of the likelihood of the presence of one or more cattle being infected with BSE, pre-clinically as well as clinically, at a given point in time, in a given country. Where its presence is confirmed, the GBR gives an

indication of the level of infection. The GBR assessment rates the presence of one or more infected cattle in a given country as:

I - Highly unlikely

II - Unlikely but not excluded

III - Likely but not confirmed, or confirmed at a lower level

IV - Confirmed at a higher level

SEAC have previously considered that the GBR status gives a very imprecise indication of BSE risk. They have stated that, whilst in relative terms the BSE risk is likely to be lower in a GBR I country compared with a GBR III country, the difference in risk could not be quantified. In terms of a more robust risk analysis, SEAC believe that it would be important to obtain a more reliable estimate of the prevalence of BSE in a country than simply GBR status, and have confidence in the quality of the surveillance data.

Nearly all of the countries fall within the level III rating and so it is difficult to distinguish between these countries in terms of their relative BSE risk solely from the GBR rating. In the following analysis, we have attempted to add granularity to the GBR ratings by exploring in more detail the methodology and findings used to complete the country assessments. No attempt is made to estimate the absolute prevalence of a country simply from this modified GBR rating, rather it is presented as a methodology for ranking countries in relative order of risk more sensitively than by using the normal GBR rating.

The GBR adopts a methodology developed by the Scientific Steering Committee (SSC)⁸. This methodology⁹ is based on the assumption that BSE arose in the United Kingdom (UK) and was propagated through the recycling of bovine tissues into animal feed. Subsequently, the export of infected animals and infected feed provided the means for the spread of the BSE-agent to other countries where it was again recycled and propagated via the feed chain. Two key components considered in the GBR assessment are the 'challenge' and 'stability' of the country.

The 'external challenge' is the likelihood and the amount of BSE agent entering into a defined geographical area in a given time period through infected cattle or meat and bone meal (MBM). The 'stability' is the ability of a BSE/cattle system to prevent the introduction and reduce the spread of the BSE agent within its borders, e.g. by avoiding the processing of infected cattle and the recycling of the BSE agent via the feed chain. A stable system would eliminate BSE over time whilst an unstable system would amplify it. Important factors in stability are surveillance and culling, which are essential for the ability of a system to identify clinical BSE-cases and to avoid these cases entering processing.

⁸ Note that the (former) Scientific Steering Committee of the European Commission provided scientific advice to the EC supporting legislation in the area of TSE and BSE until 2003. This responsibility was handed over to the European Food Safety Authority in 2003, providing from then onwards, independent scientific advice in all areas of food and feed safety including TSE, supporting the EC legislation.

⁹ Further details of the GBR methodology are given in the "Final Opinion of the Scientific Steering Committee on the Geographical Risk of Bovine Spongiform Encephalopathy (GBR) Adopted on 6/July/2000". [http://ec.europa.eu/food/fs/sc/ssc/out113_en.pdf].

The ‘internal challenge’ is the likelihood and the amount of BSE agent present and circulating in a specific geographical area in a given time period. The internal challenge in a given period is a consequence of the interaction of the stability of the system and the combined external and internal challenge to which it was exposed in a previous period. If a fully stable BSE/cattle system is exposed to an external challenge, processing and recycling of the BSE-load entering the system will be prevented and the infectivity load will be neutralised over time: no internal challenge will result from this external challenge. However, if an unstable BSE/cattle system is exposed to an external challenge, processing and recycling of the BSE-load entering the system will take place and the agent will start circulating in the system. In this way, the internal BSE-load of the system would be amplified and a BSE-epidemic could potentially develop. It is worth noting, however, that although a BSE-epidemic in cattle relates closely to the risk of BSE entering the human food chain, there are potential interventions that could reduce this risk even in the case of an epidemic.

One can use the BSE ‘stability’ and ‘challenge’ in potential source countries between 1980 and 1999 (as determined by the SSC/EFSA assessment, or the most up to date stability and challenge where later SSC/EFSA assessments are available) to establish a modified GBR rating system that allows for a wider range of ratings amongst potential source countries. We propose two different methodologies to do this:

- Method A: Table 9 shows the conversion criteria adopted to convert the challenge and stability ratings of the GBR assessment into an overall modified GBR rating. In this methodology, the GBR challenge takes a higher priority than the stability.

Table 9: Conversion criteria for establishing a modified GBR rating from the GBR challenge and stability (Method A)

GBR challenge	GBR stability	Modified GBR rating
3	any	5
2	(-3,-2,-1,0)	5
2	(1,2,3)	4
1	(-3,-2,-1)	4
1	(0,1,2,3)	3
0	(-3,-2,-1)	3
0	(0,1,2,3)	2
-1	(-3,-2,-1)	2
-1	(0,1,2,3)	1
(-3,-2)	any	1

- Method B: We have given equal weight to the challenge and stability, combining them by the equation: Combined factor = challenge – stability.

This ‘combined factor’ was then normalised to a scale of 1-5 to give the modified GBR rating (Method B).

For information, a summary of the GBR rating for a large range of countries is presented in Appendix B, alongside their adjusted GBR rating as calculated using methods A and B. Also listed are their BSE ‘stability’ and ‘challenge’ between 1980 and 1999 (as determined by the SSC/EFSA assessment).

These proposed modified GBR ratings, which add granularity to the standard GBR ratings, could be used as a means to rank the order of potential source countries in terms of their relative estimated prevalence with respect to the UK. However, it is not clear how this could be used to estimate the absolute prevalence of a given country relative to the UK. In the remainder of this paper, we propose a number of possible methodologies using vCJD and BSE incidence rates to provide an absolute estimate of this kind.

