vCJD Risk Assessment Calculations for a Patient with Multiple Routes of Exposure

Peter Bennett and Jenny Ball

Health Protection Analytical Team
Department of Health
Wellington House
133-155 Waterloo Road
London SE1 8UG

5th June 2009

Preface

This paper was developed in response to a request from the CJD Incidents Panel following the finding of abnormal prion protein in the spleen of a patient with haemophilia. Assuming that the abnormal protein represents a marker of vCJD infection, the paper sets the various possible routes through which such infection could have occurred, and considers their relative likelihood in various scenarios. As well as dealing with this specific “incident”, the paper sets out a more general methodology for assessing multiple possible infection routes. The analysis was considered by the Panel at its meeting on 20th May 2009, and informed the advice subsequently issued. This version of the paper repeats the analysis presented to the Panel, while giving slightly more background information for other readers, and is placed here for public record.
Introduction

1. This paper offers an analysis of the recent finding of abnormal prion protein in the spleen of a haemophilic. This involves a patient exposed to a large number of potential vCJD infection routes (including multiple blood component transfusions, repeated receipt of UK-sourced fractionated plasma products including some units linked to a donor who later went on to develop clinical vCJD, and several invasive biopsies) who was found post mortem to have abnormal prion protein in a spleen sample.

2. If this finding is interpreted as an instance of asymptomatic vCJD infection, this raises questions as to the operational meaning of the “prevalence” of infection. The discovery of abnormal protein in a single spleen sample was the only positive result after exhaustive investigation of tissues taken at autopsy of an elderly haemophilia patient who died of other causes with no symptoms of vCJD or other neurological condition. All other tissues from this patient tested for the presence of abnormal prion protein – fixed samples of brain, heart, liver, blood vessel, appendix, spleen and lymph node and frozen samples of frontal lobe, occipital lobe, cerebellum, lymph node and 23 other samples from the spleen – were negative. This individual would not have tested “positive” on any of the vCJD prevalence tests conducted so far, and possibly not even in a post mortem spleen survey (depending on the size of spleen sample used). Nor do we know whether someone with this limited distribution of abnormal prion protein would be infective - and if so, by what routes of transmission.

3. For present purposes, however, these issues of interpretation are ignored. We simply assume that the abnormal prion protein found in this patient is a marker for asymptomatic vCJD infection: the task is then to investigate the relative likelihood of the infection having come from the various possible routes. This is done in order to inform discussion by the CJD Incidents Panel (“the Panel”) as to the implications of the finding, and in particular whether the new evidence warrants any change to the “at risk” status of any individuals or groups.

4. The ideal would be to quantify these likelihoods in a robust way. However, this is not possible due to the multiple uncertainties involved. These are well-rehearsed. We do not know the prevalence of infectious donors – and in this instance, some of the potential routes are dependent on prevalence while others are not, so the relativities change. The probability of an infected blood component transmitting infection is uncertain - though on the precautionary approach adopted by the Panel, it is presumed to be substantial. The risks of an implicated plasma derivatives transmitting infection are even more uncertain. However, they can be estimated using methods suggested in an existing assessment by independent consultants DNV (DNV, 2003), which have been used in drawing up Panel recommendations to date. These calculations have also been regarded as “precautionary”, i.e. giving a pessimistic view of the levels of infectivity likely to be present.

5. Given these unknowns, we make no attempt at definitive probability calculations, though illustrative examples are provided. Instead, we concentrate on the more limited task of determining whether different groups in the complex chain of contacts associated with the index patient can be robustly placed under or above
the additional 1% (over the UK population risk derived from consumption of beef and beef products) “risk threshold” used by the CJD Incidents Panel to trigger decisions on notification of increased risk status. We also consider the wider implications for groups that are or might be classed as “at risk”. Although the analysis does throw some light on these questions, it also highlights some conundrums for our understanding of vCJD prevalence and transmissibility.

Summary of findings

6. Specifically, we conclude that on the evidence available:

(i) The chance of the patient having been infected via an endoscopic procedure is very small, probably comparable to that of having been infected via primary (dietary) exposure. The potential risk associated with the endoscopy can be disregarded in assessing the risks associated with the possible blood-borne transmission routes, and no specific action is called for with regard to other patients on whom those endoscopes may have been used.

