BLOOD-BORNE TRANSMISSION OF vCJD RE-EXAMINATION OF SCENARIOS

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Contact Details	Dr Peter Bennett Head of Analysis, Health Protection - & Acting Head of OR Department of Health - 3rd Floor Wellington House 133-155 Waterloo Rd, London SE1 8UG 020 7 972 4438 www.dh.gov.uk/ab/ACDP/TSEguidance/DH_125868
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BLOOD-BORNE TRANSMISSION OF vCJD RE-EXAMINATION OF SCENARIOS

Prepared by

Dr Peter Bennett and Dr Maren Daraktchiev
Health Protection Analytical Team

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Preface to web publication, September 9th 2011

Background

Variant Creutzfeldt-Jacob Disease (vCJD) is one of a small number of neurological diseases associated with an abnormal form of prion protein. Despite efforts to develop effective treatments, it has proven to be fatal in all known cases where symptoms have developed. First identified in the late 1980s, it almost certainly first spread to humans via cattle infected with Bovine Spongiform Encephalopathy (BSE), or “Mad Cow” disease. As of September 2011, there have been 175 definite or probable vCJD cases in the UK. But because it can take many years for symptoms to develop, concern remains that a larger number of people might have been infected. A previous survey of stored tissue samples (mainly appendices), published in 2004, suggests that about 1 in 4,000 people might be carrying the abnormal prion protein indicative of vCJD, though this estimate is subject to a good deal of uncertainty. Such estimates are important to help assess the likelihood of infection being passed on from person to person (“secondary transmission”) in certain circumstances. One way in which this might occur is if someone carrying vCJD, but without showing any symptoms, donates blood.

From the first identification of vCJD, UK policy has been based on the presumption that infection *might* be transmissible from person to person, and various steps have been taken to reduce the risks. To reduce the risk of blood-borne spread, all donations have undergone removal of white cells (leucodepletion). Introduced in 1999, this should reduce any vCJD infectivity present, although it is considered unlikely to eliminate it. All the transmissions identified so far occurred prior to this. Also from 1999, plasma derivatives have been fractionated from plasma imported from the US, rather than sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported. From 2004 onward, recipients of blood components have been excluded from donating blood, in order to prevent vCJD (and possibly other infections) being “recycled” within the population.

Despite a great deal of research, both on the basic science of prion diseases and on the epidemiology of vCJD, great uncertainties remain. Decisions still need to have a strongly precautionary element.

Risk assessment relies on mathematical modelling of how infection might spread, and how many clinical cases of vCJD might result. Existing models used by the Department have been based on separate inputs, for example on the level of infectivity in blood, the prevalence of infective donors and the susceptibility of recipients to clinical disease. Ranges of inputs have been used for each, consistent with the available evidence. This produces a very wide range of scenarios for the number of future vCJD cases that might be caused by blood-

borne transmission. However, the passage of time has also made it more feasible to "calibrate" model outputs against the observed numbers of clinical (symptomatic) vCJD cases. Using a combination of precautionary inputs can produce scenarios that markedly over-estimate the numbers of clinical cases seen so far. It is therefore reasonable to reconsider the consistency of modelling scenarios with epidemiological, clinical and experimental observations.

Revisions to the Risk Assessment

DH analysts prepared a paper for consideration by the TSE Risk Assessment Subgroup of the Advisory Committee on Dangerous Pathogens (ACDP). Meeting on 14th July 2011, the Subgroup reviewed the evidence on transmission of vCJD via blood components, using the DH paper as a starting point.

For the public record, the paper is reproduced here as presented, except for one factual correction and omission of information that might allow identification of individual patients. All changes are explicitly noted in the text.

In general, the ACDP Subgroup endorsed the approach suggested: the full minutes of the meeting can be accessed at http://www.dh.gov.uk/ab/ACDP/TSEguidance/DH_125868.

Three key conclusions reached by this independent expert group were as follows:

- Early findings from a survey of appendix tissues being conducted by the Health Protection Agency (HPA) confirm the previous estimates for the prevalence of prion infection within the population, and extend this finding to older age cohorts than those examined previously. This study is continuing: evidence on the existing prevalence of infection is of key importance in assessing the possible scale of onward transmission.
- Evidence now suggests a much lower estimate for the level of infectivity in blood.[1]
- It is now appropriate to calibrate transmission models against observed clinical case numbers, subject to taking a precautionary approach in estimating how many vCJD infections would have shown up as clinical cases, as well as how many known cases might have been due to blood-borne infection.

Further work

Calibration of models to case data may suggest a lower range of scenarios for future clinical vCJD cases that might be caused by transfusion – though still leaving open the possibility of a relatively large number of sub-clinical

[1] In the scenarios previously used, for example, a unit of red cells sourced from an infective donor prior to leucodepletion would have contained a large number (perhaps thousands) of "Infective Doses". The evidence now available suggests that a unit contains of the order of one "Infective Dose". The risk of transmission from donor to recipient would remain substantial, but would not occur in every case.

(asymptomatic) infections. Further modelling to clarify feasible ranges of infections and future case numbers is under way. This will be informed by further results from the HPA appendix survey and other ongoing experimental studies, which will be kept under close review.

All the changes agreed by the ACDP Subgroup will inform the work of the CJD Incidents Panel, the Advisory Committee on the Safety of Blood, Tissues and Organs and other independent expert committees advising on CJD-related risk management decisions, who will be asked to review past recommendations if necessary and use the revised inputs in future considerations.

June 24th 2011 (with modifications noted, September 2011)

SUMMARY

- Assessing the benefit of steps to reduce vCJD transmission depends critically on establishing a plausible range of scenarios as to how many future blood-borne clinical cases there could be, and how many would be due to transmissions yet to occur.
- Reflecting continuing scientific uncertainties about many aspects of vCJD, DH risk assessments have used a range of scenarios based on alternative assumptions about the prevalence of infective donors, the infectivity of blood components and recipients' susceptibility to clinical disease. Taken separately, each of these inputs may be precautionary, but all have been based on the evidence available.
- *Taken together*, however, these inputs can lead to marked over-prediction of the number of blood-borne vCJD cases seen to date. Under some of the existing scenarios, hundreds of blood-borne clinical cases would already have been seen, as compared with the small number actually observed.
- Differences of this order throw severe doubt on the existing range of scenarios. However, it is less clear what inputs or assumptions should be changed to more closely reflect experience to date.
- After discussing this "model calibration" issue, we review the existing inputs against current evidence, and in particular new research on the prevalence of abnormal prion protein in tissue samples and on infectivity in both human and sheep blood.
- We then outline how a revised approach might be developed. This draws on further work carried out by DH in collaboration with the Clinical OR Unit (CORU) at University College London, and published modelling produced by the MRC Centre of Outbreak Analysis and Modelling at Imperial College. The Imperial model establishes the relative likelihoods of scenarios with inputs sampled from all relevant parameters, requiring a very large number of simulation runs. The simpler DH/CORU model allows us to explore the effects of varying parameters singly, or a few at a time. This shows how case projections vary as assumptions are changed, and how similar outcomes can result from different combinations of inputs (e.g. high prevalence / low susceptibility, or low prevalence / high susceptibility.)
- Given similar assumptions, these different models may provide broadly compatible projections for the number and timing of future cases – though this remains to be tested given the new inputs suggested by more recent evidence. If so, a revised set of scenarios for risk assessment might draw on both approaches.
- Subject to re-calibration necessitated by new evidence, the Imperial College model might be used to assess how many vCJD cases might result from red cell transfusions *in the absence of further precautionary interventions*. Central, high and low scenarios could be used, corresponding to the median number of cases projected in the model, and the upper and lower 95% credibility intervals. Some extrapolation would be needed in order to cover usage of other blood components (Fresh Frozen Plasma, Platelets) and Cryoprecipitate.
- Because any given numerical result can be produced by many combinations of inputs (prevalence of infective donors by age cohort, level and timing of infectivity in blood,

susceptibility of recipients to clinical disease, etc), *the above scenarios need not specify values for individual parameters*. Rather, each scenario constrains the possible combinations that these can take. Although the ideal might be to have ranges for each separate input, for many purposes this is not essential.

  - For example, the impact of some risk reduction measures – e.g. importation of components or reduction of usage - would depend only on the number and timing of the transmissions that would otherwise have happened.
  - However, some measures will have impacts and consequences that do depend on individual parameters. For example, the risk reduction from any technology partially removing infectivity may depend critically on the level of infectivity initially present.

- The DH/CORU model can be used to explore alternative ways in which any given numerical result could be reached. If plausible inputs to this model are found to give results similar to the (revised) Imperial College model, it can be used to generate "families" of scenarios approximating to each of the central, high and low figures from the latter. Risk reduction measures can then be assessed against these more detailed scenarios, and results subjected to systematic sensitivity analysis.
- For such work to proceed, an essential first step is to establish an appropriate set of input ranges for both models, and criteria for calibrating the models against observed case data.
- Meanwhile, we suggest that current evidence is already sufficient to warrant a marked reassessment of the risk of being infected through *historical* exposure to blood components. A revised method is proposed, resulting in a substantially lower estimated risk "per exposure" than that currently used to inform risk management.

1. Background and Purpose

Existing models of vCJD transmission via donated blood have used wide ranges of inputs, reflecting the scientific uncertainties involved. Consequently, they produce a range of scenarios in which the projected numbers of clinical vCJD cases caused by blood-borne transmission could be small or very substantial. This extreme uncertainty makes it difficult to assess the benefit of risk reduction measures, and inevitably prompts debate as to whether the search for further measures – or indeed those already instigated – are "over-precautionary" (see e.g. Dodd, 2010; Will, 2010).

Although many of the uncertainties around the scale of blood-borne transmission remain, evidence on vCJD *cases* has gradually accumulated. It is essential to consider the consistency of transmission scenarios with these observations. One key piece of evidence is the small number of clinical vCJD cases seen so far that can plausibly be attributed to blood-borne infection.

A paper presented to SEAC in March 2010 (Bennett and Daraktchiev, 2010) summarised the key issues and reviewed the range of scenarios used in DH risk assessments. It argued that the inputs used on infectivity of blood components, prevalence of infective donors, etc, were consistent with the available evidence on each separate parameter. Taken in combination, however, they tended to over-predict the numbers of blood-borne clinical vCJD cases seen to date.

Although these arguments were accepted by SEAC, the committee did not provide specific recommendations as to how existing scenarios should be changed. Since then, however:

- Results of modelling then under way at Imperial College have appeared in peer-reviewed form (Ghani and Garske, 2010)
- The DH analysis previously presented has been further developed, in collaboration with modellers in the Clinical OR Unit, University College London.
- Results from an ongoing study confirm that experimental BSE can readily be transmitted in sheep by any of the blood components commonly transfused in humans. However, a recently-published estimate of infectivity human blood suggests titres much smaller than currently assumed - though still amounting to a significant dose per unit transfused.
- Initial evidence from a current prospective tissue survey suggests that significant prevalence of abnormal prion protein extends to an older age cohort than indicated by previous studies.
- As against this, there have been no further clinical vCJD cases attributable to transfusion in the interim.

Given the need to reconcile these different pieces of evidence, it is timely to reconsider the range of scenarios used for risk assessment. More detailed discussion of key points is provided in **Annex A,** which reviews the underlying

evidence both on vCJD and on usage of blood, and **Annex B** covering quantitative models and the results obtained.

2. Transmission via blood components: existing scenarios

Knight (2010) provides a helpful overview of key issues in assessing the potential scale of blood-borne transmission of prion diseases. There are two fundamental uses of donated blood: transfusion of components, and use of fractionated plasma products. For blood *components* (most commonly Red Cells, but also including Fresh Frozen Plasma (FFP), Platelets and cryoprecipitate[2]), each unit transfused exposes the recipient to substantial volume of material from one (or a few) donors. By contrast, plasma products – e.g. clotting agents such as Factor-VIII used to treat haemophilia - are produced by "fractionating" plasma in pools of many thousand donations. Recipients are thus exposed to tiny amounts of material sourced from very large numbers of donors. Since 1999, plasma for fractionation has been imported from the US, though a substantial number of recipients are regarded as "at risk" due to earlier exposure to UK-sourced products.[3] This paper concentrates on transmission of vCJD via components, rather than fractionated products.