5.3 vCJD incidence based methodology

Countries that have had clinical cases of vCJD form a specific sub-category with respect to this risk reduction analysis. Primary cases of vCJD have been confirmed to date (April 2008) in the UK, France, Republic of Ireland, Italy, USA, Canada, Saudi Arabia, Japan, Netherlands, Portugal and Spain. However, some of the identified cases are believed to have arisen due to the fact that the patient was resident in the UK for > 6 months in the period 1980 – 1996, and are therefore not considered to be ‘indigenous’ cases. Table 10 below summarises the current data on vCJD incidence, taken from the European and Allied Countries Study Group of CJD (EUROCJD/NEUROCJD)¹⁰.

Table 10: vCJD incidence by country

Country	Population (millions)	Primary vCJD cases	Indigenous primary vCJD cases	Estimated vCJD prevalence relative to the UK	Estimated log10 reduction in prevalence relative to UK
Canada	32.9	1	0	-	-
France	63.4	23	22	12.9%	0.9
Ireland	4.3	4	2	17.3%	0.8
Italy	59.1	1	1	0.6%	2.2
Japan	127.4	1	1	0.3%	2.5
Netherlands	16.4	2	2	4.6%	1.3
Portugal	10.6	2	2	7.0%	1.2
Saudi Arabia	27.6	1	1	1.4%	1.9
Spain	44.5	3	3	2.5%	1.6
U.K	60.8	163	163	100%	0
U.S	301.1	3	0	-	-

For countries that have confirmed indigenous cases of vCJD, we propose that the prevalence of vCJD in a given country (country A) with respect to the UK

¹⁰ <http://www.eurocjd.ed.ac.uk/vcjdworldeuro.htm>

(P^1_A) is estimated from the number of confirmed indigenous cases per head of population (N_A) in the country relative to the UK (N_{UK}). In other words,

Methodology 1:

$$\text{vCJD prevalence of country A (relative to UK)} = P^1_A = N_A / N_{UK} \quad (1)$$

The estimated vCJD prevalence relative to the UK (calculated using equation 1) is listed for each country in Table 10, expressed in terms of both a percentage and the equivalent log₁₀ reduction. However, for countries that have had no confirmed cases of vCJD to date, we propose an alternative methodology (outlined below) based on relative BSE incidence.

5.4 BSE incidence based methodology

The primary route by which blood donors could be infected with vCJD is by eating BSE infected beef. Given the probable incubation period of the disease an assessment of the risk of BSE in the food supply is relevant. We propose that a country-dependent vCJD risk assessment methodology, that is based on BSE incidence, should consider the number of BSE cases in the given country – not just at present, but since the start of the epidemic.

The World Organisation for Animal Health (OIE) has monitored the reported annual incidence of clinical cases of BSE since 1989¹¹ (more specifically, they measure the annual number of indigenous BSE cases per million bovines over the age of 24 months). In many countries there is a sharp increase in recorded clinical cases from 2001 onwards, which is in part due to the improvement of surveillance. It is important to note that the OIE figures are reported and confirmed cases of clinical BSE, and therefore inherently reflect the quality of the surveillance, which may vary quite significantly between countries (this was certainly the case in the past, less so within the E.U. at present). In section 5.5 we address this issue by adjusting BSE incidence for surveillance. The OIE classifies the cattle population of countries as either (1) a negligible BSE risk, (2) a controlled BSE risk, or (3) an undetermined BSE risk. These classifications were recently updated at the 76th General Session of the International Committee of the OIE in May 2008.

One mechanism for determining the relative prevalence of vCJD in source countries is to compare the rate of BSE incidence (I_A) for the country in question (country A) to the level of BSE incidence recorded for the UK over the same period (I_{UK}), i.e.

Methodology 2a:

$$\text{vCJD prevalence of country A (relative to UK)} = P^{2a}_A = I_A / I_{UK}, \quad (2)$$
 where I_A is based on OIE figures for BSE cases per million bovine.

Alternatively, rather than using the OIE figures for BSE cases per million bovine, one can also use the total number of positive BSE tests per head of

¹¹ http://www.oie.int/eng/info/en_esbincidence.htm

human population as a measure of relative BSE incidence between source countries (e.g. in the work of Svae *et al.*¹² discussed below);

Methodology 2b:

$$\text{vCJD prevalence of country A (relative to UK)} = P_{A}^{2b} = I_{A} / I_{UK}, \quad (3)$$

where I_{A} is the total number of positive BSE tests per human population.

However, it is worth noting again that these incidence figures also reflect the quality of surveillance, which may vary (at least historically) quite significantly between countries. This issue is addressed in section 5.5 below.

5.5 Adjustment factor: Under-ascertainment of clinical cases of BSE

Whilst the BSE incidence data is highly indicative of the risk of BSE in a given country, there is still a question over the possibility of under-ascertainment of clinical cases, which may vary quite significantly from country to country. In this section, we present two possible methodologies for estimating an under-ascertainment adjustment factor (UAF_{A}) that takes into account the relative under-ascertainment of clinical cases for a given country with respect to the UK. This can then be combined with either of the methodologies discussed in section 5.4 above for estimating the relative vCJD prevalence of a given country with respect to the UK.

