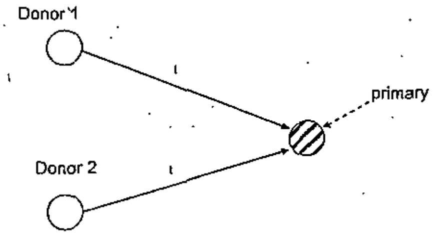
Method

7. The following analysis starts from the "reverse risk assessment" previously used by the Panel to assess the implied risks of donors to vCJD clinical cases being infected (DH, 2005a; Bennett, Dobra and Gronlund, 2006), and extends it to deal with this much more complex incident. We start with a simple example and then build up the analysis step-by-step. This is both to demonstrate how the conclusions are reached in this case, and to show how the same approach can be used to handle other complex incidents that may arise.

Example 1

8. We therefore start with a simple incident as shown in Figure 1(a). Here, a patient has received two single-unit Red Cell transfusions, one from each of two donors. The recipient goes on to develop vCJD, and the timing of the transfusions does not rule either of the donors out as the route of infection. What is the chance of each of these donors carrying vCJD infection?

Figure 1 (a) Two component donors, neither known to be infected



9. The answer to this depends primarily on the chance of transmission occurring *if* one of the donors were to be infected – i.e. the transmission probability, t. By definition, this lies between 0 and 1: if t = 1, transmission would be certain. In that case, and all else being equal[1], the patient's disease would be equally likely to have come from primary infection, or from either of the two donors having been infected. So by implication, each donor would have a 1 in 3 chance of being

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[1] "All else being equal" essentially means that there is no prior reason to suppose that donors or recipient were particularly likely or unlikely to have been infected with vCJD, e.g. through "high risk" surgery, or conversely not having lived in the UK during years of high BSE exposure.

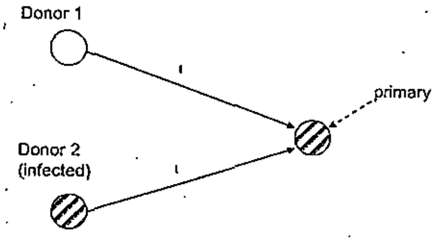
infective.[2] More generally, if there are n donors, the chance of each being infective would be $1/(n+1)$.

10. The implied risks to the donors clearly diminish if $t < 1$. However, the CJD Incidents Panel has used a precautionary approach, concentrating on scenarios in which t is at least 0.5. With t in this range, the implied risk to donors remains high unless the number of donors to the vCJD case is large. For example, if $t = 0.5$, then with two donors the chance of either being infected would be roughly 0.25. Note that none of these calculations depend on the underlying prevalence of infection, provided this is the same for donors and recipients.

Example 2

11. The situation would clearly be very different if one of the donors was later diagnosed with vCJD, as in Figure 1(b).

Figure 1 (b) Two component donors, one known to be infected



This creates a marked asymmetry between the infection routes, dependent on the prevalence of infection in the donor population. Whilst Donor 2 is now known to be infected, Donor 1's prior probability of infection is simply the prevalence of infection (p), unknown but assumed to be small. This situation provides an exemplar for analyses in which some routes are prevalence-dependent and others are not.

Let:

$P(D1)$ be the probability of the recipient's infection having come via Donor 1

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[2] The arguments expressed here can be expressed more formally using Bayes' Theorem to update probabilities in the light of new information. However, this is presentationally more clumsy, especially in the more complex examples considered below.

P(D2) be that of the infection having come via Donor 2

and P(prim) be the probability of the recipient having a primary infection

- For simplicity, suppose that the chance of the patient being infected by more than one route is negligible. Then (given that infection has occurred) P(D1), P(D2) and P(prim) must add up to 1.
- Furthermore, the "balance" between the three probabilities will be governed by t and p. Specifically:
    - P(D1) will be proportional to both p (prevalence of infection) and t (transmission probability)
    - P(D2) will only be proportional to t
    - and P(prim) will only be proportional to p

12. Provided p is small (e.g. 1/4,000 or 1/10,000) and t is not, P(D2) will be *much* larger than either of the other two probabilities. To a very close approximation, P(D2) = 1 and P(D1) and P(prim) are zero. We can be virtually certain that the infection came from Donor 2. In practical terms, this new information about Donor 2 means that Donor 1 need not be considered as "at risk" according to CJD Incidents Panel criteria.