It is also important to appreciate that components are not transfused in pure form. For example, a unit of "red cells" will actually contain a significant volume of plasma, other cells, and so on, in quantities depending on the processing method used. This is a key point in considering how much of any infectivity in a donation would end up in a transfused unit. Similar comments apply to FFP, while for some platelets and all cryoprecipitate there are additional complications due to units being produced by pooling donations from several donors. Further data on component usage are given in **Annex A1.**

Various measures have been put in place to reduce vCJD transmission risks, the most relevant being leucodepletion (removal of White Cells) from 1999 and later exclusion of transfusion recipients from donating blood (Bennett and Dobra 2006).

Three known vCJD cases are currently presumed to have been caused by transfusion. As detailed in **Annex A2**, each received transfusions from donors who themselves later went on to develop the disease (Llewelyn, Hewitt, Knights *et al*, 2004; Wroe, Pal, Siddique *et al*, 2006; Head *et al*, 2009).[4] All recipients and donors were MM-homozygotes. In addition, one MV-heterozygote recipient of blood from a MM-homozygous vCJD-infected donor showed signs of sub-clinical

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[2] Terminologically, it is not clear whether cryoprecipitate should count as a component or a product (a point that risks it being overlooked in calculations). For present purposes, however, it should be considered as a "component".

[3] One transmission of sub-clinical vCJD is thought to have occurred via Factor VIII. (Peden, McCardle, Head *et al*, 2010; Bennett and Ball, 2009). Given the numbers of patients exposed to UK-sourced plasma products prior to 1999, the lack of clinical cases amongst this group is interesting. As compared with components, estimates of "expected" numbers are complicated by major additional uncertainties regarding the distribution of infectivity, and the effects of manufacturing processes in removing it.

[4] Two had received blood from the *same* pre-symptomatic donor, which establishes blood-borne transmission beyond all reasonable doubt.

infection, after dying of unrelated causes (Peden *et al*, 2004). All had received non-leucodepleted Red Cells, with the "implicated" transfusions taking place between 1996 and 1999. The three clinical cases had onsets of clinical vCJD 6.5, 7.8 and 8.3 years after the relevant transfusion, developing symptoms in 2002, 2005 and 2006 respectively.

In addition, a small number of other vCJD cases *might* be attributable to blood-borne transmission, even though no symptomatic donor has been identified in these instances. Transfusion histories of all clinical cases are routinely investigated: as detailed below, four are known to have been transfused at times consistent with this having been the route of infection.

Although we know that blood-borne transmission can occur, quantifying the potential scale of transmission is subject to much uncertainty. As shown in Table 1, existing DH scenarios used to inform risk management decisions use the following combinations of inputs:

- Two alternative inputs for prevalence of infective UK donors: a *low* scenario of 1 in 20,000 and a *high* scenario of 1 in 4,000, both assumed to apply to all age cohorts exposed to the BSE outbreak
- Two alternative inputs for the infectivity of whole blood: a *low* scenario of 0.1 ID/ml for intravenous (i.v.) transmission and a *high* scenario of 30 ID/ml. Both take infectivity to be associated with white cells (leucocytes) and plasma, in roughly equal proportions.
- Two alternative inputs for the proportion of recipients susceptible to clinical vCJD following blood-borne infection: *low* (10%) and *high* (100%).

Table 1: Summary of eight existing scenarios

HIGH Susceptibility to clinical vCJD (100%)	**1 in 4000 (1 in 4000); HIGH Infectivity (30 ID/ml)**
	1 in 4000 (1 in 4000); LOW Infectivity (0.1 ID/ml)
	1 in 20000 (1 in 20000); HIGH Infectivity (30 ID/ml)
	1 in 20000 (1 in 20000); LOW Infectivity (0.1 ID/ml)
LOW Susceptibility to clinical vCJD (10%)	**1 in 4000 (1 in 4000); HIGH Infectivity (30 ID/ml)**
	1 in 4000 (1 in 4000); LOW Infectivity (0.1 ID/ml)
	1 in 20000 (1 in 20000); HIGH Infectivity (30 ID/ml)
	1 in 20000 (1 in 20000); LOW Infectivity (0.1 ID/ml)

The inputs on prevalence and infectivity were based on the available scientific evidence.

- On the *prevalence of infective donors*, the figures of 1 in 4,000 and 1 in 20,000 correspond to the central estimate and lower 95% Confidence Interval from a retrospective tissue survey (Hilton *et al,* 2004), which found 3 positive appendix samples in approximately 12,000 tested. As discussed below and in **Annex A3**, more recent evidence supports estimates of at least this order, though whether presence of abnormal prion protein in

tissues necessarily implies infectivity in blood (or future development of clinical vCJD) is a separate question.

- Existing inputs on *infectivity* follow previous SEAC advice, based primarily on rodent studies. It is important to appreciate the distinction between doses *per ml*, and *per unit*. An infected donation would contain many infectious doses even in the "low" scenario, and many *thousand* doses in the "high" scenario. As discussed below, more recent evidence suggests that these titres are much too high, though still implying that infected components would contain significant doses per unit.

The scenarios for *susceptibility to clinical vCJD* are rather different in nature. The "100%" scenario obviously represents the precautionary assumption that everyone is susceptible both to infection via the blood route and to then to developing clinical disease. Although incubation periods[5] depend on genotype, there is no experimental evidence to support any lower susceptibility figure. Relatively low susceptibility to clinical disease is essentially invoked as a way of reconciling the assumptions on prevalence and infectivity with the paucity of observed secondary cases. The choice of the "low" 10% scenario was somewhat arbitrary, but similar to an existing hypothesis advanced to reconcile the Hilton *et al* prevalence result with the modest number of primary cases (Clarke and Ghani, 2005). Restricting susceptibility to clinical disease rather than *to infection* is the more precautionary approach. It allows the possibility of many of those exposed remaining in a long-term, and possibly infectious, "carrier state", rather than being resistant to vCJD infection.[6]

3. The "calibration" problem

To be regarded as plausible, we suggest that scenarios for vCJD transmission:

- *Must be* consistent with human evidence – both "positive" and "negative" – especially on the incidence of clinical cases.
- *Should be* broadly consistent with findings from most relevant animal models – though without assuming that these can necessarily be translated directly into the human context.

While positive evidence consists of - often quite prominent, rare and fully-investigated - events, negative evidence arises as a gradual accumulation of non-events. Models nevertheless require calibration against negative evidence. This provides a necessary reality-check, especially where models multiply worst-case assumptions for several separate parameters. Early in the vCJD outbreak, risk

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[5] Throughout, we use "incubation period" to refer to the duration of asymptomatic infection, up until the appearance of clinical vCJD. Some other authors use this term to refer to time from infection to death. Figures have been adjusted as necessary in referring to such work.

[6] The assumption that susceptibility *to infection* is not confined to MMs is supported by the discoveries of abnormal prion protein in other genotypes in the Hilton *et al* survey (Ironside, Bishop, Connolly *et al*, 2006), and in patients in receipt of red cells (Peden *et al*, 2004) and plasma products (Peden, McCardle, Head *et al*, 2010). Susceptibility to clinical vCJD may be illustrated by one possible MV case (Kaski, Mead , Hyare *et al*, 2009).

assessment had necessarily to be based on precautionary inputs, and the existing input ranges are evidence-based. With the passage of time, however, it becomes increasingly meaningful to compare model projections with actual numbers of clinical cases.

Taken together, existing inputs produce scenarios in which very large numbers of blood-borne transmissions would have occurred. These are difficult to reconcile with the small number of observed clinical cases. This “calibration” problem can be illustrated by considering four key questions. Each is illustrated with some simple initial calculations, in which susceptibility to clinical vCJD is assumed to be 100%.

(a) Why have more blood-borne cases not appeared?

The most fundamental question is why more blood-borne cases have not been seen so far. To illustrate, suppose that exposure to BSE led to a 1 in 10,000 prevalence of vCJD infection, spread throughout the donor population and typically occurring circa 1990-1. Since then, there have been of the order of 3m transfusions of components (Red Cells, FFP, and Platelets) each year. If the dose in an infective donation were sufficient to transmit infection, there would therefore have been roughly 300 transmissions *every year*, from about 1991 onward.

Clearly, recent transmissions would not yet have shown up as clinical cases, and some infected recipients would have died of unrelated causes. However, this does not suffice to explain the lack of many observed cases. For illustration, suppose that only MM recipients (40% of the population) would have Incubation Periods short enough for symptoms to develop within about 10 years. Data on post-transfusion survival suggest that 25-30% of components are transfused into patients surviving at least this long.

Using the lower survival figure, the net effect would be that 1 in every 10 transmissions would result in a clinical vCJD case within 10 years. In the 10 years from 1991 to the start of 2001, there would have been 3,000 infections, which “should” have produced 300 clinical cases by the start of 2011. *Where have all these cases gone*?

This simplistic illustration ignores statistical distributions around the time at which donors were infected, and around incubation periods amongst those infected. As will be seen, more elaborate modelling can – up to a point - provide some greater realism and further insights. But it does not remove the basic problem of “over-prediction”.

(b) Why did blood-borne cases not appear earlier?

Under any of the existing scenarios, a large number of infected units would have been transfused from about 1990 onwards. The three MM recipients linked to infected donors all had incubation periods of under 10 years. It is therefore surprising that such cases did not appear until 2002. An earlier paper (Dept of Health, 2003) suggested delayed onset of infectivity in blood as one explanation. This remains a relevant factor: one would not expect blood to become infectious instantaneously. The known human transmissions involved donations taken fairly close to onset of symptoms in the donor - the largest interval being just under 3.4 years - leaving infectivity earlier in the incubation period as an open question.

However, sheep transfusion experiments discussed below show that blood taken no more than 25% through the donor animal's incubation period – or possibly earlier - can infect the recipient. In summary, there might plausibly have been a few years' delay before significant infectivity appeared in the blood of human donors, with those infected at the peak of the primary outbreak typically becoming infective in the early-to-mid 1990s – e.g. circa 1994. This would go *some* way toward explaining the absence of earlier secondary cases, but does not provide anything like a full explanation.

(c) Why have there not been more subsequent cases?

It is perhaps more difficult to explain why the three cases linked to infected donations were not the precursor to a more substantial wave, resulting from more frequent transmissions as more donors became infective. Instead, there has been a gap of over 5 years since onset of symptoms in the last such case (Feb. 2006). As discussed further below, we cannot conclude that there have been *no* cases of transfusion-transmitted vCJD, but the small overall incidence of cases means that there could only have been a few.

One explanation might be that leucodepletion reduces Red Cell transmission risks to a greater extent than is now generally assumed - the implication being that vCJD infectivity in human blood is relatively low and/or largely associated with white cells rather than plasma. That would have created a relatively narrow "window" of significant risk, confined to blood donated after onset of infectivity – typically about 1994, as argued above – and the full implementation of leucodepletion completed in October 1999.

As will be seen, such a hypothesis makes it much easier to explain the timing of the red cell-associated cases seen so far, though not completely explaining their small number. It has other attractions in terms of explaining the human data, but is difficult to reconcile with recent evidence from animal models.

(d) Infections and cases amongst the highly-transfused

The distribution of units transfused is highly skewed, with a few recipients receiving disproportionately many units. This does not greatly affect the total number of blood-borne vCJD cases to be expected: if patients are receiving multiple units, there is some double-counting of transmission risk, but this effect is minor. However, their *distribution* is important. The chance of exposure to an infective donor rises with the number of units received, and some patients have received hundreds of units (Department of Health, 2009). The CJD Incidents Panel currently advises that those exposed to 80 or more donors through receipt of blood components[7] should be subject to precautionary measures, and notified of their increased risk status, if they present for CNS or posterior eye surgery.