Methodology 2a (adjusted for under-ascertainment of clinical cases of BSE):

$$\text{vCJD prevalence of country A (relative to UK)} \\ = P_{A}^{2a,UAF} = (1+UAF_{A})/(1+UAF_{UK}) * P_{A}^{2a} = (1+UAF_{A})/(1+UAF_{UK}) * I_{A} / I_{UK} \quad (4)$$

Methodology 2b (adjusted for under-ascertainment of clinical cases of BSE):

$$\text{vCJD prevalence of country A (relative to UK)} \\ = P_{A}^{2b,UAF} = (1+UAF_{A})/(1+UAF_{UK}) * P_{A}^{2b} = (1+UAF_{A})/(1+UAF_{UK}) * I_{A} / I_{UK} \quad (5)$$

An EU requirement that all cattle over thirty months old (OTM) slaughtered for consumption must be tested for the presence of BSE infectivity has resulted in the establishment of screening programmes across Europe. These active surveillance programmes have identified test-positives among apparently healthy animals (subject to normal slaughter) in a number of countries, to varying degrees. The OTM surveys represent an independent dataset from the official OIE BSE incidence rates, allowing under-ascertainment of BSE cases to be examined. In a paper by Donnelly *et al.*¹³, the per-head incidence of infection in cattle born between 1993 and 1997 in a number of European Union countries is estimated using the OTM surveys. The authors estimate per-head incidence of infection in EU countries for the 1994, 1995, 1996 and

¹² "Prion safety of transfusion plasma and plasma-derivatives typically used for prophylactic treatment", Tor-Einar Svae, Andrea Neisser-Svae, Andrew Bailey, Herwig Reichl, Lothar Biesert, Torben Schmidt, Andrea Heger and Jurgen Romisch, *Transfusion and Apheresis Science* (2008) **39**, 59–67.

¹³ "Implications of BSE infection screening data for the scale of the British BSE epidemic and current European infection levels", Christl A. Donnelly, Neil M. Ferguson, Azra C. Ghani and Roy M. Anderson, *Proc. R. Soc. Lond. B* (2002) **269**, 2179–2190.

1997 birth cohorts using back-calculation analysis on testing data from the period January to October 2001. As anticipated on the basis of the incidence of confirmed clinical cases, the infection incidence in the 1994 and 1995 cohorts was highest in UK, but the rates across Europe were more similar in the 1996 and 1997 cohorts.

Using a similar idea, we can compare the number of test positives for OTM cattle in a given EU country (T_A) with their respective official BSE incidence figures (I_A) over a given period. Note that, due to test sensitivity and specificity, we do not expect the number of test positives to be the same as the BSE incidence rates. Furthermore, we have not carried out the back-calculation analysis presented by Donnelly *et al.* in order to relate these test positives to the past infection incidence. However, comparing the ratio of the test positives to BSE incidence rate for a given country (R_A) to that of the UK (R_{UK}) gives an estimate of the under-ascertainment adjustment factor (UAF_A), which takes into account the relative under-ascertainment of clinical cases of country A relative to the UK.

Methodology (i):
 BSE under-ascertainment adjustment factor for country A

$$= UAF_A^i = R_A / R_{UK} = (T_A / I_A) / (T_{UK} / I_{UK}) = (T_A I_{UK}) / (T_{UK} I_A) \quad (6)$$

This can be combined with either methodology 2a or 2b (equations 4 or 5 respectively) to estimate the relative vCJD prevalence of a given country with respect to the UK.

Svae *et al.*¹⁴ present a potential epidemiological model for estimating the risk of vCJD-contaminated units of whole blood from countries within the EU. Their results show quite wide geographical variation, but for non-UK source countries they estimate a risk that is less than or equal to approximately 1 per 10 million donations. Put in context, this is equivalent or lower than the risk of human immunodeficiency virus with an extensive nucleic acid amplification screening of the donor population. The methodology of Svae *et al.* uses adjusted BSE incidence rates per head of human population (rather than per million bovine), where their adjustment is based on an estimated average ratio of sub-clinical to clinical BSE cases in the EU. They calculate the sub-clinical to clinical BSE ratio from the total number of BSE cases in the EU in 2005 identified by the active monitoring systems, relative to the total number of cases identified in the EU by passive surveillance (i.e. from the evaluation of reported BSE suspects). The authors use this ratio to adjust the BSE incidence numbers for the period up until 2000, arguing that the expanded EU BSE monitoring program started in 2001.

Using a similar idea, one can estimate the ratio of sub-clinical to clinical BSE cases (S_A) in a given country from the total number of BSE cases in that country in a given period identified by the active monitoring systems (IA_A),

¹⁴ “Prion safety of transfusion plasma and plasma-derivatives typically used for prophylactic treatment”, Tor-Einar Svae, Andrea Neisser-Svae, Andrew Bailey, Herwig Reichl, Lothar Biesert, Torben Schmidt, Andrea Heger and Jurgen Romisch, *Transfusion and Apheresis Science* (2008) **39**, 59–67.

relative to the total number of cases identified by passive surveillance (IP_A). Comparing this ratio for country A ($S_A=IA_A/IP_A$) to that of the UK ($S_{UK}=IA_{UK}/IP_{UK}$) gives an estimate of the under-ascertainment adjustment factor (UAF_A), which takes into account the relative under-ascertainment of clinical cases of country A relative to the UK.

Methodology (ii):

$$\begin{aligned} \text{BSE under-ascertainment adjustment factor for country A} &= UAF_A^{ii} \\ &= S_A / S_{UK} = (IA_A / IP_A) / (IA_{UK} / IP_{UK}) = (IA_A IP_{UK}) / (IA_{UK} IP_A) \end{aligned} \quad (7)$$

This factor may then be used with either methodology 2a or 2b (equations 4 or 5 respectively) to estimate the relative vCJD prevalence for a given country with respect to the UK. Note that methodology 2b, in which BSE incidence rates are based on the country's absolute number of positive tests per head of human population rather than the number of BSE positives per million cattle, more closely mirrors the work of Svae *et al.*

5.6 Adjustment factor: Imports of UK Beef

Whilst the prevalence of vCJD in a particular country is highly dependent on the prevalence of BSE infections in domestic cattle, it is also dependent on the amount of beef consumed in that country that originated from the UK. In this section we address this issue by proposing a UK beef adjustment factor (BAF_A) to account for significant imports of UK beef to the country being risk assessed (country A). This can then be combined with methodologies 2a or 2b to estimate the relative vCJD prevalence of a given country with respect to the UK.