(ii) Comparing the blood-borne routes, the patient is much more likely to have been infected through receipt of plasma products, rather than any of the 14 units of red cells known to have been received. The implied risk of each of these 14 donors being infected appears to lie below the 1% threshold that would trigger “at risk” status.

(iii) Given the large pool sizes involved (of the order of 20,000 donations per pool), the risk differential between “implicated” and “non-implicated” batches of blood product is not marked. Unless the prevalence of infection is very low, there is a strong possibility of any given batch of blood products prepared from large pools sourced from UK donors in the period 1980-2001 containing at least one infected donation. This reinforces the logic of the CJD Incidents Panel’s 2004 decision to consider all haemophilia and blood disorder patients exposed to such UK-sourced plasma products as an “at risk” group. There is no strong case for differentiating between sub-groups.

(iv) Given the precautionary assumptions in the DNV risk assessment, any patient exposed to substantial quantities of UK plasma product (as this haemophilia patient was) would almost certainly have received a substantial infective dose, whether or not any of the batches were “implicated” (i.e. traceable to a donor who later went on to develop clinical vCJD). In fact, this patient may have been more likely to have been infected by receipt of large quantities of “non-implicated” plasma, than by the smaller quantities of “implicated”.

(v) The lack of any clinical vCJD cases to date amongst patients with haemophilia may suggest that the DNV infectivity scenario is overly-pessimistic. Risk assessments carried out elsewhere assume that a greater proportion of the infectivity would be removed during the manufacturing processes. This raises issues beyond the scope of this paper. Nevertheless, we have re-run the analysis using a markedly lower infectivity assumption with regard to plasma products, and the conclusions listed in (ii) – (iv) above still hold.
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 equal¹, 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 infected.

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. 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](image)

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:

\[
P(D1) \text{ be the probability of the recipient’s infection having come via Donor 1}
\]

---

\(^2\) 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:
  o P(D1) will be proportional to both p (prevalence of infection) and t (transmission probability)
  o P(D2) will only be proportional to t
  o 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:
  o 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
  o 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:
  o P(D1) will be proportional to p and \( t_1 \)
  o P(D2) will be proportional to \( t_2 \)
  o and P(prim) will be proportional to p
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:

$$P(D1) = 1/12 \quad P(D2) = 10/12 \quad \text{and} \quad P(\text{prim}) = 1/12$$

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

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**

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)**

<table>
<thead>
<tr>
<th>Prevalence, ( p )</th>
<th>1 in 4,000</th>
<th>1 in 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission probability, ( t_1 )</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Probability implicated plasma products</td>
<td>98%</td>
<td>97%</td>
</tr>
<tr>
<td>Probability of each of the 14 component donors</td>
<td>&lt;0.3%</td>
<td>&lt;0.3%</td>
</tr>
<tr>
<td>Probability primary</td>
<td>&lt;0.3%</td>
<td>&lt;0.3%</td>
</tr>
</tbody>
</table>

*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

---

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.
applying additional measures to those with known exposure to implicated batches.

27. This specific haemophilia patient had received such large quantities of Factor VIII – almost 400,000 units, the majority since 1980] - that on these calculations, the cumulative risk from the “non-implicated” batches may well have exceeded that from the smaller number of “implicated” ones. This can be illustrated by considering the expected number of ID$_{50}$ received via each route. This is illustrated in the second part of Annex A. In summary:

- If the two “implicated” pools contained 3 infected donations, this route would have exposed the patient to a total dose of 0.6 ID$_{50}$.
- If the other “non-implicated” pools each contained 2 infected donations, this route would have exposed the patient to an expected total of 24 ID$_{50}$.

28. Simple application of the linear dose-response model would then suggest that whereas Factor VIII from the two “implicated” pools would have contained a dose liable to transmit infection with a probability of 0.3, the large number of units sourced from “non-implicated” pools would have contained more than enough infectivity to transmit. Crudely, this suggests that the “non-implicated” pools represent the more probable source of infection, by a factor of just over 3.\(^4\)

29. This last calculation is reflected in Table 2 below, for prevalence scenarios of both 1 in 10,000 and 1 in 4,000. However, we stress that this is very simplistic. It rests on accepting the linear model uncritically, and assuming that doses received on successive occasions can simply be added together in calculating an overall risk of infection. Nevertheless, the comparison between “implicated” and “non-implicated” routes is instructive, in showing how the sheer number of exposures may come to dominate the presence of a known infection.