Example 3

13. In the last two examples, the two secondary routes had the same transmission probability, t. But suppose now that there are routes with different values of t – e.g. transfusion of blood components and receipt of fractionated blood products. Figure 2 below shows a situation in which the calculations need to balance two contrasting secondary routes:

    - a blood component transfusion, associated with a high transmission probability (t_1) *if* the donor (D1) is infected, but with no reason to believe that this is the case, and

    - a plasma product pool with a contributing donor (D2) now known to be infected , but with a low transmission probability (t_2)

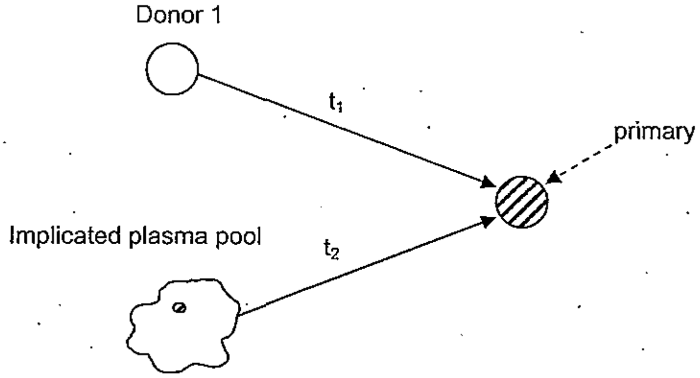
    As before, the three probabilities P(D1), P(D2) and P(prim) must add up to 1, and now:

    - P(D1) will be proportional to p and t_1

    - P(D2) will be proportional to t_2

    - and P(prim) will be proportional to p

Figure 2: One component donor, not known to be infected: plasma pool, containing an implicated donation



14. To illustrate numerically, suppose p is 10^{-4} i.e. prevalence of infection is 1 in 10,000, that $t_1 = 1$ and $t_2 = 10^{-3}$ (that is, transmission via the product pool is less efficient than via the transfused component by a factor of 1,000).

    In that case, it can be shown that:

    $P(D1) = 1/12$ $P(D2) = 10/12$ and $P(prim) = 1/12$

    The infected plasma pool is thus clearly the most likely transmission route, by a factor of 10 over each of the other two possibilities.

15. The principles used to analyse these simple cases are now extended to consider the case of the haemophilic patient with a finding of abnormal prion protein in the spleen.

Analysis

16. Potential secondary transmission routes in this instance consisted of the following (where an "implicated" donor means one for which there is now evidence of having been infected with vCJD):

    - 5 invasive endoscopic procedures (biopsies) and a larger number of endoscopies without biopsy.
    - exposure to 14 units of Red Cells, each from different ("non-implicated") donors
    - exposure to just over 9,000 units of Factor VIII made from two plasma pools with an "implicated" contributing donor (8,025 units from one batch and 1,000 from the other)

- exposure to many other units of UK-sourced pooled products, including nearly 400,000 units of Factor VIII, with no *known* links to "implicated" donors

To simplify the subsequent discussion, we consider the relative risks from each of these routes in turn.

Transmission risks from the endoscopies

17. vCJD transmission risks from endoscopy have been examined by an ACDP TSE WG subgroup, informed by an outline risk assessment. It is important to appreciate that these procedures involve a very small instrument (head) being passed down a very long, thin, channel. The possible "mechanics" of infection therefore differs from other surgical procedures. The group considered that any significant risk of onward transfer of infective material to a receptive site would require the procedure to be invasive, as distinct from examinations that involve the instrument sliding against the wall of the gut. On that argument, the relative risk from endoscopic procedures *not* involving biopsy would be negligible.

18. So concentrating on procedures involving biopsy, the question arises of whether the heads used would have been single-use. This would reduce the transmission risks considerably, but not eliminate them (due to the possibility of the new head being contaminated on its way down the endoscopy channel. Although we do not know whether the heads involved in these procedures were single-use, let us suppose they were not.

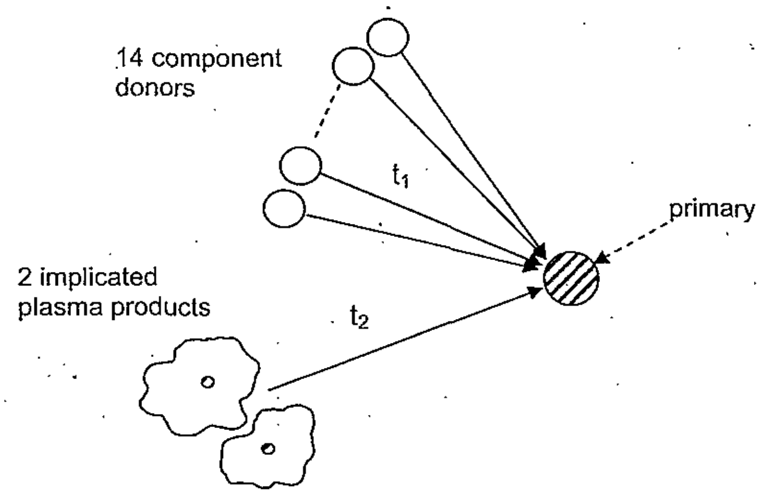
19. For endoscopy with re-useable heads, the best existing analogy is with the current surgical risk assessment as applied to procedures encountering lymphoid tissue. Depending on assumptions on the efficacy of decontamination, the "standard" model suggests that indefinite re-use of a set of instruments might cause 1 – 10 secondary infections per operation on an infective patient. The infection risk to a random patient resulting from all previous re-uses of the instruments would be in the same range multiplied by the prevalence of infection (p). However, the surgical model considers the transmission risks from a set of 20 instruments, rather than just one (very small) biopsy head. For the latter, it therefore seems reasonable to reduce the estimated risk by a factor of at least 10. Even on pessimistic assumptions, therefore, the risk of infection from a "random" biopsy would be in the range (0.1 – 1)p. In other words, the chance of the patient being infected via any of 5 such biopsies would be similar to the risk of having been infected through the "primary" route of dietary exposure.