Methodology 2a (adjusted for imports of UK beef):

$$\begin{aligned} \text{vCJD prevalence of country A (relative to UK)} \\ = P^{2a,BAF_A} &= BAF_A + (1 - BAF_A) * P^{2a} = BAF_A + (1 - BAF_A) * (I_A / I_{UK}) \end{aligned} \quad (8)$$

Methodology 2b (adjusted for imports of UK beef):

$$\begin{aligned} \text{vCJD prevalence of country A (relative to UK)} \\ = P^{2b,BAF_A} &= BAF_A + (1 - BAF_A) * P^{2b} = BAF_A + (1 - BAF_A) * (I'_A / I'_{UK}) \end{aligned} \quad (9)$$

The UK beef adjustment factor (BAF_A) can be calculated by comparing the average annual amount of UK beef imported to a given country for human consumption (B_A) between 1980 (the start of the BSE epidemic in the UK) and 1996 (start date of the British beef export ban) with the country's average annual total beef consumption (C_A) over the same period – effectively calculating a proxy for the proportion of beef consumed within that country over the period 1980 - 1996 that originated from the UK.

It should be noted that data availability and limitations may present difficulties in calculating this adjustment factor. In particular it may be difficult to ensure

that UK beef export figures only include beef that originated from the UK and not beef that was imported into the UK and then exported on. It may also be difficult to determine whether beef exported from the UK was for human consumption rather than for other purposes.

Methodology:

$$\text{UK beef adjustment factor for country A} = \text{BAF}_A = B_A / C_A \quad (10)$$

This adjustment factor can be combined with methodologies 2a or 2b (equations 8 or 9 respectively) to estimate the relative vCJD prevalence for a given country with respect to the UK.

It may be appropriate to use both the under-ascertainment adjustment factor (UAF) discussed in section 5.5 and the UK beef adjustment factor (BAF) discussed above. In this case methodologies 2a or 2b would first be adjusted for under-ascertainment (equations 4 and 5 respectively) and then adjusted for UK beef imports (equations 8 and 9 respectively).

6. Summary

Table 11 overleaf summarises each of the methodologies presented above, listing their main parameters and figure 2 sets out a flow diagram that can be used to determine which methodology should be used under given circumstances.

Table 11: Summary of the proposed risk assessment methodologies and their parameters

Methodology	Methodology based on (1) vCJD or (2) BSE incidence	BSE cases defined by (a) cases per million bovine or (b) test positives per human population	Under-ascertainment adjustment factor (UAF) based on (i) OTM test positives or (ii) active and passive surveillance test positives	UK beef imports adjustment factor (BAF) used?
P ¹	(1) vCJD	-	-	-
P ^{2a}	(2) BSE	(a)	-	-
P ^{2b}	(2) BSE	(b)	-	-
P ^{2a} with UAFi	(2) BSE	(a)	(UAFi)	-
P ^{2b} with UAFi	(2) BSE	(b)	(UAFi)	-
P ^{2a} with UAFii	(2) BSE	(a)	(UAFii)	-
P ^{2b} with UAFii	(2) BSE	(b)	(UAFii)	-
P ^{2a} with BAF	(2) BSE	(a)	-	(BAF)
P ^{2b} with BAF	(2) BSE	(b)	-	(BAF)
P ^{2a} with UAFi and BAF	(2) BSE	(a)	(UAFi)	(BAF)
P ^{2b} with UAFi and BAF	(2) BSE	(b)	(UAFi)	(BAF)
P ^{2a} with UAFii and BAF	(2) BSE	(a)	(UAFii)	(BAF)
P ^{2b} with UAFii and BAF	(2) BSE	(b)	(UAFii)	(BAF)