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[7] At least in theory, exposures at any time from 1984 onward are counted, though in practice it has only proven possible to trace back to the start of electronic record-keeping, typically in the early 1990s.

The skewed nature of exposure is reflected in the records of transfused vCJD cases.[8] But if the existing scenarios for prevalence and transmissibility are true, the lack of cases amongst the "highly-transfused" is very surprising. It is estimated that at least 30,000 *living* recipients have received blood components sourced from 80 or more donors.[9] Given a historical prevalence of 1 in 4,000 donors infective, each individual would have *at least* a 2% probability of having been infected. Even with a "low" prevalence of 1 in 20,000, each would have an infection risk of over 0.5%, giving a minimum of around 150 infections amongst this group.

Highly-transfused patients are thus highly significant from an epidemiological point of view, representing a "sentinel" group that should be followed up if possible.

4. Existing scenarios, case data and recent evidence

This section looks in more depth at the available case data, and at how existing scenarios relate to both this evidence and the most recent research on prevalence and infectivity.

Interpretation of case numbers

Evidence for transfusion-associated vCJD comes primarily from the UK Blood Services' Transfusion Medicine Epidemiology Review (TMER) study (Hewett *at al*, 2006), which investigates both donors and recipients. Like any other investigation, this process is in principle fallible. Firstly, 100% case ascertainment of vCJD cannot be taken for granted: there *might* be under-reporting, especially in age groups in which dementia is relatively common and post mortem investigations rare. However, checks currently in place, and the level of research interest in prion disease, make gross under-reporting unlikely. In addition, the "calibration" calculations primarily compare actual clinical cases with numbers predicted *amongst MM homozygotes*. Such cases are less likely to have been missed, whereas any presentation of vCJD in other genotypes may be more uncertain.[10]

A more significant question is that of *when to attribute a vCJD case to blood-borne transmission*. The three instances in which both donor and recipient have developed clinical vCJD provide a minimum estimate. More of the cases already known might be linked to donors who have not developed disease – and might never do so, especially if non-MM individuals remain in a long-term infective but asymptomatic "carrier state". As noted, some other vCJD cases have histories of transfusion. Disregarding transfusions that took place prior to 1990 (and one case whose onset of symptoms precludes transfusion having been the source of infection), four of these cases were exposed to 2, 3, 4 and 103 donors. A "reverse

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8 The three linked to "vCJD donors" all received other transfusions, with exposure to 5, 23 and 56 donors in total: as discussed in the following section, the four "unlinked" cases were exposed to 2, 3, 4 and 103 relevant donations.

9 See http://www.dh.gov.uk/en/AdvanceSearchResult/index.htm?searchTerms=secondary+vCJD. Note that we are referring to components here. Exposure to *many* more donors will occur through receipt of fractionated products, but as already noted, the quantities of material involved are much smaller and infectivity more uncertain.

10 For MM homozygotes, there is no evidence of the strain of the agent or the characteristics of disease changing significantly following blood-borne infection (Head *et al*, 2009).

risk assessment" (Dept of Health, 2005; Bennett, Dobra and Gronlund, 2006) has been used to determine the likelihood of such cases being due to blood-borne rather than primary infection, and the implied risk of the donors being infected. All 112 donors have been notified that they are at increased risk of carrying the infection. The calculations in the assessment are independent of population prevalence, though obviously dependent on the chance of vCJD being transmitted via an infected transfusion. Assuming that transmissibility is high, all four cases appear more likely to have resulted from blood-borne rather than primary infection. For the recipient exposed to 103 donors, blood-borne transmission is much more likely, even though the implied risk is small for each individual donor.

These four cases might therefore be regarded as "possibly" (or perhaps one "probably" and three "possibly") blood-borne, making a maximum of seven clinical cases in total. All these transfusions were of non-leucodepleted components, except for that involving exposure to two donors.[11] If these cases were indeed blood-borne, the implied incubation periods from transfusion to onset of symptoms range from 4.6 to 6.25 years.[12] The recipient with three exposures received Fresh Frozen Plasma, and this *might* therefore represent a transmission via FFP, at the rather early transmission date of 1993.

Other than these, there are no cases in which any recorded transfusion provides a plausible route of transmission. Transfusion records may not be complete, despite follow-up of individual cases, but gross under-ascertainment of blood-borne cases appears unlikely, especially if the cases identified in the "reverse risk assessment" are included. By comparison, some existing scenarios "predict" incidence of blood-borne cases greatly exceeding the *total* number of clinical cases (currently 175).

As an upper bound, we suggest that plausible transmission scenarios should "predict" no more than 10 blood-borne clinical vCJD cases to have occurred by the start of 2011. This represents an incidence of about one case per year during the period 2000-2010. The maximum of 10 cases allows for all the additional four just discussed, plus some "margin of error" for undetected transfusions or linkages.

Results from existing scenarios

In comparing scenarios with case data, it is instructive to consider both the cases predicted to have come via Red Cell transfusions and those via transmission from all components – i.e. Red Cells, FFP, platelets and cryoprecipitate. This was discussed at greater length in the previous paper for SEAC (Bennett and Daraktchiev, 2010). To illustrate the "calibration" problem more fully, we assume that:

- Donors infected in the primary outbreak would typically have been infective from 1994 onward – i.e. with some delay between infection and onset of infectivity.

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[11] The original draft of this paper was incorrect on this latter point, and was amended at the subgroup meeting.

[12] See: http://www.cjd.ed.ac.uk/TMER/reverse.htm The case with 103 exposures received a variety of components, including Red Cells, FFP, platelets and cryoprecipitate, as well as one unit of whole blood, all during 1993.

- 2.5m units of Red Cells have been transfused in each subsequent year.

Infections within each age cohort, and the probability of recipients surviving, can be calculated using NHSBT data (which suggest a conservative estimate of 28% of Red Cell units going to recipients who survive at least 10 years). Table 2 below then shows the results of using two alternative calculations regarding incubation periods. The first represents a simple "deterministic" model whereby 40% of the population (i.e. MM homozygotes) have a 10 year incubation period, the other 60% having 20 years. The second assumes that incubation periods are subject to a Gamma distribution calibrated to reproduce the same cumulative percentages at 10 and 20 years.[13]

For simplicity, the table distinguishes between high and low scenarios for susceptibility and prevalence, but not for infectivity. The choice between "high" and (relatively) "low" infectivity makes very little difference to model predictions, as only a very small proportion of these historical transmissions would have involved leucodepleted Red Cells. This helpfully eliminates one source of variability in comparing predictions with case data.

Table 2: Clinical vCJD cases from Red Cell transmission expected by 2011 in existing scenarios

Scenario		Deterministic Distribution	Gamma Distribution
High Susceptibility (100% of population)	**High prevalence (1 in 4,000)**	**420**	**371**
	Low prevalence (1 in 20,000)	**84**	**74**
Low Susceptibility (10% of population)	**High prevalence (1 in 4,000)**	**42**	**37**
	Low prevalence (1 in 20,000)	**8**	**7**

The equivalent calculations for all components, assuming annual transfusion of 3.2m units and slightly lower overall 10-year survival rates, produce figures roughly 25% greater (with "top line" figures of **509** or **449** cases).

These scenarios clearly over-state the reported number of cases - often grossly – despite assuming delayed onset of infectivity. Only those combining "low" susceptibility and prevalence are within the suggested upper bound of 10 cases.

There are many simplifying assumptions, but these cannot account for such pronounced over-prediction. Indeed, some of the simplifications *reduce* the numbers of cases predicted. For example, the estimates for cases transmitted via

[13] This use of a single distribution follows Clarke and Ghani (2005) and the US Food and Drug Administration (FDA, 2005). The more fully-developed models discussed later consider incubation periods separately for MMs and other genotypes.

all components ignore the increased exposure resulting from pooled production of cryoprecipitate and (some) platelets. As detailed in Annex A1, historical usage of Red Cells varied somewhat year on year, but 2.5m represents a conservative average figure (the gradual decline in usage shown also means that projecting historical calculations will slightly over-state the scale of current and future transmissions). Post-transfusion survival, though subject to some uncertainties, is estimated on a conservative interpretation of reasonably firm data.

Inputs and assumptions revisited

We now consider each of the key inputs in turn, given the most recent evidence available.

Infectivity

As noted, existing scenarios are based on evidence from rodent models, applying infective titres found *per ml* to human blood. As detailed in **Annex A4**, this approach leads to very large estimated doses (up to 7,000 ID) *per unit* of donated blood. Any infective component transfused would contain more than enough infectivity to infect any susceptible recipient. Any significant reduction in "predicted" transmissions would require hypothesised doses per unit to fall very substantially. Further evidence is now available from the results of ongoing experimental work on transmission of prion disease through sheep-to-sheep transfusion, while the passage of time allows more conclusions to be drawn from evidence on human transmission.

Ovine transmission of BSE (Houston *et al*, 2008; McCutcheon, Alejo Blanco, Houston *et al* 2011[14]) arguably provides the best available analogue to the human situation. Not only are sheep more similar to humans in many ways (as compared with rodents), but blood and its components can be transfused in similar volumes.[15] This in turn makes it possible to prepare components for experimental purposes using the same procedures as for human transfusions. Results from these studies confirm that prion infection can be efficiently transmitted by any of the components commonly transfused, and suggests that infectious doses *per unit* (as distinct from per ml) are substantial.

A recent paper by Gregori, Yang and Anderson (2011) estimates the levels of infectivity likely to be present in human blood, based on evidence both from human transmissions (detailed here in Annex A2, in updated form), and the sheep experiments already referred to – though excluding the most recent results, which have yet to be published. They find that both calculations support similar conclusions. The human data suggest an infectivity in the range 0.3-0.75 intravenous Infectious Doses (ID) per unit of (non-leucodepleted) red cells, depending on the method of calculation (the method supporting the higher figure appears the more realistic). This in turn suggests that an infective donation of Whole Blood would contain a few IDs. Their analysis of the published ovine data

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[14] (Note added, September 2011) This paper was provided to the subgroup prior to publication, but has since appeared: the reference has been updated accordingly.

[15] Gregori, Yang and Anderson argue that rodent models continue to provide a quick and convenient means of investigating infectivity, but that inevitable differences in the volume of inoculum make it problematic to apply findings on infectivity titres *per ml* to the human situation.

suggests a dose of the order of 0.8 ID per unit, equivalent to roughly 0.002 ID per ml.

To illustrate, a dose of 0.7 ID per unit transfused would imply a risk of transmitting infection very close to 50%.[16] As compared with existing scenarios, the numbers of infections and cases "predicted" for non-leucodepleted red cells would thus be halved. Though not sufficient to prevent model "over-prediction" as compared with case data, this would obviously be reduced. Perhaps more importantly, doses of this order make it easier to explain why large numbers of blood-borne cases have not appeared with short incubation periods - as might have been expected following receipt of very large doses via an efficient person-to-person route. Finally, lower levels of infectivity per donation would go some way toward explaining the otherwise-puzzling lack of clinical cases amongst recipients of plasma derivatives, including those *known* to have been exposed to vCJD-infected donors (Zaman *et al*, 2011). If a revised range of assumptions is accepted, risk assessments for these recipients will need to be re-visited, and this may lead to changes in those groups regarded and notified as being "at risk for public health purposes" by the CJD Incidents Panel.

A further key question is the distribution of infectivity within a donation of whole blood, which affects both the risks associated with the different components "as transfused", and the effects of leucodepletion. Existing DH models assume that infectivity is associated both with white cells and plasma, in roughly equal quantities: the former would be (almost completely) removed through leucodepletion, whereas the latter would be unaffected. For example, Gregori *et al* (2004) suggest that leucodepletion removes roughly 40% of the infectivity present in a whole blood donation, the remainder being associated with plasma. Both red cells and platelets "as transfused" contain significant quantities of plasma.

