

BLOOD-BORNE TRANSMISSION OF vCJD: REVISIONS TO RISK ASSESSMENT

Background

1. The scientific uncertainties around the risk of vCJD being transmitted via donated blood mean that assessment has justifiably been based on a highly-precautionary approach. With the passage of time, however, the small number of clinical vCJD cases that might plausibly be attributed to blood-borne infection provides increasingly significant evidence on which to draw. Models of transmission need to be “calibrated” against this evidence – to provide a range of scenarios consistent with what has been seen so far. In particular, *scenarios that combine precautionary inputs for several parameters* – e.g. infectivity levels in blood, prevalence of infective donors and susceptibility of recipients to clinical vCJD – may grossly “over-predict” the number of clinical seen to date, even after allowing for limited post-transfusion survival and lengthy incubation periods for many of those infected.
2. Given the need to review the existing risk assessments, DH analysts prepared a paper for consideration by the newly-formed TSE Risk Assessment Subgroup of the Advisory Committee on Dangerous Pathogens (ACDP). This note summarises the conclusions reached, and sets out some implications for consideration by the Panel. Although the DH paper concentrated on transmission via blood components, some of the conclusions reached also have significant implications for the risks associated with plasma products.

Conclusions from the ACDP TSE Risk Assessment Subgroup

3. Meeting on 14th July 2011, the Subgroup reviewed the evidence on transmission of vCJD via blood components. The review used the DH paper as a starting point, and addressed a structured series of questions. The paper itself, and the minutes of the meeting, will shortly be made available in public form. **A draft of this material is provided to the Panel in confidence.**
4. Several of the sub-group’s findings significantly affect the basis of risk assessment. Further modelling is needed to explore the possible range of *future* cases given these new inputs, and empirical research is also proceeding. Nevertheless some key points were agreed, of which **the most relevant can be summarised as follows:**
 - a) It is now appropriate to calibrate transmission models against observed case numbers, subject to taking a precautionary approach in estimating how many infections would have shown up as clinical cases, as well as how many cases might actually have been blood-borne.
 - Specifically, transmission models should “predict” *no more than 10* clinical vCJD cases to have occurred so far due to transmission via blood components. (These include the 3 cases linked to vCJD-infected donors, 4 other cases with known transfusion histories and a further “margin for error”.)

- b) There is sufficient evidence to adopt a *much* lower infectivity estimate – of the order of 1 Infectious Dose per unit of non-LD red cells, rather than hundreds or thousands as in previous scenarios.
 - This change comes from using human and ovine data to estimate infectious doses per unit directly, rather than scaling up doses per ml from rodent models.
- c) Early findings from the ongoing appendix survey being conducted by HPA so far confirm the existing Hilton *et al* result for the 1960-85 birth cohort, but the prevalence of prion infection appears to be at least as high in the 1941-60 cohort.
 - The existing DH / CJDIP approach does not assume that the “Hilton cohort” has a greater prevalence of infection, so to that extent the new result supports it.)
 - Investigation of younger cohorts, especially those born since 1996, is now a priority, if possible to be combined with an international comparison.
- d) In the absence of evidence to the contrary, the default assumption should remain that detectable prion protein in lymphoid tissue is a indicator of infectivity in blood.
- e) Where there is no indication of any specific donor having been infected, historical exposure to blood components can be estimated as carrying a 1 in 30,000 chance of leading to vCJD infection. As explained in the attached note endorsed by the ACDP subgroup [**Annex A**], this calculation uses precautionary assumptions about the proportion of infections that might have led to identifiable clinical cases.
- f) Enhanced follow-up and surveillance of individuals at increased risk of infection is strongly recommended, including the “highly-transfused” who constitute a key sentinel group within the population.

Implications

- 5 In general, calibration to case data suggests a lower range of scenarios for **future clinical cases** that might be caused by transfusion – though leaving open the possibility of a large number of sub-clinical infections. Further modelling to clarify feasible ranges of infections and future case numbers is under way.
- 6 For blood **components**, the lower infectivity per donation still produces substantial transmission risks per unit transfused, so the reduction in expected case numbers (though significant) is not dramatic. Nevertheless, a lower starting titre also makes it more plausible that leucodepletion would have had a significant effect in reducing risk. This is subject to ongoing experimental work.
- 7 For exposure to **pooled plasma products**, the reduction in assumed infective dose per donation will lead to a very marked reduction in the estimated risks of infection, both for batches with and without a known “implicated” donor.