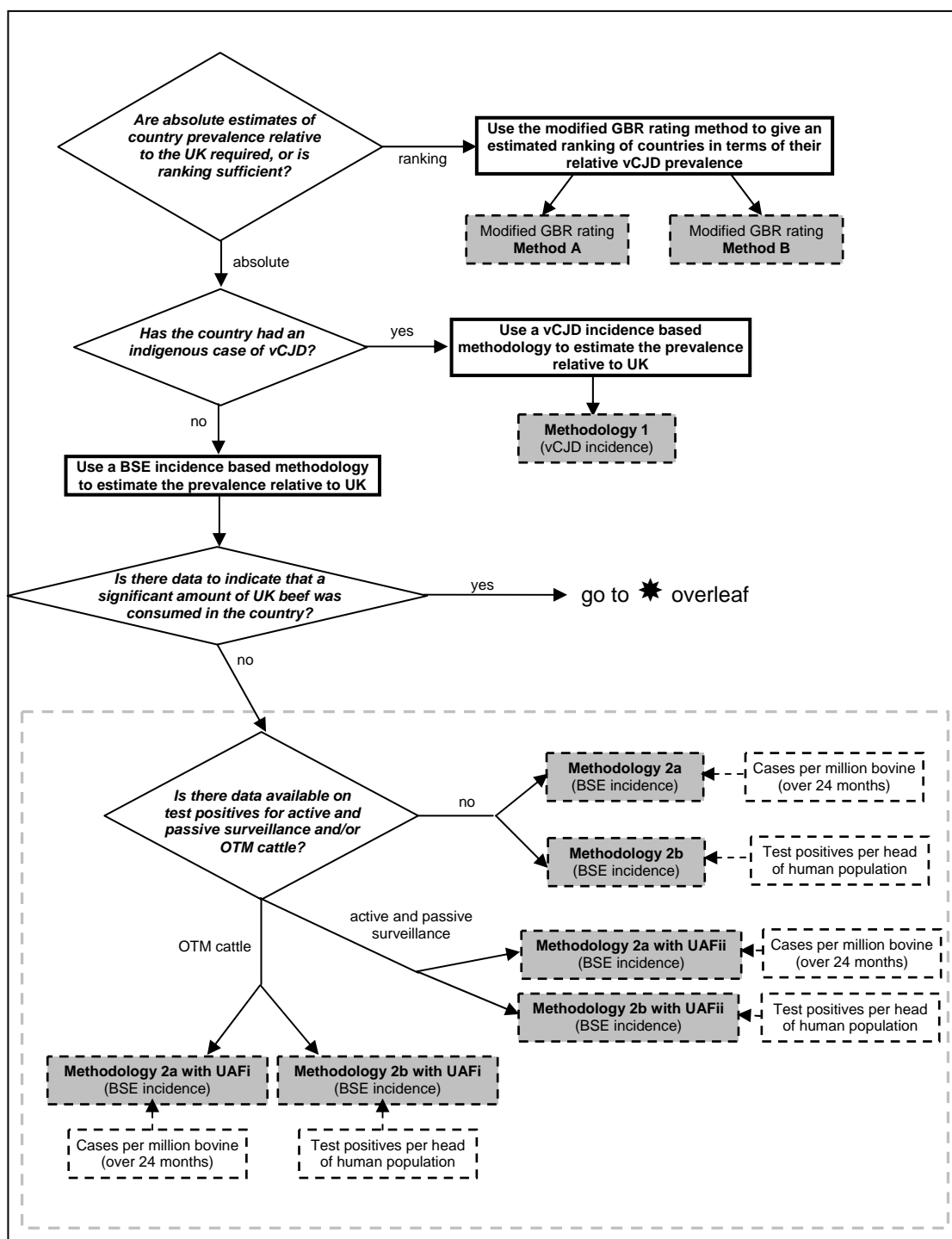


Figure 2: Flow diagram showing the decision path of the proposed risk assessment model (continued overleaf)

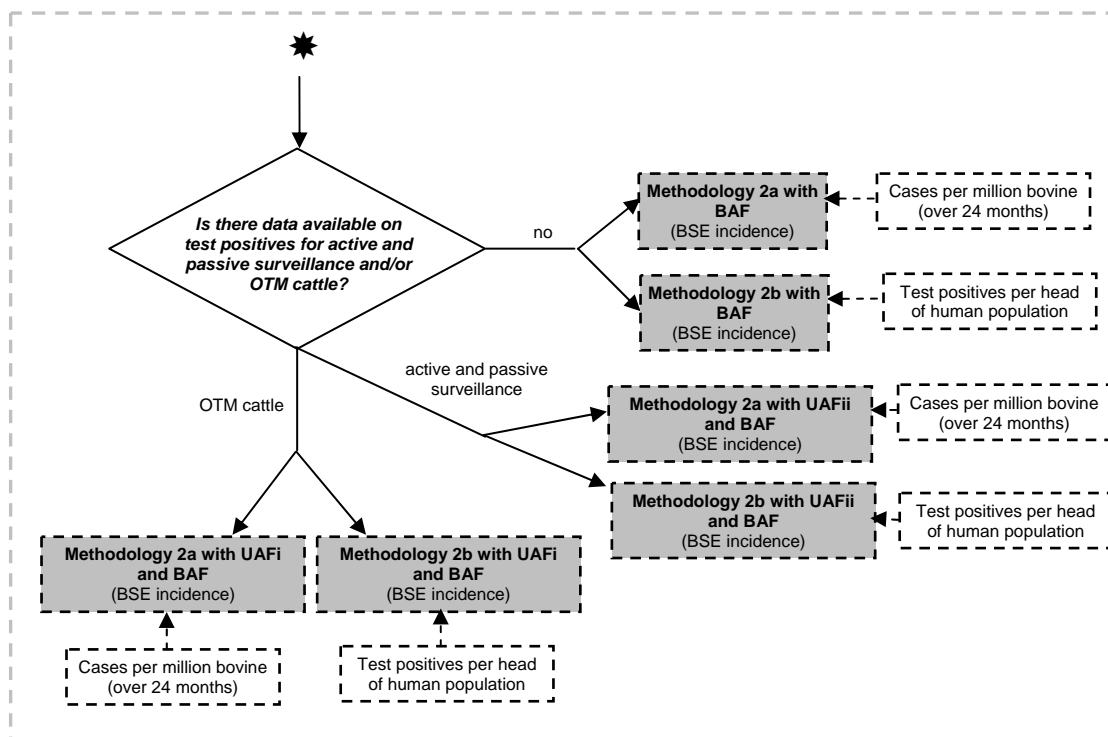


Figure 2: (continued)

In Appendix C we present example estimates for vCJD prevalence relative to the UK for a number of countries using each of the methodologies discussed above. These are provided as an illustration of the range of results obtained from the different methods and an indication of the order of magnitude of risk reduction derived from these methodologies.

Appendix A

The SEAC position statement on TSE infectivity in blood (SEAC, July 2006).

Issue

1.1. The UK blood services and Department of Health (DH) asked SEAC to consider data on the nature of transmissible spongiform encephalopathy (TSE) infectivity in blood and the implications for transmission of variant Creutzfeldt-Jakob disease (vCJD) via transfusion of blood products. The committee considered four specific issues:

- (i) the level of TSE infectivity in whole blood and the distribution of infectivity amongst individual components of blood,
- (ii) the change in the level of TSE infectivity in blood over the course of the incubation period of disease,
- (iii) the relative efficiencies of the intracranial (ic) and intravenous (iv) routes of inoculation,
- (iv) the dose-response relationship for TSE infection.

Background

2. Blood has been shown to carry TSE infectivity in a number of different animal models ¹⁻⁴. Three cases of probable vCJD transmission via transfusion of non-leucodepleted red blood cells provide strong evidence that blood from humans infected with vCJD can carry the infectious agent during the pre-clinical stage of the disease ⁵⁻⁷.