Significant association of infectivity with plasma is also supported by the published and ongoing research on sheep-to-sheep transmission already noted, which show that leucodepletion does not eliminate the risks of transmission. In this model (McCutcheon S, Alejo Blanco AR, Houston EF *et al, op cit*), transmissions of BSE have been observed following transfusions of all components (red cells, plasma and platelets), whether leucodepleted or not.

As against this, the pattern of human cases associated with red cell transfusion is difficult to explain unless leucodepletion had *some* effect. In the four years leading up to implementation of this measure (1996-99 inclusive) there were three presumed transmissions of vCJD, in which both donor and recipient developed the disease. All were associated with Red Cell transfusion. Had transmissions continued at a similar rate, and with similar doses leading to similar incubation periods, one would have expected (roughly) three more during the following four years, and for these to have been detected by the end of 2010. None has appeared. Though the small numbers prevent this argument from being conclusive, the "no effect" hypothesis appears implausible.

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[16] This dose thus corresponds almost exactly to 1 ID50 in a linear dose-response model. For a discussion of Linear and Poisson models, and the relationship between them, see Annex A4.

In any discussion of leucodepletion, it is important to distinguish between effects on the infective dose present in whole blood, on that present in a unit of red cells, and on the resulting probability of transmission. These do not necessarily vary in the same way.

- For example, if 40% of the infectivity in a whole blood donation is associated with white cells, leucodepleting whole blood would achieve a 40% reduction in infectivity (as previously suggested by Gregori et al, based on a scrapie/hamster model). However, this is *not* equivalent to reducing the infectivity of the red cell transfusions by 40%. The latter will contain almost all the white cells in the original donation, but less than 10% of the plasma. (Further studies referred to by Gregori, Yang and Anderson (*op cit*) suggest that approximately 20% of the infectivity present in whole blood remains in the red cell component.) Removal of White Cells will thus have a much greater proportionate effect on the infectivity of Red Cell units than it has on the infectivity on a whole blood donation.
- Nor does a percentage reduction in infectivity in the component transfused necessarily produce a similar reduction in transmission risk. Notably, in the existing "high infectivity" scenarios, each component would contain so many infectious doses per unit that orders of magnitude reductions would be required to produce any significant change in risk.

Calculations for a wide range of scenarios are provided in **Annex A4**. Clearly, it is difficult to reconcile all the pieces of evidence just cited. However, it is possible to construct scenarios *of the right order of magnitude* to be consistent with most of the above arguments. To illustrate:

- Suppose that a donation of infective whole blood contains roughly 4 Infectious Doses (IDs) of which 1 ID is associated with White Blood Cells (WBC) and 3 with plasma.
- Empirically, a unit of red blood cells as transfused contains 8% of the original plasma (for Top/Top processing), or 4% for the now more common Bottom-and Top (BAT) method (see Annex A4).
- *Without* leucodepletion, the red blood cell unit would therefore contain:

  1 ID associated with WBC + 0.2 in plasma = **1.2 ID** for Top/Top processing
  1 ID associated with WBC + 0.1 in plasma = **1.1 ID** for BAT

- *Leucodepletion* reduces the WBC count by a factor at least 10,000, so that cell-associated infectivity would be negligible compared to that in plasma. The residual infectivity per unit would thus be:

  0.2 ID for leucodepleted T/T units, or
  0.1 ID for leucodepleted BAT units

In this scenario, whole blood contains the "few IDs" suggested by Gregori, Yang and Anderson, 25% of it (rather than 40%) associated with WBC. A unit of non-leucodepleted red cells would contain about 25% of the infectivity in the whole donation, close to their suggested 20% – with the absolute levels somewhat higher than their estimated range. Though not eliminating the risk, leucodepletion would have a substantial effect on transmission rates. [**Note**: the consistency of this with

the latest, unpublished ovine data requires discussion.] It is also noteworthy that in scenarios such as this, the progressive replacement of Top/Top processing by BAT would have led to a significant further decrease in expected transmissions.

Clearly, this illustrative scenario does not provide a perfect fit with all the evidence: it could probably be improved. In particular, one might attach different weights to the evidence on human transmission via non-leucodepleted red cells with that on ovine transmission via leucodepleted components: these may be impossible to reconcile completely. Alternatively, there is a case for simply adopting the Gregori, Yang and Anderson estimate of 0.3 – 0.75 ID for non-leucodepleted red cells (or the upper end of this range), given that no animal model can be expected to mirror the human situation exactly. Any estimate used in risk assessment calculations should be subject to extensive sensitivity analysis. Nevertheless, there now seems to be no justification for persisting with the previous "high infectivity" scenario.

Prevalence - of abnormal prion protein and of infectivity

As discussed more fully in Annex A4, the key evidence for subclinical infection in the population comes from testing tissue samples for prevalence of abnormal prion protein. There are three key studies:

- Until very recently, estimation was entirely reliant on the retrospective Hilton *et al* (2004) study, which found three "positive" appendices in approximately 12,000 tested, using Immunohistochemistry (IHC). This suggested a prevalence of abnormal prion of the order of 1 in 4,000, with 95% confidence intervals ranging from approximately 1 in 20,000 to 1 in 1,200. All three samples were from patients born between 1961 and 1985, and it was suggested that this might represent a "high risk" cohort, with infection being rarer in both older and younger groups. Such a hypothesis would be broadly consistent with the age distribution of clinical cases.
- A large scale prospective survey of tonsils was then instigated, the NATA (National Anonymous Tonsil Archive) study (Clewley, Kelly, Andrews *et al*., 2009). This will complete in Spring 2012, but has already tested large numbers of samples from different cohorts. All tested negative using the methods originally specified (dual ELISA and Western Blotting). Discussion then ensued as to the consistency or otherwise of this negative result with the Hilton survey – and, indeed, whether one would necessarily expect consistent results from different tissues tested in different ways. However, 10,000 samples in the "Hilton cohort" were then re-tested, this time using IHC. One sample was found to be positive (de Marco *et al*, 2010), albeit with limited presence of the abnormal protein. This re-test result of 1 in 10,000 in the same cohort is clearly consistent with the Hilton study, while also casting doubt on the negative results obtained using the original methods in the other age cohorts.
- A further, large-scale appendix survey is now in progress, aiming to test samples from 30,000 patients (20,000 in the 1961-85 "Hilton" cohort, and 10,000 in the older 1941-1960 cohort) using IHC. This is due to complete in

Autumn 2012**,** but initial results have been received indicating that positives have been found in both cohorts.[17]

Although interim results generated by the discovery of positives may over-state the results of a full study, this finding casts serious doubt on any presumed differential between cohorts. All results to date would be highly consistent with a uniform prevalence of abnormal prion protein of (say) 1 in 10,000 or 1 in 5,000 for all those subject to the bulk of BSE exposure. There would still be some case for assuming a lower prevalence for the relatively narrow cohort born between 1985 and 1st 1996, given that exposure to BSE should have started to decline. However, there is at present no IHC evidence relating to this cohort. **A precautionary approach would be to apply a uniform prevalence estimate to all groups born up to 1st January 1996.** After this date, we continue to assume that measures in place to prevent BSE entering the human food chain would have led to a negligible incidence of new primary vCJD infections.

The most fundamental question, however, is whether presence of abnormal prion protein somewhere in an individual's body - whether in appendix, tonsil, or some other tissue - should be regarded as indicating that his or her blood would necessarily be infective. The precautionary approach to risk assessment purposes has been to assume that those *infected* with abnormal prion protein would uniformly be *infective* (at least after a fairly short period post-infection), with consequent transmission risks not only via donation of blood, tissues and organs but also from re-use of surgical and dental instruments. Only for CNS tissue has relatively late onset of infectivity been assumed. Implicitly at least, a single notion of "prevalence" has been assumed to characterise all these risks. As discussed further in **Annex A3**, accumulating negative evidence has made this simple view less tenable.[18] Any discussion of prevalence requires careful specification as to what is meant, whether prevalence of people with abnormal prion protein in a specific site, or "somewhere in the body", or prevalence of specific forms of infectivity.[19]

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17 (Note added September 2011) When this paper was written, there had been reports of two positive samples. One (from the first 8,200 tested) was in the 1961-85 cohort, and the other (from the first 2,400 tested) from the 1941-60 cohort. A further report was provided at the subgroup meeting, indicating at least two further positives (one in each cohort). The findings to date are due to be published simultaneously with this paper on the HPA website at http://www.hpa.org.uk.

18 For potential transmission of vCJD via re-use of surgical instruments, the relevant DH risk assessment, was last revised in 2005 (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4113541). Since then evidence on the efficacy of instrument decontamination has (if anything) lent more weight to scenarios toward the pessimistic end of the ranges considered. Yet there have still been no detected cases of vCJD transmitted via surgery. Although any association with surgery may be more difficult to establish than a link to transfusion, and there are obvious issues of survival – especially for neurosurgical patients - this absence is difficult to explain. On a "moderately pessimistic" interpretation of the available evidence, a prevalence of 1 patient in 10,000 infective would lead to the order of 100 transmissions *per year* from neurosurgical operations alone.

19 Indeed, the effects of fixation mean that no conclusions can be drawn from the failure of the positive Hilton samples themselves to transmit infection to transgenic mice (Wadsworth, Dalmau-Mena I Joiner et al, 2011).

If this view is accepted, scenarios for the prevalence *of infective donors* do not necessarily have to be bounded by the Confidence Intervals produced by tissue surveys. Receipt of an infected donation might then be seen as a *very* rare, though high-risk event. This provides one way of reconciling the high blood-borne transmissibility implied by animal models with the small number of cases seen.[20]

Susceptibility to clinical disease

As already noted, any value could be chosen for susceptibility in order to reduce the predicted number of cases. However, the existing "low susceptibility" scenarios already restrict the recipients amongst whom symptoms of vCJD might have been seen to just 10% of MM homozygotes (i.e. 4% of recipients). Any further restriction risks being entirely arbitrary, unless some biological basis for restricted susceptibility can be found.

A further possibility is that susceptibility to clinical vCJD following transfusion might be markedly *age-dependent*, for example through some maximum age "cut-off". This is explored in **Annex B3,** which shows that such a cut-off would have a relatively modest effect, after allowing for age-related differentials in post-transfusion survival. In addition, two of the three vCJD cases who received blood from donors who went on to develop the disease were aged over 60 at transfusion, and the other under 20. This indicates that neither youth nor comparative old age precludes development of vCJD through this infection route. Restricting susceptibility to recipients aged at least 65 would reduce the expected number of cases only by about 30%.

Incubation periods

This is the other main factor determining the projected number of clinical cases (Bishop et al, 2006). Without making some assumptions about likely incubation periods following blood-borne infection, it is impossible either to calibrate a transmission model or to use it to assess future risks. Current DH models assume a mean incubation period (from infection to symptoms) of 10 years for susceptible MM-homozygotes. This is longer than for any of the three cases linked to vCJD donors (6.5, 7.8 and 8.3 years), or the four others with relevant transfusion histories (if these cases were in fact due to blood-borne infections). However, one would naturally expect cases with shorter-than-average incubation periods to appear first. For comparison, a rough estimate of 10-12 years for primary infections amongst this genotype is often cited, based on the timing of the peak in onsets as compared with that in BSE exposure.

Clearly, projected case numbers would be reduced if typical incubation periods for MM homozygotes were *much* greater than 10 years. However, that would require secondary incubation periods to be as long, or longer, than for primary infections in this genotype. Given that secondary (within-species) incubation periods are usually shorter, that seems unlikely – at least if the per-unit infectivity of blood components

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[20] Even so, we suggest that for modelling purposes – and in the absence of contrary evidence – that the prevalence of infective donors be regarded as *proportional to* that of abnormal prion protein in tissues. In other words, if the prevalence of prion protein is fairly constant across pre-1996 age cohorts, so is the that of infective donors.

is significant. The current working assumption of a 10 year mean for blood-borne infection is precautionary in assuming only a small differential between routes.[21]

For both other genotypes, our baseline assumption is of a mean secondary incubation period of 20 years: given that no such cases have been observed, this is inevitably speculative to some extent, but appears plausible. This parameter can be varied widely without affecting the number of cases "predicted" to date. One could also separate the assumptions made for MV and VV genotypes, but little is currently known about the likely relativities between these groups. Their relative proportions in the population – 50% MV versus 10% VV – also suggests that any numerical projections will be strongly dominated by the former.