- An early task will be to review the risk calculations for plasma products: inspection of the existing calculations suggests that the new infectivity assumptions for whole blood would reduce all risk calculations by a factor of roughly 100.¹ (This assumes that no other changes are made, e.g. as regards the distribution of infectivity, prevalence of infective donors or the effects of manufacturing processes.) *It should be possible to re-run the HPA risk calculator for each batch of implicated clotting factor: to estimate the effect on calculated risk to patients, UKHCDO could be asked to review the total treatment given to some or all of the patients on their database.*
 - *The Panel is requested to review the necessity for “blanket” notification of recipients of “high-risk” UK-sourced products once these calculations are available, and to consider the feasibility and merits of a more selective approach.*
6. For **vCJD cases with multiple routes of exposure**, the relative probabilities of different sources of infection need to be re-calculated.
1. *If the revised calculations lead to substantially different conclusions, the Panel will be requested to reconsider its previous recommendations (e.g. as regards notification of individuals). It is not expected that many notifications would be affected.*
7. Both the last two points can be illustrated by revisiting the haemophiliac, sub-clinical case previously analysed in June 2009 (see **Annex B**).
8. For **donors to vCJD cases** (the “reverse risk assessment”), calculations are somewhat modified. However, there appears to be no case for changing the Panel’s existing approach. This is essentially to notify all donors to cases, but only notify other recipients where the number of donors to the case is small, implying a comparatively high risk of each individual carrying infection.
9. **For the highly-transfused**, the new calculation for historical exposures suggests that the 1% threshold for “at risk” status would be reached by recipients of approximately 300 or more units² of Red Cells, FFP, platelets or cryoprecipitate.
- *This may provide the opportunity for a new approach to this group: the Panel is asked consider this, including (for example):*
 - a) *Whether recipients of 300 or more units should be regarded as “at increased risk for public health purposes”, and steps taken to notify them proactively.³*

¹ The existing calculator draws on a precautionary scenario for infectivity originally proposed by DNV, whereby an infected donation of whole blood would contain approximately 900 i/v ID₅₀. In the new scenario, each such donation would contain “several” infectious doses. Taking a conservative view on the equivalence of different dose-response models, this corresponds to a dose of the order of 9i/v ID₅₀.

² With lower infectivity assumptions, there is less need to distinguish between numbers of donor exposures and units received.

³ This was previously agreed in principle for a “very highly transfused” group with 800+ exposures, but has not so far been implemented. For information, existing analyses based on EASTR data suggest that there are likely to be a few hundred individuals in receipt of 300+ units across the UK

- b) Whether the current risk management approach, attempting to interdict patients with 80+ exposures if and when they present for “high-risk” surgery, is still appropriate.*
- c) How those receiving many transfusions might be subject to epidemiological monitoring and follow-up with or without notification. (For some purposes, the existing threshold of 80 exposures might remain appropriate.)*

Dr Peter Bennett
Head of Analysis, Health Protection,
Department of Health,
31st August 2011

Estimating the risk of vCJD infection from past receipt of blood components

Dr Peter Bennett
Health Protection Analytical Team
Dept of Health
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Issue

The scientific uncertainties regarding the possible scale of vCJD transmission via infected blood donations have been well-rehearsed, especially as they affect the potential number of future clinical cases. For risk management purposes, there is also a need to estimate the risk of having been infected by historical exposure to blood and blood products, even where there is no known link to any infected donor. This short note concerns the risk associated with receipt of blood components (including Red Cells, Platelets, FFP and cryoprecipitate). Risk assessment for recipients of UK-sourced plasma products (e.g. Factor VIII) will be discussed in a subsequent note.

Why this is important

Decisions on management of those who may be at increased risk of vCJD infection may depend on assessing the historical risk from potentially-infective blood donations. The CJD Incidents Panel frequently has to make recommendations as to whether people are at sufficiently increased risk to warrant notification, triggering precautions against onward transmission. Clearly, notification is not to be undertaken lightly, and the challenge is to balance possible harm to those notified against the need to minimise any risks of further transmission. In general, the Panel recommends notification unless the risk of infection is estimated to be less than 1%, calculated using precautionary assumptions.