3. Precautionary measures, including leucodepletion and importation of fresh frozen plasma for children, have been implemented by the UK blood services to reduce the risk of vCJD transmission via blood transfusion. Additional blood processing technologies that may further reduce transmission risks are under consideration. Assessment of the potential effectiveness of new technologies relies on assumptions about the nature of the infectivity in blood, particularly the level and distribution of vCJD infectivity in blood components. However, there is much uncertainty about the nature, level and distribution of infectivity in blood. An assessment produced by Det Norske Veritas Consulting (DNV) and reviewed by SEAC provides a working model for the level of vCJD infectivity in blood and the distribution of infectivity between blood components ⁸.

4. At SEAC 92, SEAC reassessed some of the assumptions in the DNV risk assessment by consideration of recent published literature and unpublished data presented by a number of researchers ⁹⁻¹³. Many of the available data were derived from animal studies that have used prion strains, inocula and routes of administration that may not be directly applicable to the human blood transfusion situation. Most of the data are from studies of infectivity in hamster blood infected with hamster scrapie ^{3,10,13,14} and mice infected with mouse adapted vCJD ². Many of the hamster studies have not yet been published and therefore, have not been subject to the usual peer review process. Extrapolation of data from studies of hamster scrapie to vCJD is complicated by differences in the pathogenesis of these diseases, particularly

the low level of lymphoreticular system (LRS) involvement in the pathogenesis of hamster scrapie in contrast to vCJD. Limited data, that may be more relevant, are available from ongoing studies of the infectivity in the blood of sheep experimentally infected with BSE or scrapie as the pathogenesis of these diseases involve the LRS in this model ¹¹.

Level of TSE infectivity in whole blood

5. The levels of infectivity reported in rodent studies to examine the infectivity in blood of animals with TSEs vary widely, ranging from about one to 300 infectious doses*(ID)/mL of blood. One large unpublished study ¹⁰ involving a series of experiments to measure the infectivity in samples of pooled blood from large groups of hamsters with hamster scrapie suggests a mean level of infectivity of around 10 ID/mL of blood (range of two to 24 ID/mL of blood). In a published study, levels of mouse adapted vCJD infectivity within this lower range were found in blood components from mice at late pre-clinical or clinical stages of infection ². There are no data on the infectivity in the blood of humans with vCJD to assess the relevance of these data to humans.

Origin of blood infectivity

6. The source of infectivity in blood is not understood. Unpublished comparisons of the infectivity in blood from intact and splenectomised hamsters suggest that the spleen is not the source of infectivity in blood ¹⁰. Unpublished comparisons ¹⁰ of the rate of increase of infectivity in pooled blood and brain from infected hamsters during the incubation period of hamster scrapie suggest that it is not the result of leakage from the central nervous system (CNS) into the blood supply ¹⁰. However, a single published study that measured abnormal prion protein (PrP_{Sc}) in the buffy coat (white blood cells and platelets) from single hamsters infected with hamster scrapie suggests that PrP_{Sc} concentrations in blood are bimodal with a peak in the pre-clinical phase from peripheral replication in the spleen and other lymphoid tissues, followed by a larger rise in PrP_{Sc} concentrations leading into the clinical stage of the disease from leakage from the CNS ¹³.

Distribution of infectivity in blood components

7. Published and unpublished data from studies of the infectivity in components of blood from hamsters with hamster scrapie show that around one half of the infectivity in blood can be removed by depleting blood of white blood cells ³, and that the infectivity associated with the white blood cells can be substantially depleted by extensive washing ¹⁰. In addition, infectivity is not, or is minimally, associated with platelets ¹⁴ or red blood cells ¹⁰. These data suggest, at least in this model of TSE infection, that infectivity may be distributed equally between plasma and white blood cells but is weakly bound to white blood cells. Data from published experiments to measure mouse adapted vCJD infectivity in components of blood taken at the late pre-clinical or clinical stages of disease also suggest that infectivity is principally associated with plasma and white blood cells, minimally associated with red blood cells but that there may be some association with platelets ². The buffy coat from sheep with scrapie or BSE has also been shown to transmit

infection by transfusion to healthy recipient sheep ^{1,11}. It is possible that there are inter-species and inter-strain differences in the distribution of TSE infectivity in blood components. Therefore, additional research to examine the infectivity in blood components, particularly from models using TSE strains closely related to vCJD, will allow assessment of the relevance of these data to humans infected with vCJD.

Change of infectivity during the incubation period

8. A number of studies in animals have examined the level of infectivity in blood during both the pre-clinical and clinical stages of TSE infection ^{2,9,11}. An unpublished study ¹⁰ examined the infectivity in the blood of hamsters after ic inoculation with hamster scrapie at a number of time points during the preclinical stage of infection. Infectivity was first detected at the mid-point of the incubation period with the level of infectivity increasing linearly towards the clinical stage of infection. Extrapolation of these data suggests infectivity may first appear in blood at around a third of the way into the incubation period. Similar findings were obtained when the experiment was repeated using oral inoculation. Although the relationship between PrP_{Sc} and infectivity is unclear, PrP_{Sc} concentrations in the blood of hamsters infected with hamster scrapie show a bimodal profile (as described in paragraph 7) ¹³. Studies of mouse adapted vCJD ^{2,9} and sheep infected with scrapie or BSE ^{1,11} only examined the level of infectivity at one point during the preclinical stage of infection but show that blood is infectious during the second half of the incubation period. Two cases of probable blood transfusion associated transmission of vCJD from blood donors 20 months ⁵ and 3.5 years ⁷ prior to the onset of disease have been identified, indicating that human blood can be infectious in the preclinical phase. More extensive data, particularly from models using TSE strains closely related to vCJD, will inform on the relevance of the findings in the hamster scrapie model to changes in infectivity in the incubation period of vCJD in humans.