### Table 2: Relative probabilities of potential infection routes (including “non implicated plasma” products)

<table>
<thead>
<tr>
<th>Prevalence, $p$</th>
<th>1 in 4,000</th>
<th>1 in 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission probability, $t_I$</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Probability implicated plasma products</td>
<td>38%</td>
<td>38%</td>
</tr>
<tr>
<td>Probability of each of the 14 component donors</td>
<td>&lt;0.03%</td>
<td>&lt;0.03%</td>
</tr>
<tr>
<td>Probability primary</td>
<td>&lt;0.03%</td>
<td>&lt;0.03%</td>
</tr>
<tr>
<td>Probability non-implicated plasma products</td>
<td>61%</td>
<td>61%</td>
</tr>
</tbody>
</table>

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

---

\(^4\) Note that the differential between infectious doses is much greater, but the practical effect is limited by infection being regarded as certain once the dose reaches 2 ID$_{50}$. As seen in following paragraphs, the risk differential between routes is therefore more pronounced in lower-infectivity scenarios.
30. As can be seen, the previous conclusion about the low implied risk to each of the 14 component (red cell) donors still applies, with even greater force. However, these results also highlight something of a paradox. Combined with the infectivity scenario taken from the DNV assessment, the pool size / prevalence calculations suggest that many recipients of plasma products would have received very high infectious doses, whether or not they had received any “implicated” units with known linkage to an infected donor. This opens the question of why no clinical vCJD cases have been seen in the population of haemophilia / blood disorder patients designated as “at risk” because of their exposure to UK sourced blood products.\(^5\) It might therefore be argued that the infectivity assumptions applied to plasma products are overly pessimistic.

31. Although this question is impossible to answer definitely, and in any case raises issues beyond the scope of this paper, it is appropriate to check that the conclusions we have already suggested about relative likelihoods would not be overturned were we to assume lower levels of infectivity in plasma derivatives. The DNV report itself suggests two possible methods for calculating the infectivity present in each plasma derivative, using different assumption about the effect of the various manufacturing steps. In line with the generally precautionary approach adopted by CJD Incidents Panel, the calculations so far use figures based on the more pessimistic of these. The less pessimistic alternative suggested by DNV (using the “highest single clearance factor” in the manufacturing process) leads to an infectivity estimate for Factor VIII that is lower by a factor of 4. However, it should also be noted that risk assessments carried out elsewhere take the clearance factors achieved at different stages to be at least partly additive, which would lead to much smaller infective loads.

32. In fact, reducing the assumed infectivity increases the relative chance of infection via “non-implicated” as compared to “implicated” plasma. For example, suppose the presumed infectivity in all the Factor VIII received was reduced by a factor of 100 (2 logs). Modifying the calculations in paragraph 27, this patient would then have received an expected:

- 0.006 ID\(_{50}\) from the two “implicated” pools (representing a transmission risk of 0.003)
- 0.24 ID\(_{50}\) from all the other “non-implicated” pools (representing an infection risk of 0.12).

33. Albeit with the same caveats as before about using the linear model to quantify the cumulative risks from successive doses, this suggests that the latter risk would outweigh the former by a factor of 40. Table 3 shows how the previous results for this patient would change, under this revised infectivity scenario. As can be

\(^5\) Possible explanations include the following: that prevalence of infection amongst donors is much lower than in the scenarios considered here; that much more infectivity is removed during processing of plasma products than suggested by the DNV analysis; and/or there is a threshold dose-response effect and most recipients fall below this. Genotype effects may also be relevant (in providing resistance to infection or extending the time to clinical disease), but one would expect a substantial proportion of this group to be MM homozygotes – the most susceptible genotype.
seen, the previous conclusions still hold, in particular regarding the small implied risk to each of the 14 red cell donors.