At present, the Panel uses the highly-precautionary assumption that for any recipient of blood components, every donor exposure (in theory, since the start of the BSE outbreak) would have carried a 1 in 4,000 chance of causing vCJD infection. Given the continuing scientific uncertainties, a precautionary approach is certainly warranted. However, there is also a need to ensure that estimates of past risk are consistent with all available evidence, including the small number of clinical vCJD cases presumed to be associated with blood borne transmission seen to date. Overestimating the probability of infection via blood components could have at least two serious and unwelcome consequences:

- (a) For someone whose only vCJD “risk factor” has been receipt of blood components, over-estimating the resulting chance of infection could lead to inappropriate notification. This would have personal consequences for the individual, while the concomitant risk management precautions could lead to additional health service costs.
- (b) In other circumstances, risk assessment starts with a known clinical case, and considers the relative likelihood of that infection having come from different routes. For example, the individual may have undergone surgery, as well as receiving blood. In this situation, over-estimating the chance of

the infection having come from one route risks *underestimation* of the chance of it having come from another.

The former consideration applies particularly (though not exclusively) to “highly transfused” patients with no links to known vCJD-infected donors, for whom calculated risks are entirely dependent on estimates of historical prevalence and transmissibility. Management of this group has been subject to much debate. Mindful of the dangers of inappropriate notification, and using a threshold of 80 (rather than 40) donor exposures, the Panel has advised that this step should only be taken if patients present for “high risk” surgery. In practice, this has resulted in almost no appropriate notifications.

Proposed approach

Despite the many remaining uncertainties about future transmission risks, we suggest that evidence is now sufficient to justify a new approach. Risks from historical exposure need to be assessed in a way more consistent with case numbers seen to date, while remaining both precautionary and simple to apply.

In particular, any attempt to “calibrate” historical transmission risks against observed case numbers must acknowledge that only a very small proportion of vCJD infections might have led to recognisable clinical cases. The latter may thus be the tip of a much larger “iceberg” of sub-clinical infections.

This can be considered as follows, starting from what is known:

- Approximately 3 million units of components were transfused annually during the 1990s.
- During the following decade, three cases of vCJD occurred in patients who had received blood (non-LD Red Cells) from donors who subsequently developed vCJD: these are presumed to have been blood-borne. Relevant transfusions were in 1996 and 1997(2) and onsets for the recipients in 2002, 2005 and 2006.
- Another four vCJD cases had relevant transfusion histories. Their infections might have been blood-borne, though none of the donors has developed symptoms of vCJD. If so, the relevant transfusions occurred from 1993 onward.
- All these cases were MM-homozygotes. All had incubation periods from transfusion to onset of symptoms of under 10 years (including the four just noted, *if* their infection was caused by transfusion).

Taking a precautionary view, suppose that all these 7 vCJD cases were in fact caused by infective donations. Suppose further that a few clinical cases (or transfusion histories) might have been missed, bringing the hypothetical total to 10. This amounts to an incidence of roughly **1 blood-borne clinical vCJD case per year**, spread over the last decade.

To assess historical rates of infection, the key question is that of the ratio between infections and recognisable cases. How big might the “iceberg” be, relative to the observable “tip” of cases? Given the period that has elapsed since the peak of BSE exposure, and the incubation periods for the observed cases, this question can be posed more precisely:

- ***How many blood borne transmissions of vCJD infection might plausibly lead to 1 clinical case appearing within 10 years of transfusion?***

This will depend on two main factors, one known and one unknown. The known factor is the survival of transfusion recipients. A conservative estimate is that 25% of all units are transfused to patients who survive at least 10 years.

The unknown factor is the proportion of the population susceptible to developing clinical vCJD within 10 years of receiving an infected transfusion. So far, symptomatic patients remain confined to the MM group. Let us therefore suppose that all other genotypes have incubation periods longer than 10 years, by a factor sufficient for no clinical cases to have occurred.