The distribution of incubation periods is also of some significance - the shape of the curve that will determine when cases appear amongst those infected. Most models, including the DH/CORU one outlined below, use Gamma distributions to characterise this, allowing the shape of the curve to be varied quite flexibly and facilitating sensitivity analysis. (The Imperial College model also discussed below uses an even more flexible distribution, with four independent parameters rather than three.) The common assumption, however, is that these distributions are unimodal – i.e. have a single peak – for each of the three codon-129 genotypes. For primary infections, for example, this model implies that the single wave already seen is "the" MM wave, now apparently coming toward its end. Though there may be subsequent waves of MV and VV cases, their expected size is limited by knowing that MMs comprise 40% of the population and that later waves will be more attenuated by deaths from other causes. The same arguments apply to secondary cases.

This view would fail, however, if the distributions had two or more peaks. For example, if relatively short incubation periods were confined to those who are *both* MM at Codon 129 *and* have some other, fairly rare, characteristic. The cases seen so far might comprise only a small part of the overall MM "wave". Similarly for other genotypes and other transmission routes. Though hypothetical, this would prove another way of reconciling relatively high prevalence of infection with small case numbers: it would also make the small number of blood-borne cases seen so far a poor guide to future numbers. **Advice as to whether this has any plausibility, and if so how it might be investigated, would be welcome**. The hypothesised gap between peaks is also significant. Were they to be widely spaced, few of those who would have appeared in subsequent peaks might survive long enough to develop symptoms. The situation would become equivalent to that characterised by non-susceptibility to clinical disease.

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[21] There is no evidence from sheep experiments of adaptation of the infective agent to the host species, which in studies of other TSEs has led to shorter incubation periods. Our understanding from presentations of this ongoing research is that there is a preliminary indication that the reverse might happen.

5. Establishing more credible projections

Although the calculations just given suffice to show the implausibility of some current scenarios, it is more difficult to determine what should be changed. Establishing a more plausible range requires a rather more sophisticated modelling approach. In particular:

- Plausible scenarios may be bounded by *combinations* of inputs, rather than by separate ranges for each. For example, if we assume that an infected unit is highly-likely to transmit vCJD and that prevalence of infective donors has been relatively high, then consistency with case data requires us to take a low value for susceptibility to blood-borne disease. Conversely, 100% susceptibility would imply a very low prevalence of infective donors. We need to characterise the "feasible space" created by these trade-offs.
- We need to consider *cohort effects* that could be caused by the prevalence of infective donors varying by age. Without having done so, we cannot assume that past rates of transmission would necessarily be an appropriate guide to the future.

Throughout, we need to distinguish between secondary infections *that would have already shown up* as clinical cases (critical for model calibration), past infections that *have not (yet) led to cases*, and infections that *have yet to occur*. Only the last could still be prevented. Changes in scenario inputs will change each of these in different ways.

Scenario inputs in combination

Because expected case numbers depend on a combination of factors, calibration requires us to consider an "envelope" in which these factors are combined.

This can be illustrated by considering alternative scenarios each predicting about one clinical case per year during the10 years up to the end of 2010 - roughly the maximum credible rate. The following tables set out the *maximum possible prevalence of infective donors* during the 1990s compatible with this rate, given different assumptions about the proportion of infected recipients liable to develop symptoms within 10 years, including one scenario with an upper age cut-off as discussed above. Column (a) assumes that transmission via an infective donation would be virtually certain, Column (b) a probability of 50% (as suggested by the Gregori, Yang and Anderson model discussed earlier). All figures are "rounded" in ways that widen the feasible range of scenarios – e.g. taking conservative estimates of 3m units of components transfused annually, with 25% going to recipients surviving at least 10 years.

These simple calculations demonstrate the trade-offs between key parameters. For example, suppose an infected component is virtually certain to transmit. If we assume that all infected (and surviving) MM homozygotes would develop symptoms of vCJD within 10 years of transfusion, then over-prediction of cases can only be avoided by assuming a historical prevalence *of infective donors* of at most 1 in 300,000. By contrast, if the transmission probability is taken to be 50%, and development of symptomatic vCJD within 10 years is confined to just 10% of MMs, then historical prevalence could have been as high as 1 in 15,000.

Table 3: Prevalence of infective donors leading to 1 clinical case per year after 10 years: alternative scenarios.

% infected recipients symptomatic within 10 years	**Prevalence of infective donors**	
	(a) With certain transmission	(b) With 50% chance of transmission
All MM homozygotes (40% population)	**1 in 300,000**	**1 in 150,000**
MMs aged under 65 at transfusion (70% of the above)	**~ 1 in 200,000**	**~ 1 in 100,000**
10% of MMs, regardless of age	**1 in 30,000**	**1 in 15,000**

Despite the complexities involved in projecting future numbers of clinical cases, we suggest that this simple "envelope" approach provides a way of delimiting the risks of vCJD infection arising from *historical* exposure to blood components. This is an important question for risk assessments that inform current risk management decisions affecting specific individuals and groups, as discussed in Section 6.

Modelling cohort effects

Clearly, the prevalence of infective donors may vary by age group: if so, historical rates of transmission might not be a good guide to current and future risks. One possibility that has attracted attention is that of prevalence being confined to – or at least concentrated in - the 1961-85 "Hilton cohort". The expected rate of blood-borne transmissions would then vary over time, as more individuals in that cohort became eligible to donate blood, then eventually too old to do so. As noted earlier, the latest evidence from the current appendix survey makes this less plausible. Nevertheless, there are great uncertainties as to how prevalence of infective donors might vary by age, and it is important to explore the consequences of alternative scenarios.

It is generally accepted that any risk of primary infection amongst those born from 1996 onward should be very small, given the precautions by then in place to remove BSE from the food chain. These individuals are not yet eligible to donate blood, but will be so within a few years. As a greater proportion of donors are drawn from this group, future blood-borne transmission risks will gradually decrease and should – over the course of several decades – eventually disappear.[22] Risk assessment needs to take this dynamic into account. It may also be feasible to speed the decrease in risk by deliberately recruiting younger donors in the coming years: this will be subject to further analysis.

The rest of this section outlines and illustrates two different age-structured models, which might play complementary roles in future risk assessments.

The Imperial College Model

This is a complex stochastic simulation produced by the MRC Centre of Outbreak Analysis and Modelling (Ghani and Garske, 2010). Building on earlier work (e.g.

[22] This depends on there being no potential for the outbreak becoming "self-sustaining" through onward transmission of infection. This now appears to be a reasonable working assumption. As discussed further below, the prohibition on recipients of blood components from donating is beneficial in this respect, but it is not necessary to assume 100% compliance.

Clarke and Ghani, 2005), it covers both primary and blood-borne vCJD infections, though the latter includes only transmission via Red Cell transfusion.

The model uses a Bayesian approach, based on updating probabilities. Fifteen different "unknown" parameters for the vCJD epidemic (transmissibility, mean incubation period and shape, proportion of cases subclinical, etc) are given prior probability distributions, based on a mixture of available evidence and reasonable assumptions. All parameters are then sampled in combination, generating a very large number of scenarios for the resulting incidence of clinical cases. The basic results come from running the model with over 1.5 million combinations of inputs, with further runs for sensitivity analysis. Each scenario has a posterior likelihood – that of any one scenario amongst so many obviously being small. (The authors have kindly provided a spreadsheet with the 2000 "most likely" model runs, which we have been able to explore.) The overall result is expressed in terms of a distribution of scenarios characterised by a median result with upper and lower credibility bounds.

Throughout, the population is stratified by both age and genotype. Incubation periods[23] are assumed to be highly genotype-dependent, with a constant ratio between primary and blood-borne incubation periods for each genotype (MM, MV and VV). Susceptibility is taken to be highly age-dependent for primary infection, but not for blood-borne transmission.

Prevalence of infection in the population is not treated as a input: rather, it derives from the model. However, the model is at present calibrated to (probabilistically) fit the Hilton *et al* study. In practice, most of the resulting scenarios - and especially the more probable ones - force prevalence of infected donors toward the 1 in 20,000 lower-bound confidence interval for the 1961-1985 cohort, and to very low levels for the others.

Blood-borne clinical cases are classed as "identifiable" or "unidentifiable" according to whether the infective donor also develops clinical vCJD rather than dying of other causes. The model is calibrated so that the number of "identifiable" blood-borne cases predicted by the end of 2009 approximates to the three identified (and similarly for the number of predicted primary cases). By this definition, over 90% of all blood-borne cases would be "unidentifiable", most having come from infected non-MM donors who may never develop clinical vCJD.

This terminology is problematic, in that blood-borne cases with no identifiable source of infection may be identified as such through the "reverse risk assessment", at least on balance of probabilities. Indeed, the four already discussed may be examples of the "unidentifiable" cases predicted by the Imperial model. In addition, if two or more recipient cases were linked to a single donor - as happened with two of the three "known" cases – transmission would be established beyond reasonable doubt, whether or not the donor developed vCJD (Bennett, Dobra and Gronlund, *op cit*). However, this terminological point does

[23] In this model, "incubation period" is defined as duration of infection to death, rather than to appearance of symptoms.

not affect the predicted number of cases, nor their division into *those linked to a symptomatic donor* and those *not* so linked. This remains an important distinction.

The Imperial model is calibrated against the three "identified" cases seen by the end of 2009, rather by considering the total number of blood-borne cases predicted, though most scenarios generated have fewer than 10 "unidentified" cases occurring by the end of 2009. Nevertheless, model calibration might helpfully be extended by considering both totals, and by updating the period during which the cited numbers have been observed. This is in addition to incorporating the new evidence both on prevalence of abnormal prion infection and on infectivity already noted.

On the effectiveness of existing risk reduction measures:

- Leucodepletion is taken to reduce transmission rates by 40% in the baseline scenarios.[24] However, scenarios with no effect are considered in sensitivity analysis, as discussed further below.
- Baseline scenarios take the ban on previously-transfused donors already referred to as being 90% effective, rather than assuming complete compliance. However, sensitivity analysis shows this figure not to be critical. Most transmissions would come from donors infected in the primary outbreak, with few tertiary or higher-order transmissions expected given even moderate compliance with the "transfused donor" ban.

Results from this model are reproduced in Figure 1 and Table 4 below. These show the numbers of clinical cases that might be eventually by expected to appear, by genotype and transmission route. The simulations run up to 2179, though almost all predicted cases would have occurred by about 2080, as can be seen. Although a wide range of scenarios remains possible, the most likely outcome is a long-drawn-out series of secondary cases, typically a few each year and peaking at roughly ten in about 2030. The large majority would be amongst MM genotypes, and unlinked to donors who would develop clinical vCJD. Re-running the model with no new transmissions from 2010 onward shows that a large proportion of future cases would be caused by transfusions yet to happen. This reflects the long-drawn-out nature of the predicted epidemic curve, in which significant numbers of those infected in the primary outbreak may survive for long periods in an asymptomatic but infectious "carrier state".

A long-run comparison of these results with the existing DH scenarios is offered at **Annex B1**. Whilst the ranges generated by the two approaches intersect, the Imperial model predictions are generally lower: in particular, the most pessimistic DH scenarios fall well above the Imperial 95% Confidence Interval. The differences in shorter-term (e.g. 10-year) projections are more marked. Projecting the DH scenarios shown in Table 2 forward would lead one to expect about 60 new clinical cases per year, as compared with the small numbers illustrated for this period in the graphs of Figure 1.