Table 3: Relative probabilities of potential infection routes (including “non implicated plasma” products and using lower infectivity estimates for plasma products)

<table>
<thead>
<tr>
<th>Prevalence, p</th>
<th>1 in 4,000</th>
<th>1 in 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission probability, t1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Probability implicated plasma products</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Probability of each of the 14 component donors</td>
<td>&lt;0.05%</td>
<td>&lt;0.09%</td>
</tr>
<tr>
<td>Probability primary</td>
<td>&lt;0.09%</td>
<td>&lt;0.09%</td>
</tr>
<tr>
<td>Probability non-implicated plasma products</td>
<td>97%</td>
<td>97%</td>
</tr>
</tbody>
</table>

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

References

Bennett PG, Dobra SA and Gronlund J (2006): The Implications for Blood Donors if a Recipient Develops Variant Creutzfeldt-Jakob Disease OR INSIGHT 2006, VOL 19; 4: 3-13


Annex A: Application of DNV Risk Calculation to Factor VIII Units

(a) Implicated Donations

Key points: FHB4547

- There was one implicated (presumed infective) donation in a start pool of 26,303 donations (pool size supplied by Professor Frank Hill via email)
- Factor VIII is derived from cryoprecipitate, which has an estimated infectivity of 60 $ID_{50}$s / donation of infected whole blood according to the DNV model
- 70.45kg of cryoprecipitate was made from the start pool, of which 21.58kg was used in the FHB4547 batch
- This implies that (21.58kg / 70.45kg) of the 60 $ID_{50}$s made its way into the FHB4547 batch (18.38 $ID_{50}$s)
- 1,844 vials each of 500 units (iu) were made from the batch, which results in an estimate of 0.00997 $ID_{50}$ per vial or $1.99 \times 10^{-5}$ $ID_{50}$s per iu

Professor Frank Hill's report indicates that the index case received 8,025 units from this batch, giving an estimated 0.16 $ID_{50}$ from the implicated donation.

Key points: FHC4237

- There was one implicated (presumed infective) donation in a pool of 21,330 donations (pool size again supplied by Professor Frank Hill)
- Factor VIII is derived from cryoprecipitate, which has an estimated infectivity of 60 $ID_{50}$ / donation of whole blood
- 67.6kg of cryoprecipitate was made from the start pool, of which all was used in the FHC4237 batch
- This implies that the full dose of 60 $ID_{50}$ made its way into the FHC4237 batch
- 5,074 vials each of 250 iu were made from the batch, resulting in an estimate of 0.0118 $ID_{50}$ per vial or $4.73 \times 10^{-5}$ $ID_{50}$s per iu

Professor Frank Hill's report indicates that the index case received 1,000 units from this batch, giving an estimated dose of 0.05 $ID_{50}$.

Conclusion

In total, these calculations suggest that index case would have received an estimated 0.21 $ID_{50}$ from the “implicated” donor. Using a linear dose-response model (where 1 $ID_{50}$ translates into a transmission probability of 0.5 and 2 $ID_{50}$ or more translates into transmission probability of 1) this represents a transmission probability of 0.104 or 10.4%.
(b) Non-implicated Donations

In addition to the implicated donations, we have also to consider the possibility of other donors contributing to a pool being infective. With pool sizes of the order of 20,000 donations, each pool will be likely to contain contributions from one or more infected donors by chance, unless \( p \) is very small. For implicated pools, these will be in addition to the “known” implicated donor.

With a prevalence of 1 in 10,000, one might therefore expect the two implicated pools to contain two further infected donations, taking the total from 1 to 3 per pool.

This would make the infective dose received via the implicated units three times that calculated above, i.e. a total of roughly 0.6 \( ID_{50} \), yielding a transmission probability of 0.3.

This patient also received approximately 391,000 iu of UK-sourced Factor VIII plasma treatment not known to be associated with any infected donor. In round figures, this can be visualised in terms of 20 exposures to pools of 20,000 donors, each typically containing 2 donations from infected donors. The exact infective dose passed on to the patient will vary from batch to batch. However, the two examples given in part (a) suggest an eventual dose of \( 2.5 \times 10^{-5} \ ID_{50} \) per unit, per infected donor. For illustration, therefore, suppose that each unit exposed the recipient to \( 6 \times 10^{-5} \ ID_{50} \). 400,000 such units would therefore have exposed the recipient to \( 24 \ ID_{50} \).