Taken together, these two factors produce a 10:1 ratio of infections to cases: for every 10 infected recipients, only one would be an MM homozygote surviving at least 10 years after transfusion.

However, the large gap between prevalence of vCJD infection in general (evidenced by tissue surveys) and observed case numbers suggests a more precautionary approach, in which we assume that *only 10% of MM homozygotes* would develop recognised symptoms of vCJD following receipt of an infective transfusion, despite this being regarded as a highly-efficient transmission route. The implication is that a very large majority of infections (99 out of every 100) would have so far remained “silent”.

Rough consistency with case numbers then permits a worst case in which the historical risk of vCJD infection would have been **1 in 30,000 per donor exposure**.⁴

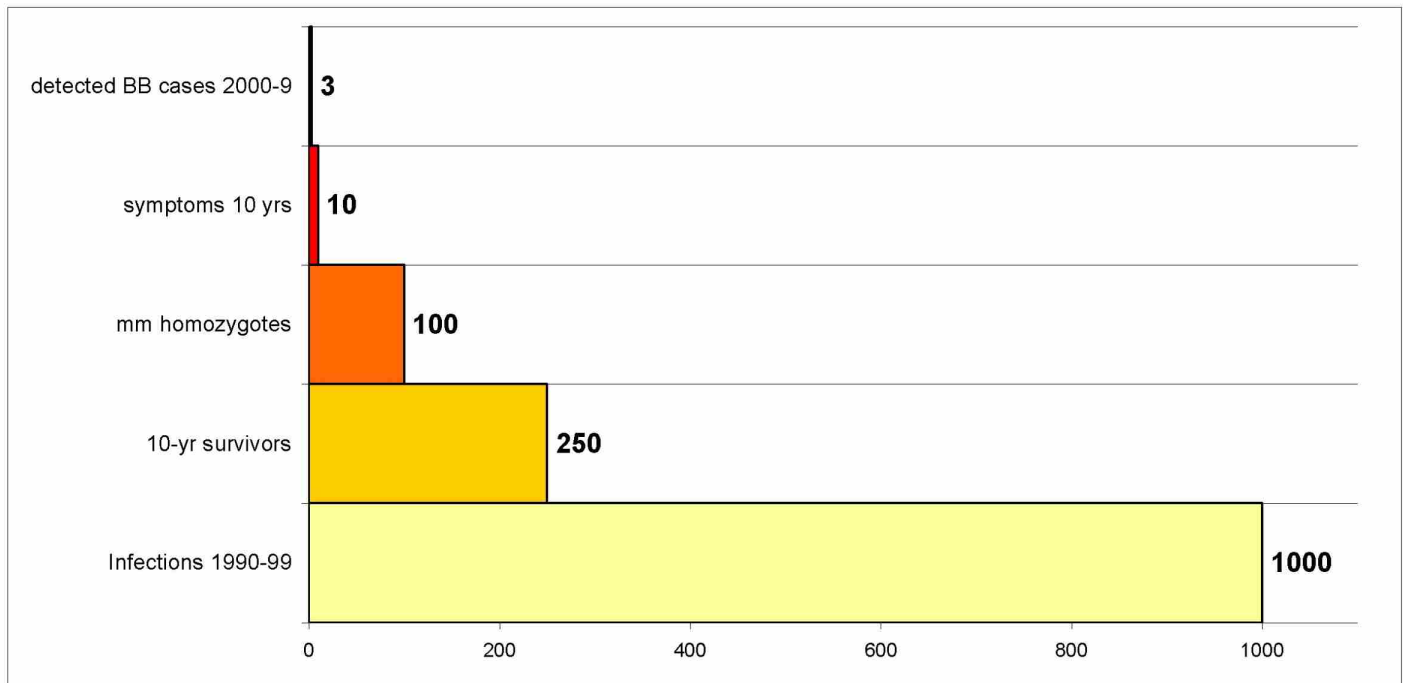
This is a scenario in which:

- 3,000,000 blood component units were transfused each year
- 100 of these (1 in 30,000) caused infection in recipients
- 25 of these recipients (25%) survived for at least 10 years
- 10 of these surviving patients (40%) were MM homozygotes
- 1 of these surviving MM homozygotes developed clinical symptoms of vCJD

Note that this calibrates transmission to a hypothetical case of 10 blood-borne clinical cases to date, with one such case occurring per hundred historical infections. The comparison with the blood-borne cases *so far detected by TMER* is 3 cases per 1,000 infections. In other words, only 0.3% of blood-borne infections would have been detected. This is illustrated graphically in Figure 1.