Relative efficiency of the ic and iv routes of transmission

9. The efficiency of transmission varies depending on the route of administration, host, TSE strain, source of inoculum and how it is prepared. Most measurements of TSE infectivity are derived from bioassays using the ic route of administration. Since the efficiencies of the ic and iv routes of transmission may not be equivalent, the infectivity of an inoculum measured by the ic route may not reflect the infectivity of the same inoculum administered by the iv route, this latter route being the most relevant to blood transfusion. A small number of studies using different animal models have compared the infectivity of brain homogenate or purified blood components administered by the ic or iv routes. These studies suggest that the efficiency of transmission by the iv route is between 10% and 100% of the efficiency of ic route ^{2,4,9,14,15}. One unpublished study ¹⁰, comparing the efficiency of iv transfusion of intact whole blood and ic inoculation of sonicated whole blood from hamsters with hamster scrapie showed the iv route to be considerably less efficient than suggested by this range. In addition, a published study ² showed that mouse adapted vCJD could be transmitted equally efficiently from inoculation of buffy coat from infected animals by the ic or iv routes but

the transmission efficiency from inoculation of plasma was lower by the iv compared with the ic route. These studies suggest that the form of inoculum may strongly influence the relative transmission efficiencies of inoculation by different routes.

Dose-response relationship

10. Evidence from animal studies ¹⁰ suggests that TSE infectivity is quantal in nature. An infectious dose diluted by distribution to a number of individuals reduces the risk of transmission to an individual. However, at the population level, one of the exposed individuals would be still be expected to become infected. Higher doses split between individuals would lead to more than one infection. The implication of this relationship between dose and probability of infection for strategies to reduce the public health risks in relation to blood transfusion is that pooling blood to dilute infectivity does not decrease the risks to public health. Indeed, depending on the dose, pooling is likely to increase the risks to public health. Strategies to remove or inactivate infectivity in blood would reduce the risks of transmission to both the individual and at the population level.

Conclusions

11. The available data show that blood is infectious during the preclinical stage of vCJD. Although the precise time in the incubation period of vCJD at which blood becomes infectious is unclear, data from animal models suggests it may be infectious from at least, if not before, the middle of the incubation period. The source of infectivity in blood is not understood. Data from rodent studies suggests that infectivity in whole blood is around 10 ID/mL and that it mostly resides in the plasma and white blood cell components with infectivity associated with white blood cells substantially depleted by extensive washing. However, additional information from other animal models is required to assess whether these findings may be closely representative of vCJD infectivity in human blood. It is clear that an infectious dose in blood can be disseminated but not diluted by distribution to a large number of recipients. Consequently, pooling of potentially infectious material, or in other ways disseminating infectious material between a number of recipients, will not reduce the number of people infected, and is likely to increase the number of people infected.

SEAC
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Appendix B

This provides a summary of the GBR rating for a large range of countries, alongside their adjusted GBR rating as calculated using methods A and B discussed in section 5.2.

Country	GBR rating	Modified GBR rating (Method A)	Modified GBR rating (Method B)
Australia	I (2000)	1	2
Austria	III (2002)	1	1
Belgium	III (2000)	4	3
Canada	III (2004)	5	5
Denmark	III (2000)	3	2
Finland	III (2002)	1	1
France	III (2000)	4	3
Germany	III (2000)	4	3
Ireland	III (2000)	3	2
Italy	III (2000)	4	3
Netherlands	III (2000)	4	3
New Zealand	I (2005)	1	3
Norway	II (2005)	1	1
Poland	III (2001)	5	4
Portugal	IV (2000)	5	3
Spain	III (2000)	5	3
Sweden	II (2004)	1	1
Switzerland	III (2001)	3	2
U.K	IV (2000)	5	3
U.S	III (2004)	5	5

The BSE 'stability' and 'challenge' in various countries between 1980 and 1999, as determined by the SSC/EFSA assessment.

Country		1980	1985	1990	1995	1999	Most recent SSC/EFSA assessment	Modified GBR rating - method A	Modified GBR rating - method B
Australia	Stability	-2	-2	-3	-2	-2	-2	1	2
	Challenge	-2	-2	-1	-3	-3	-3		
Austria	Stability	-1	-1	-1	0	0	3	1	1
	Challenge	-3	-3	0	-1	-2	-2		
Belgium	Stability	-3	-3	-3	-2	1	1	4	3
	Challenge	-3	1	2	2	2	2		
Canada	Stability	-3	-3	-3	-2	-2	-3	5	5
	Challenge	-2	-2	-1	-1	-1	2		
Denmark	Stability	?	-3	-3	0	2	2	3	2
	Challenge	?	-1	0	1	1	1		
Finland	Stability	-2	-2	-1	0	1	3	1	1
	Challenge	-1	-1	0	0	-1	-1		

France	Stability	-3	-3	-2	-1	2	2	4	3
	Challenge	?	1	3	3	2	2		
Germany	Stability	-2	-2	-2	-1	0	0	4	3
	Challenge	-1	1	2	2	2	2		
Ireland	Stability	-3	-3	-2	-2	3	3	3	2
	Challenge	-3	0	2	3	2	2		
Italy	Stability	-2	-2	-2	-1	0	0	4	3
	Challenge	1	1	2	3	2	2		
Netherlands	Stability	-2	-2	-2	0	1.5	1.5	4	3
	Challenge	1	1	2	3	2	2		
New Zealand	Stability	-3	-3	-3	-3	-2	-3	1	3
	Challenge	-3	-3	-3	-3	-3	-3		
Norway	Stability	-3	-3	0	1	2	3	1	1
	Challenge	-3	-3	-3	-3	-3	-2		
Poland	Stability	-2	-2	-2	-2	-2	-2	5	4
	Challenge	-3	-2	1	2	2	2		
Portugal	Stability	?	-3	-3	-2	1.5	1.5	5	3
	Challenge	?	1	2.5	3	3	3		
Spain	Stability	?	-3	-3	-1.5	0	0	5	3
	Challenge	?	-1	2	2	2	2		
Sweden	Stability	-3	-2	-2	0	1	3	1	1
	Challenge	-2	-2	0	0	-1	-1		
Switzerland	Stability	-3	-3	-1	2	3	3	3	2
	Challenge	?	0	3	3	1	1		
UK	Stability	-3	-3	1	1	3	3	5	3
	Challenge	0	2.5	3	3	3	3		
US	Stability	-3	-3	-3	-2	-2	-3	5	5
	Challenge	-3	0	0	-1	-1	2		