20. As will be seen below, the chance of this particular patient having been infected by the primary route are very small (in all scenarios) as compared to that of infection through a blood-borne route. On the above argument, the same applies to the endoscopic route. For simplicity, this route will therefore be disregarded in the following calculations. It should be noted that even if the risks of transmission via endoscopy were much greater than suggested here, the only effect on subsequent calculations would be to reduce the probabilities associated with all the blood-borne routes slightly.

Blood components and "implicated" plasma products

21. We now consider the relative probability of the patient's infection having come from the implicated plasma products, versus the 14 Red Cell transfusions. As discussed in the "methods" section, we need to balance the greater transmission probability for blood components (Red Cells in this instance) against the existence of an implicated donor contributing to the pooled plasma products. The situation is shown schematically in Figure 3, omitting for now the other "non implicated" plasma products.

Figure 3: 14 component donors, none known to be infected; 2 plasma products, each from a pool containing an implicated donation



22. The key additional variable here is t_2 – the chance of transmission from an implicated pool. This can be quantified using the infectivity assumptions originally generated in DNV's risk assessment (DNV, 2003). As discussed further below, the calculations initially use the more pessimistic of alternative infectivity scenarios considered by DNV.

23. For the present, we also suppose that the *only* infected donation in the plasma pools came from the identified infected donor – though this is reconsidered below. As detailed in the first part of Annex A, calculations then suggest that this one infected donor would have resulted in the Factor VIII received by the patient containing a total infective dose of about 0.2 ID_{50} (0.16 via one pool and 0.05 via the other). Using the simple linear dose-response model that has informed Panel recommendations to date, this implies a transmission probability t_2 of approximately 0.1.

24. We can then use the approach set out before to assign probabilities to the possible infection routes in different scenarios. Table 1 below shows the results, using this value for t_2 and alternatives of 1 and 0.5 for t_1 and 1 in 4,000 and 1 in

10,000 for the prevalence, p. The successive rows show the probability of infection having come from the implicated plasma products, from any *one* of the 14 component (Red Cell) donors, and from the primary outbreak. It can be seen that in all scenarios, the first route strongly dominates. Note that these are illustrative figures, using assumptions subject to much uncertainty. Nevertheless, they do suggest that the infection is much more likely to have come from the plasma products, with the implied risk to the component donors remaining clearly below 1%.

Table 1: Relative probabilities of potential infection routes (omitting "non implicated plasma" products)

Prevalence, p	1 in 4,000		1 in 10,000	
Transmission probability, t1	0.5	1	0.5	1
Probability implicated plasma products	98%	97%	99%	99%
Probability of each of the 14 component donors	<0.3%	<0.3%	<0.1%	<0.1%
Probability primary	<0.3%	<0.3%	<0.1%	<0.1%

Note: these are illustrative calculations only. All figures are rounded to the nearest %, or (for small probabilities) indicate an upper bound.

Implicated and "Non-implicated" plasma products

25. Although the above analysis provides some robust conclusions about the infection routes considered so far, the calculations ignore one further factor: the chance of the infection having come from the "non-implicated" plasma products – i.e. those manufactured from plasma pools not *known to have* an infected contributing donor. The problem here is that because the pool sizes are so large (of the order of 20,000 donations each), there is a high probability that many of them did, in fact, contain infective donors even if one has not been identified. Crudely, if the prevalence were 1 in 10,000, one would expect each pool to contain about 2 infected donations.[3]

26. This argument does not entirely remove the distinction between implicated and non-implicated pools. Where there is known to be an infected contributing donor (and nothing is known about the rest), the other donors to that pool also have the same probability p of being infected. So with a prevalence of 1 in 10,000 and typical pool sizes of 20,000, one would reasonably expect a "non-implicated" pool to contain 2 infected donations and an "implicated" pool to contain 3. Nevertheless, this is not a great differential. The calculation suggests that unless the prevalence of infection is very low - much lower than considered here, there is only a modest difference in the risks posed by receipt of implicated and non-implicated plasma. This observation supports the existing policy of considering recipients of UK-sourced plasma products as a group, rather than

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[3] More strictly, the expected number of infected donations in each pool will be subject to a binomial distribution. However, the distribution is not essential to the argument, especially for patients receiving high volumes of product sourced from many different pools, when these statistical fluctuations will tend to even out.