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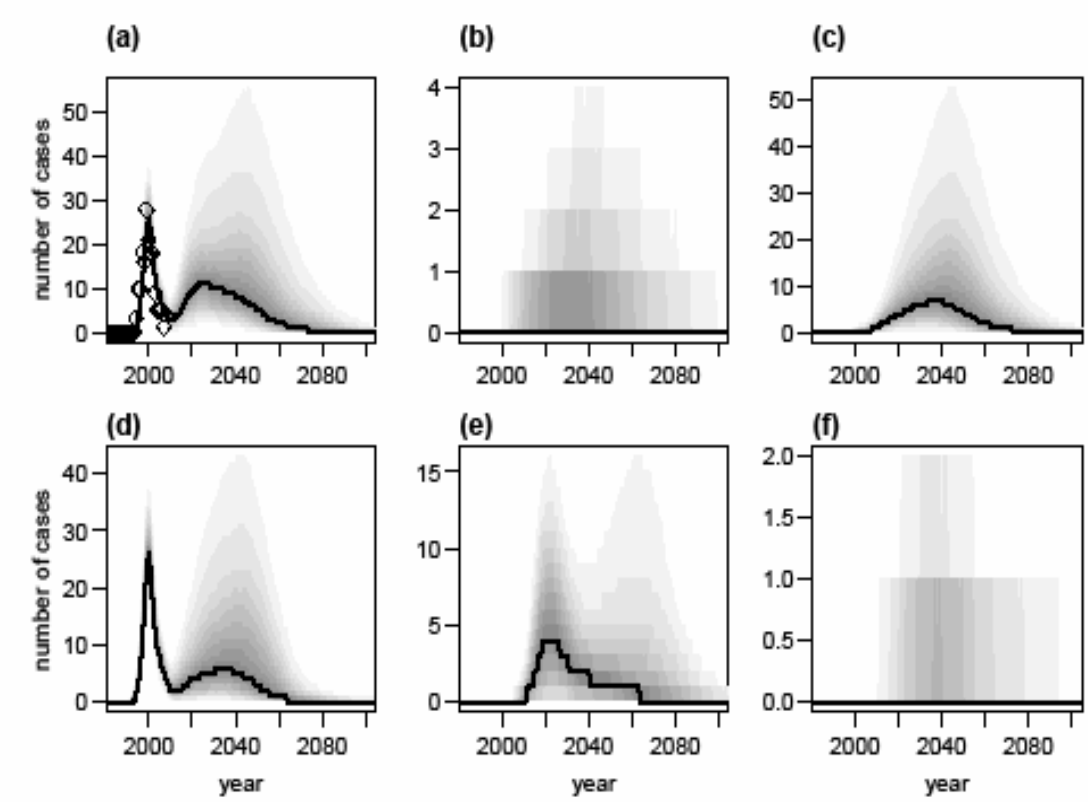
[24] This is based on the evidence from Gregori et al (2004). As already discussed, however, this estimate is for whole blood in hamsters. Even if the same percentage applies to human blood, it does not carry across to risks from red cell transfusion.

Figure 1: Results from Imperial Model, from Ghani and Garske (2010)



Note: Table (a) shows total number of cases, with sharply peaked primary wave followed by the more long drawn-out secondary wave due to red cell transfusion. Tables (b) and (c) shown identifiable and non-identifable blood-borne cases, while tables (d) (e) and (f) break down the total case numbers into MM, MV and VV genotypes. Solid line indicates median scenario from model.

Table 4: Numerical summary, showing medians and 95% credibility intervals.

	clinical cases 2010 - 2179 by genotype and infection route			
genotype	**Total**	**Primary**	**"Identifiable" blood**	**"Unidentifiable" blood**
All	390 (84 – 3000)	100 (11 - 220)	**17 (1 - 220)**	**260 (30 - 2700)**
MM	200 (20 – 2200)	1 (0 – 6)	12 (0 – 160)	190 (16 – 2000)
MV	160 (4 – 980)	91 (1 – 210)	4 (0 – 57)	51 (1 – 760)
VV	13 (0 – 85)	7 (0 – 36)	0 (0 – 5)	5 (0 – 51)

If leucodepletion is taken to be ineffective, the effect on projected case numbers is mixed.

- The upper 95% credibility limit for blood-borne cases roughly doubles
- However, the median prediction *decreases*, to just over 300.

The latter might seem counter-intuitive, but can be explained by the model being calibrated against observed cases. If leucodepletion is ineffective, the model must

compensate for this to avoid over-prediction of case numbers. Other parameters are then more likely to take less “pessimistic” values: the net result is to decrease, rather than increase, expected case numbers in the more likely scenarios.

DH/CORU model

This extends the previous DH approach, primarily by allowing prevalence of infective donors (treated as an input) to vary by age. For example, if there is a “higher risk” cohort, this shows how transmission rates would change as these individuals became old enough to donate, and then eventually too old to do so.

In generating scenarios, the model also allows the choice of various additional inputs:

- distributions for time of infection and onset of infectivity in donors,
- gamma distributions for secondary incubation periods, with means and shape parameters chosen separately for MM and non-MM recipients
- the facility to vary the effect of leucodepletion – if any - on transmission rates before and after 1999
- a facility to “turn off” new infections rapidly, to show how many future cases are caused by transmissions that have already happened

The model remains relatively simple, and does not attempt to capture every possible aspect of transmission risk. However, it does provide a way of rapidly exploring what happens as individual parameters are varied, and how different scenarios – including those highlighted by the Imperial model – might occur.

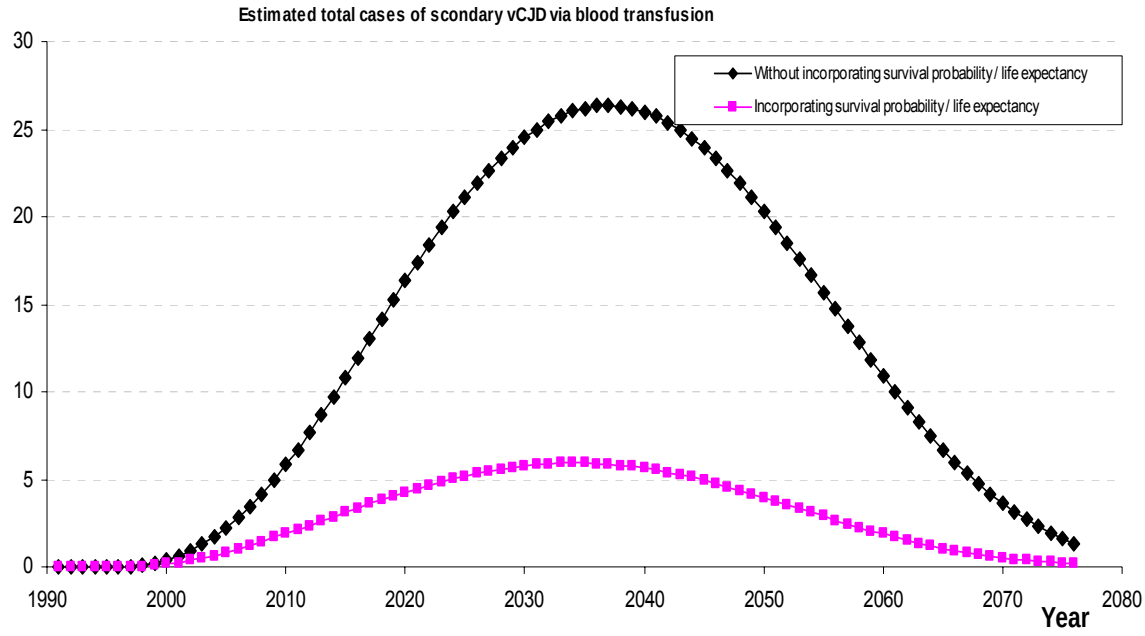
The model is illustrated further in **Annex B2**, using various combinations of inputs. These show that:

- Running the model with “blanket” prevalence of 1 in 4,000 donors infective produces over-prediction of the same order as in the simple calculations provided earlier in this paper. With 100% susceptibility, over 500 clinical cases resulting from Red Cell transmission would have been seen by the start of 2011.
- Confining infective donors to the “Hilton” cohort, and limiting prevalence to 1 in 20,000 is *not* sufficient to prevent over-prediction if susceptibility is 100%. Combining these inputs with a modest delay in onset of infectivity, the model “predicts” roughly 50 clinical cases to date.
- If leucodepletion is assumed to have stopped transmissions from 1999 onward, it is easy to produce scenarios matching the timing of cases seen so far (though their number is still exaggerated unless susceptibility is significantly below 100% or prevalence of infective donors below 1 in 20,000).

This relatively simple model can also reproduce key features of the *published* Imperial model. Plausible assumptions for the relevant parameters also produce a long drawn-out pattern of secondary cases, peaking around 2030 - 2040. If susceptibility is adjusted to 35% to prevent over-prediction of cases to date, the

model produces numerical results close to the existing Imperial median scenario. For example, that shown below has 231 future cases from Red Cell transfusion (as compared with 267), with 10 having appeared by the end of 2010 – the maximum suggested above for model calibration. Underlying assumptions are set out more fully in Annex B2.

Figure 2: DH/CORU model output similar to Imperial median scenario [~ 1 in 20,000 donors born 1961-85 infective; 35% of recipients susceptible to clinical vCJD].



Blood-borne clinical cases: 10 prior to 2011, 231 thereafter

This model output can be generated by many combinations of inputs, for example on prevalence of infective donors, transmission probability and susceptibility to clinical vCJD, e.g.:

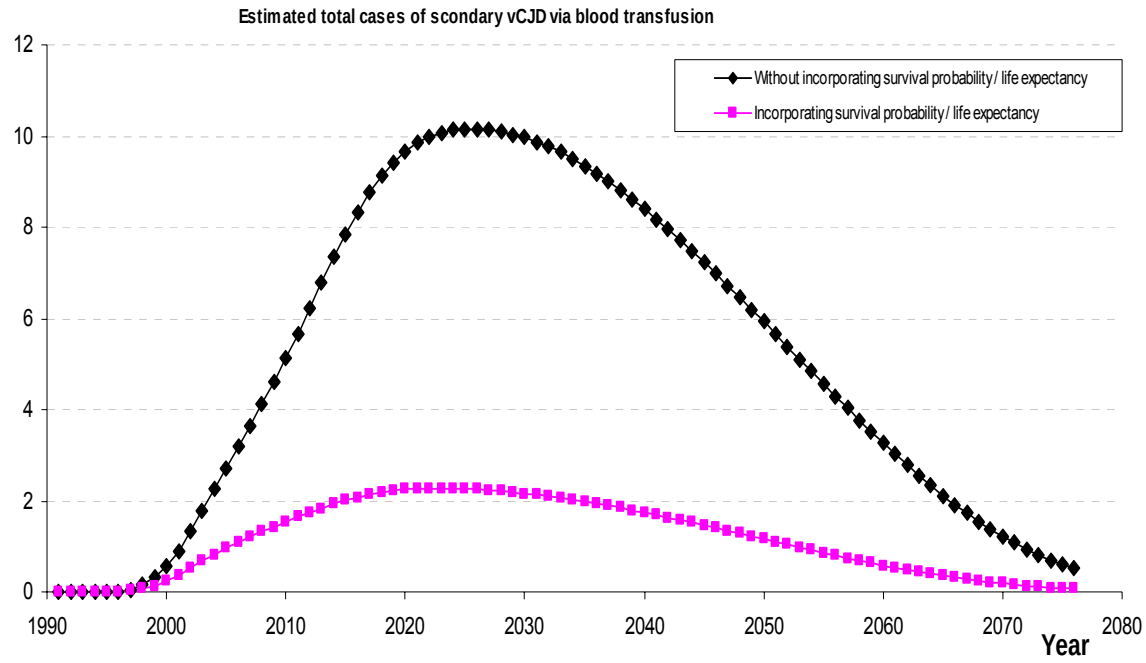
- prevalence 1 in 20,000 donors infective in the “Hilton” cohort, certainty of transmission and 35% of recipients susceptible to clinical disease;
- the same prevalence, 50% transmission probability and 70% susceptibility
- prevalence of 1 in 30,000 infective donors in the cohort, 50% transmission and 95% susceptibility.
- and so on…..