⁴ This could be reached by different combinations of prevalence and transmissibility (e.g. 1 in 30,000 donors being infective, and certain transmission, or 1 in 15,000 and 50% transmission probability). The difference between these is immaterial for present purposes. Given the lower infectivity inputs suggested by recent analysis, pooled production of platelets and cryoprecipitate may have comparatively little impact on transmission risks. It may therefore be unnecessary to distinguish between risks per unit and risks per donor exposure.

Figure 1: Numbers of infections over a 10-year period, related to vCJD cases resulting in the following decade.



Conclusions

- We suggest that calculations of exposures should count all transfusions from 1990 onward, and continue to treat historical risks per donor exposure as constant.
 - it appears unlikely that more complex calculations dependent on the age distribution of the donor base are justified as there is now less support for a strong “cohort effect” for historical prevalence of infection – e.g. that it was largely confined to the 1961-85 “Hilton cohort”.
 - other variations may have existed (e.g. delay in onset of infection making earlier donations less risky, while later donations would have been subject to leucodepletion and other precautionary measures) but these are insufficiently known and may tend to cancel each other out.
- Use of this method would produce a substantially smaller estimate of infection risk than that used to date. Nevertheless, the calculation remains precautionary, in assuming:
 - (a) that only a small minority (4%) of secondary vCJD infections amongst recipients surviving at least 10 years would have shown up as recognisable clinical cases, and
 - (b) that more vCJD cases may have been caused by blood-borne infection than the 3 identified so far.
- If accepted as “appropriately precautionary”, a historical risk of vCJD infection of 1 in 30,000 per donor exposure would retain a simple – but arguably more credible – rule of thumb for risk assessment and management purposes.

Annex B: Preliminary re-analysis of vCJD infection with multiple routes of exposure

1. This refers to a subclinical vCJD infection found post mortem in a patient with haemophilia, who had been exposed to multiple infection routes comprising endoscopy, “implicated” and “non-implicated” batches of UK-sourced fractionated products, and component transfusion, in addition to dietary exposure to BSE. Analysis previously provided in June 2009 is available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_100357. The existing paper already considers reduction of all blood-borne doses by a factor of ~ 100 as a piece of sensitivity analysis. For an illustrative prevalence of 1 in 10,000 donors infective, estimated infective doses coming from each potential infection route would be as follows:
 - Plasma products from both "implicated" batches: 0.006 (rather than 0.6) ID₅₀, carrying 0.003 (0.3%) risk of infection
 - All other, non-implicated batches 0.24 (rather than 24) ID₅₀, carrying 0.12 (12%) risk of infection.
2. The previous analysis suggested that a patient such as this would have received many ID₅₀s in total. This made it difficult to understand why we have not seen a substantial number of clinical vCJD cases amongst bleeding disorder patients. The new calculations help remove this gross anomaly.
 - Secondly, it remains true that the risk from non-implicated units dominates that from the much smaller number of implicated ones. With pools of 20,000 donations, this will always happen for recipients of many units unless prevalence of infective donors is *very* low.
 - It also remains true that the plasma products are the most likely source of infection in this case (as compared with primary infection, component transfusions or endoscopy)
3. Finally, consider this patient as an example of the current "at risk" group of UK-sourced plasma recipients, in receipt of a fairly high (but not exceptional) total of about 400,000 iu of Factor XIII. Given the assumptions set out, this would result in an infection risk of about 12%. This obviously remains above the 1% notification threshold, but now only by one order of magnitude. Such calculations are now much more dependent on other assumptions, some of which - notably on removal of infectivity during manufacture - are highly precautionary. In addition, the calculation given is based on receipt of standard product. If high purity products can be assumed to carry 25x less infectivity, 400,000 units should leave such a recipient well under the risk threshold. Though by no means a definitive calculation, this illustrates the case for revisiting the current blanket approach.