Stability: -3=extremely unstable; -2=very unstable; -1=unstable; 0=neutral;

1=stable; 2=very stable; 3=optimally stable

Challenge: -3=negligible; -2=very low; -1=low; 0=moderate; 1=high; 2=very high; 3=extremely high

Rating: 1=very low; 2=low; 3=moderate; 4=high; 5=very high

The table also shows the modified GBR rating based on the stability and challenge, determined by the two different methods described in section 5.2.

Appendix C

Table 12 below provides a summary of the estimated vCJD prevalence for a number of potential source countries, expressed as a log reduction with respect to the UK for each of the potential methodologies discussed in Part III of this paper. These estimates are provided as an illustration of the range of results obtained from the different methods and an indication of the order of magnitude of risk reduction derived from these methodologies. Table 13 summarises each of the methodologies listing their main parameters.

Table 12

Country	Estimated log reduction in prevalence relative to UK												
	P ¹	P ^{2a}	P ^{2b}	P ^{2a}	P ^{2b}	P ^{2a}	P ^{2b}	P ^{2a}	P ^{2b}	P ^{2a}	P ^{2b}	P ^{2a}	P ^{2b}
	no UAF			with UAFi		with UAFii		no UAF		with UAFi		with UAFii	
	no BAF							with BAF					
Australia	-	'Infinite'	-	-	-	-	-	4.1	-	-	-	-	-
Austria	-	3.8	3.9	2.8	3.0	4.1	4.2	2.9	2.9	2.6	2.7	2.9	2.9
Belgium	-	2.6	2.4	1.8	1.6	2.8	2.6	2.6	2.4	1.8	1.6	2.8	2.6
Canada	-	4.6	4.5	-	-	-	-	4.2	4.2	-	-	-	-
Denmark	-	3.3	3.1	2.8	2.5	3.6	3.4	2.0	2.0	1.9	1.9	2.0	2.0
Finland	-	4.1	4.2	4.4	4.5	4.4	4.5	3.5	3.5	3.6	3.6	3.6	3.6
France	0.9	2.7	2.3	2.1	1.7	2.4	2.0	1.2	1.2	1.1	1.1	1.2	1.1
Germany	-	2.7	4.3	2.4	4.0	3.0	4.6	2.0	2.1	1.9	2.1	2.1	2.1
Ireland	0.8	1.9	0.9	1.6	0.6	1.8	0.9	0.7	0.6	0.7	0.4	0.7	0.5
Italy	2.2	2.9	3.1	1.9	2.1	3.2	3.4	2.1	2.2	1.7	1.9	2.2	2.2
Netherlands	1.3	2.9	2.8	2.2	2.1	3.2	3.1	1.6	1.6	1.5	1.5	1.6	1.6
New Zealand	-	'Infinite'	-	-	-	-	-	4.3	-	-	-	-	-
Norway	-	'Infinite'	-	'Infinite'	-	'Infinite'	'Infinite'	3.2	-	3.2	-	3.2	-
Poland	-	3.7	3.5	3.2	3.0	4.0	3.8	3.6	3.4	3.2	2.9	3.8	3.6
Portugal	1.2	1.4	1.5	0.4	0.5	0.9	1.0	1.4	1.5	0.4	0.5	0.9	1.0
Spain	1.6	2.3	2.3	1.4	1.4	2.3	2.4	2.1	2.1	1.3	1.4	2.1	2.2
Sweden	-	5.2	-	5.5	-	5.5	-	3.2	-	3.2	-	3.2	-
Switzerland	-	1.9	1.7	-	-	-	-	1.9	1.7	-	-	-	-
UK	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
U.S	-	5.2	6.0	-	-	-	-	4.9	5.1	-	-	-	-

Table 13: Summary of the proposed risk assessment methodologies

Methodology	Methodology based on (1) vCJD or (2) BSE incidence	BSE cases defined by (a) cases per million bovine or (b) test positives per human population	Under-ascertainment adjustment factor (UAF) based on (i) OTM test positives or (ii) active and passive surveillance test positives	UK beef imports adjustment factor (BAF) used?
P ¹	(1) vCJD	-	-	-
P ^{2a}	(2) BSE	(a)	-	-
P ^{2b}	(2) BSE	(b)	-	-
P ^{2a} with UAFi	(2) BSE	(a)	(UAFi)	-
P ^{2b} with UAFi	(2) BSE	(b)	(UAFi)	-
P ^{2a} with UAFii	(2) BSE	(a)	(UAFii)	-
P ^{2b} with UAFii	(2) BSE	(b)	(UAFii)	-
P ^{2a} with BAF	(2) BSE	(a)	-	(BAF)
P ^{2b} with BAF	(2) BSE	(b)	-	(BAF)
P ^{2a} with UAFi and BAF	(2) BSE	(a)	(UAFi)	(BAF)
P ^{2b} with UAFi and BAF	(2) BSE	(b)	(UAFi)	(BAF)
P ^{2a} with UAFii and BAF	(2) BSE	(a)	(UAFii)	(BAF)
P ^{2b} with UAFii and BAF	(2) BSE	(b)	(UAFii)	(BAF)