Whether the difference between these assumptions matters or not will depend on the intervention being considered.

Like the published Imperial model, however, the above scenario takes prevalence of vCJD infection to be concentrated in the “Hilton” cohort. Suppose now that – as may be suggested by most recent appendix survey findings - prevalence of infection is spread evenly across all pre-1996 birth cohorts. The effect is to make the projected curve of cases flatter, with a higher ratio of “past” to “future” cases. If the chance of transmission is still assumed to be high, avoiding over-prediction of cases to date requires lower susceptibility to disease amongst recipients and/or

fewer donors to have had infective blood. This in turn reduces the projected number of future cases. For example, the scenario shown in Figure 3 below has a uniform1 in 20,000 donors infective, amongst all born 1941-1996. Calibrating this as before to produce 10 cases to date requires only 10% of recipients to be susceptible to clinical vCJD. The final result is a scenario with less than half the number of future cases.

Figure 3: Scenario with 1 in 20,000 of all donors born before 1996 infective [10% of recipients susceptible to clinical vCJD]



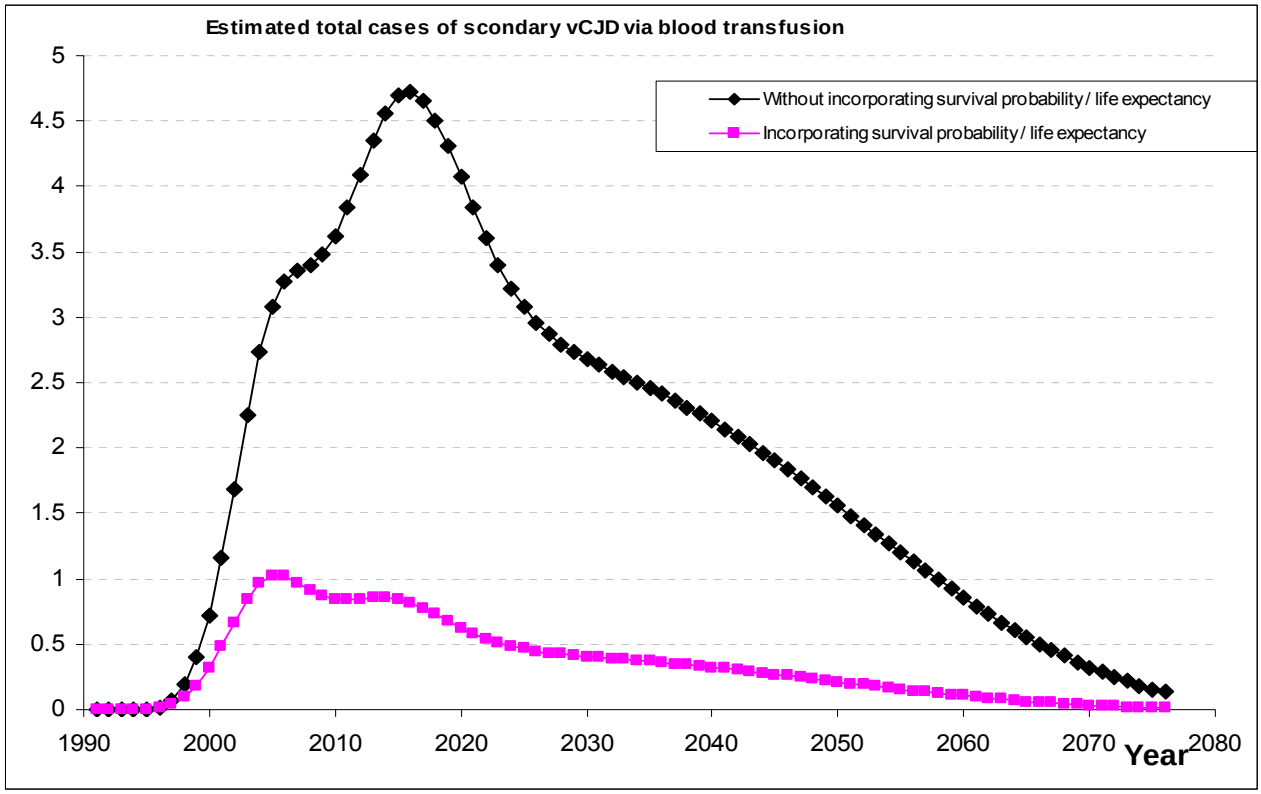
Blood-borne clinical cases: 10 prior to 2011, 89 thereafter

The scenarios illustrated so far retain the assumption of transmission being essentially certain from any infected unit, with or without leucodepletion. However, the analysis can be generalised to allow for variation in transmission probability. For example, the output shown in Figure 4 below is based on the infectivity scenario suggested in Section 4 (p.12), with units containing 1.2 ID prior to the introduction of leucodepletion, and 0.1-0.2 ID thereafter. The corresponding transmission probabilities would then be 70% and roughly 15% (the latter depending on the relative proportions of Top/Top and BAT units transfused). Lower historical transmissibility means that consistency with case numbers to date can be maintained with a higher susceptibility to clinical disease (25% rather than 10% in the previous scenario). Even so, the impact of leucodepletion on the expected number of future cases is great. (In addition, a higher proportion of future cases would result from transmissions that have already occurred.)

Like the others, this scenario is presented as an illustration only, pending advice on what ranges of inputs and assumptions are now appropriate. Note that successive calibrations have been carried out by crudely adjusting susceptibility to disease:

this could equally have been done by adjusting prevalence of infective donors, or some combination of parameters. The key point is that the ratio between past and future cases is set by the shape of the curve shown. If calibration against cases to date is required, the output is then scaled up or down accordingly - as reflected in the changes in vertical scale on the graphs.

Figure 4: Scenario as above, but with lower per-unit infectivity
[25% of recipients susceptible to clinical vCJD]



Blood-borne clinical cases: 9 prior to 2011, 21 thereafter

6. Suggested Approach to Risk Assessment

For practical purposes, Risk Assessment needs to provide:

- a range of scenarios for the number and timing of future vCJD cases in the absence of further interventions, and how many would be caused by transmissions yet to occur.
- ways of exploring the possible impacts of potential future interventions
- ways of estimating risks of blood-borne vCJD infection from historical exposure.

We consider each of these in turn.

Future cases in the absence of further interventions

The Imperial methodology provides a model for both primary and secondary (Red Cell) transmission, taking account of a multiplicity of parameters. Critically, it also provides estimates of the *relative likelihood* of different outputs, rather than just a range of possibilities.

There is thus a strong case for using this approach to establish a range of baseline projections. Subject to any necessary recalibration, the median result from the Imperial model, and its upper and lower 95% credibility limits, might be taken to provide the most likely, worst and best reasonable projections of case numbers caused by Red Cell transmission.

Although the Imperial model deals with Red Cell transfusion only, most of the inputs and assumptions read across to transmission via FFP, platelets and cryoprecipitate. Unless there is any evidence to the contrary, future cases transmitted by these components could be estimated by applying the model results pro-rata to the numbers of units transfused. For example, the number of units of FFP transfused annually has typically been around 15% of the number of Red Cell Units (see Annex A1).[25] Assessing the risks of transmission via components subject to pooling (some platelets and all cryoprecipitate), introduces additional uncertainties. In the worst case of high infectivity, a unit might contain a high-enough dose to infect for certain if *any* of the contributing donors were infective. If "high infectivity" scenarios are to be retained (despite the arguments advanced in this paper), an additional set of calculations would be needed, with expected case numbers proportional to the number of donor exposures rather than units transfused.

Effect of future interventions

To assess the potential effect of any future risk reduction measures, it would be helpful to have a simple model, to explore the consequences of changing *single* parameters, in ways that would affect *future* transmissions only. The Imperial model is not set up for this – and is resource-intensive to run.

We therefore propose to investigate whether plausible inputs to the DH/CORU model can be used to generate families of scenarios with case numbers similar to each of the median, upper and lower "Imperial" scenarios. The example given in the previous section illustrates the principles involved. As already noted, however, both models require adjustment to take account of the latest empirical evidence, and there is no guarantee that this could be achieved with the revised models.

An alternative approach would be to use the Imperial College model to ascertain the likely future pattern of primary cases, and the number and age distribution of those infected by that route. This could then be used as a starting point for a separate analysis of blood-borne secondary transmission. This would have some advantages in terms of model transparency, but lose the possibility of comparing results obtained from two different methods.

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[25] As noted previously, at least one of the clinical cases seen to date *might* have been caused by transfusion of FFP.

Assessing risks from historical exposure

Key decisions on management of those who may be at increased risk of vCJD infection depend critically on assessing the historical risk from potentially-infective blood donations. Such decisions are subject to advice from the CJD Incidents Panel, which often has to make recommendations as to whether people are at sufficiently increased risk to warrant notification, so that precautions against onward transmission can be implemented (CJD Incidents Panel, 2005). 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 (Pryer and Hewitt, 2010). In general, the Panel recommends notification unless the risk of infection is estimated to be less than 1%, calculated using pessimistic (precautionary) assumptions.

At present, the Panel uses the highly-precautionary assumption that 1 in 4,000 donors would have been infective, in theory since the start of the BSE outbreak, and regardless of age cohort. As we have seen, this is difficult to reconcile with the number of cases actually appearing. Establishing a more credible working assumption is particularly important in assessing:

(a) risks to "highly transfused" patients with no links to known vCJD-infected donors, where calculated risks are entirely dependent on estimates of historical prevalence and transmissibility.

(b) the relative likelihood of a *known* vCJD infection having come from different routes – e.g. for an individual exposed to blood components, and implicated and non-implicated plasma products.

In both contexts, decisions as to whether estimated levels of risk warrant notification can have critical impacts on individuals' lives. In addition, the second situation can require us to compare the probabilities of alternative infection routes, where some calculations depend on prevalence of infective donors and others do not[26] (Bennett and Ball, 2009). Overstatement of the former could therefore lead to underestimation of the latter.

Despite the many remaining uncertainties about future transmission risks, we suggest that current evidence is now sufficient to justify a marked revision of existing calculations. Risks from historical exposure need to be assessed in a way more consistent with case numbers seen to date, while remaining precautionary. This can be done using the rationale set out in the first part of Section 5. Specifically, Table 3 sets out different combinations of inputs consistent with observed clinical case numbers. The most precautionary basis for "calibration" is to suppose that only 10% of MM homozygotes infected via transfusion would have shown clinical symptoms within 10 years, meaning that the large majority of infections 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.** This could be reached by different combinations of prevalence and transmissibility

[26] In general, prevalence estimation is *not* required when there is a known "index case" – e.g. in calculating risks to recipients of blood components or products sourced from a vCJD donor, donors to vCJD cases and those involved in most surgical incidents.

(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 in assessing the resulting risk of having been infected.

If accepted, this would retain a simple – but more credible – rule of thumb for risk assessment and management purposes.[27] We suggest that calculations of exposures should count all transfusions from 1990 onward. Clearly, 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 infections amongst recipients surviving at least 10 years would have shown up as clinical cases, and (b) that historic levels of transmission risk would have persisted until now, despite the introduction of leucodepletion and other precautionary risk reduction measures.

7. Concluding comments

This paper has set out the problem of calibrating models of blood-borne transmission against both "positive" and "negative" evidence on human cases, while taking account of relevant results from animal models. We have also noted some very recent evidence on both population prevalence of prion protein and infectivity in blood.

We have suggested a methodology for arriving at a revised range of scenarios for projecting future numbers of cases. While further work is required on this, we would welcome endorsement of the proposed approach, or suggested changes to it.

We have offered more specific suggestions on the assessment of historical risks from exposure to blood components: if accepted, these would have significant implications for CJD Incidents Panel recommendations on the management of exposed individuals and groups. Though this is a separate point, the suggested revision of assumptions on infectivity would also have significant implications for the risks associated with fractionated plasma products.

Clearly, many scientific uncertainties remain, some of which should be reduced by research already under way. On prevalence of abnormal prion protein, for example, the prospective appendix survey already described is expected to conclude in Autumn 2012. Attempts have also been made to set up a survey of spleen (and brain) tissues to be collected post mortem, and different ways of setting this up have been piloted. However, the practical difficulties have proven to be considerable, and any progress is now unlikely.

A further point is that none of the tissue surveys has been subject to a *negative control* – i.e. testing of samples from a population with no appreciable exposure to BSE or vCJD. This leaves open the possibility that some low prevalence of

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[27] The more complex alternative of calculating historical risks dependent on the age distribution of the cohort base might be justified if there was a strong and proven "cohort effect" for prevalence of infection, but this now appears less likely, as discussed earlier.

abnormal prion protein occurs naturally in most or all human populations. Research on this might be worth pursuing – e.g. though international comparison.

In the longer term, a more direct measure of blood-borne transmission risks could be offered by adapting an assay developed for screening purposes to investigate prevalence Eglin, Soldan, Newham *et al*, 2007). However, this would require a test with acceptably good sensitivity, to detect "true positives" reliably. This has yet to be achieved, though promising lines of development exist. The ideal would be the ability to investigate infectivity, rather than just presence of abnormal prion.

Meanwhile, thorough follow-up of "at risk" individuals remains essential if both "positive" and "negative" evidence on transmission risks is to accumulate. This includes the "highly transfused" as a key sentinel group. However, this has proven to be problematic. Although there have been suggestions for gathering of follow-up data without consent, this is seen as ethically problematic. Consent can only be sought if individuals are notified. The present policy is to identify and notify patients with 80 or more donor exposures only if they present for "high risk" (brain of posterior eye) surgery. Although this has logic in reducing onward transmission risks while avoiding a large-scale notification the small numbers being followed up provide no meaningful epidemiological information.[28] The analysis offered above suggests that a larger number of exposures – perhaps 300 – would be needed for recipients to reach the Incidents Panel's 1% "risk threshold". This supports the decision not to notify all those exposed to 80-plus *en masse*, but does not resolve the surveillance issue. If the current analysis is accepted, there would be a strong case for reviewing the follow-up of the highly-transfused from first principles, perhaps combining proactive notification of those reaching the (revised, higher) exposure "threshold" with some form of more basic "un-consented" follow-up of those meeting some lower threshold. (For example, the HPA currently defines a group subject to "low or uncertain" risk.) Although any specific recommendations lie beyond the scope of this discussion, advice on the principles involved would be helpful.

We have also stressed the continuing uncertainties in the basic science of TSE disease. Notably, model calibration could be made much more definite given a better understanding of incubation periods and susceptibility to clinical disease following blood-borne exposure to infection.

Comments and suggestion on priorities for further research would of course be welcome. The main current concern, however, is to arrive at a set of working hypotheses on blood-borne transmission risks that are more fully consistent with the evidence now available.

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[28] It has also been agreed in principle to proactively notify the most highly-transfused, starting with those exposed to 800 or more donors. However, this has been put on hold to allow evaluation of the "surgical" notification route.

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ANNEX A: RELEVANT EVIDENCE AND RESEARCH

Annex A1: Usage of Blood Components and post-transfusion survival

Total usage of components

Leaving aside a small historical use of whole blood, the annual provision of components by the four UK blood services is shown in the following Table:

Table A1.1: Summary of issues by UK Blood Services 1999–2009 (SHOT, 2010)

Year	Red Blood Cells	Platelets	FFP	Cryoprecipitate	Totals
1999–2000	2,737,572	249,622	365,547	94,114	**3,446,855**
2000–2001	2,706,307	250,259	374,760	95,456	**3,426,782**
2001–2002	2,679,925	251,451	385,236	88,253	**3,404,865**
2002–2003	2,678,098	251,741	377,381	92,768	**3,399,988**
2003–2004	2,607,410	264,539	372,855	95,417	**3,340,221**
2004–2005	2,428,934	258,528	313,019	102,719	**3,103,200**
2005–2006	2,316,152	259,654	320,852	106,139	**3,002,797**
2006–2007	2,235,638	255,474	306,444	116,672	**2,914,228**
2007–2008	2,174,256	258,419	295,085	117,699	**2,845,459**
2008–2009	2,209,153	266,312	306,740	121,555	**2,903,760**

These figures refer to units issued rather than transfused, so some allowance should be made for wastage. Nevertheless, a conservative estimate for units transfused around the start of the period shown would be **2.5m** red cells, and **3.2m** components in total.

All components are sourced from UK donors, with the exception of small proportions of FFP (no more than 20,000 units used for recipients aged under 16 and 50,000 for TTP patients, a condition requiring particularly high usage). These supplies are now imported, but the change is too recent to have any bearing on the calculations of historical exposure.

These units do not consist of the stated component in “pure” form. For example, a unit of red cells contains a significant quantity of plasma, the amount depending on the method of manufacture. Each also contains white cells, in numbers greatly reduced by the process of leucodepletion, introduced in 1999.

Each unit of red cells or FFP comes from a single donor. Platelets (which also contain significant amounts of plasma) can be sourced from a single donor through a process known as apheresis. Although the majority of units are now produced that way, historically most were produced by pooling four separate donations. Cryoprecipitate also involves pooling of several donations. Pooling significantly increases vCJD transmission risks in the worst-case scenario where infectivity

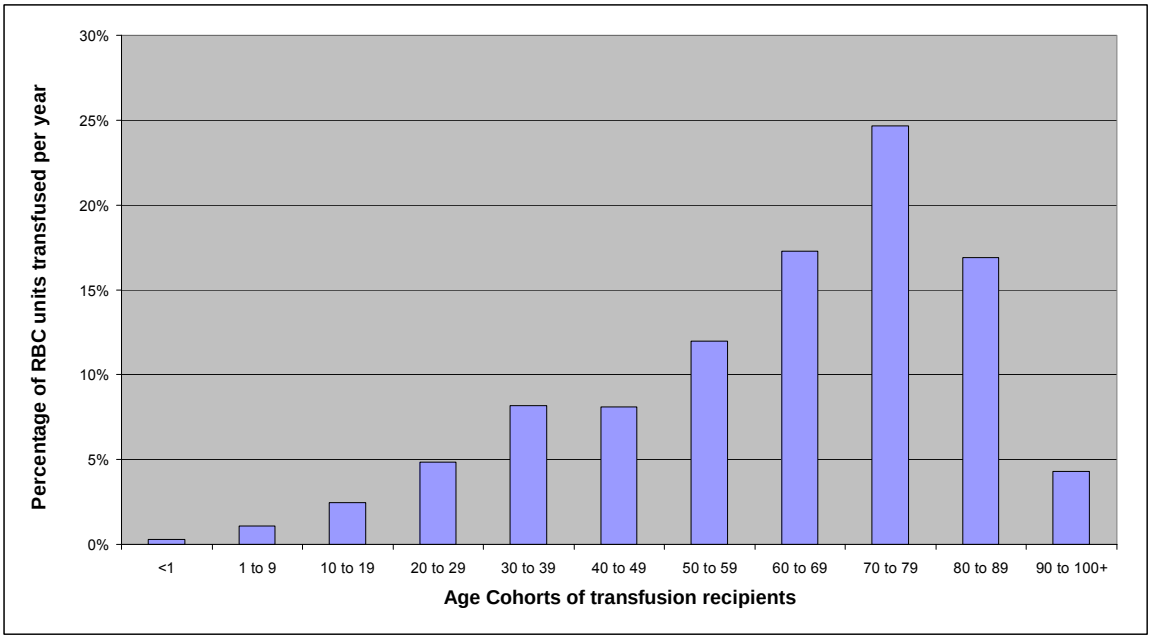
levels are such that transmission would occur if *any* of the four contributing donations were infective. This additional effect is ignored in the illustrative analysis provided here, but has been considered in more detailed assessment of the relative vCJD risks associated with alternative ways of procuring plasma. This is reflected in efforts to increase the proportion produced via apheresis.

Distribution of units by age and types of recipients

The distribution of transfusions to recipients by age is calculated using data from the Epidemiology and Survival of Transfusion Recipients (EASTR) study conducted by NHSBT (Llewelyn, Wells, Amin *et al*, 2009; Wells, Llewelyn, Casbard *et al*, 2009). This is the only national survey of transfusion recipients in England and North Wales (i.e. the population served by National Blood Service), and has provided valuable information on the number of units transfused for the 12-month study period, in 2001/2.

For Red Blood Cells, for example, data show that approximately 65,830 patients were transfused during one year in 29 representative NHS hospitals (stratified into 14 large, 9 medium and 6 small according to red cell usage). Appropriately weighted and scaled up, this suggests that approximately 433,000 patients were transfused with 2,115,650 units of red blood cells in NBS hospitals across England and North Wales in 2001/2002. This would scale up to about 2.5m units for the UK. The distribution of units by recipient age is shown below.

Figure A1.1. Distribution of RBC units transfused, by age of recipient



As can be seen, a high proportion of units go to older recipients. For example, roughly 75% of all RBC transfused went to recipients aged over 50. Clearly, this is a snapshot for a single year. For the purposes of analysis, we assume that this distribution has not changed significantly during the period covered by our models.

Post-transfusion survival

Clearly, the number of clinical vCJD cases resulting from blood-borne transmission will have been reduced by the limited survival of many recipients. Two substantial UK studies on survival are available: the “Newcastle” survey of long-term survival after blood transfusion in the North-East (Wallis *et al*, 2004), and the more recent EASTR study already referred to. The latter is a larger study, covering a wider geographical area, whereas the former may be more relevant to transfusions taking place in the late 1990s. The two sets of results are generally similar, with EASTR study suggesting slightly higher survival rates. Using either study to estimate long-term survival involves extrapolation of the available data (which currently covers up to7 years). In general, however, recipients who have survived a few years beyond a transfusion have longer-term life expectancy similar to that typical of their age. Therefore, their life expectancy can be estimated from the Interim Life Tables (produced by the Office for National Statistics).

The “Newcastle” study suggests that 47% of all transfused patients were alive after 5 years, and 41% at 7 years. After that, there is about 2.8% mortality per year reflecting the age distribution of transfusion patients. This would suggest a 10-year survival of 33%. However, the risk of exposure to vCJD rises with the number of units received, and survival is also generally shorter among those requiring multiple units. The better measure for our purposes is therefore to consider the *proportion of units transfused* that go into patients surviving long-term. From the same study, 41% of Red Cell units were transfused to 5-year survivors, with slightly lower figures for FFP and platelets. Applying the same linear mortality rates suggests that at least 28% of Red Cell units were transfused to recipients still alive after 10 years. The equivalent (weighted average) figure for all components was 26.6%.

The different transmission models discussed here treat post-transfusion survival somewhat differently. In particular, the CORU outlined in Annex B2 follows earlier analysis by DNV in distinguishing between “acute” and “chronic” recipients. The former receive transfusions on specific occasions (e.g. following surgery or major trauma), whereas the latter typically receive regular, repeated transfusions in response to some long-term medical condition. The survival of these two groups is somewhat different, with acute patients more likely to die during or immediately after transfusion. However, all the models are calibrated against the same empirical data for longer-tern survival, so the differences do not significantly affect their outputs regarding the proportion of any patients infected with vCJD who would survive long enough to develop clinical disease

Survival generally varies according to age, as one would expect. For example, estimated 10-year post-transfusion survival rates by age group are shown in Figure 2 and Table 2. Rates are the highest for recipients under 40 and decrease steeply with age, to about 1% for recipients aged over 90.

Figure A1. 2: 10-year post-transfusion survival, by age at transfusion

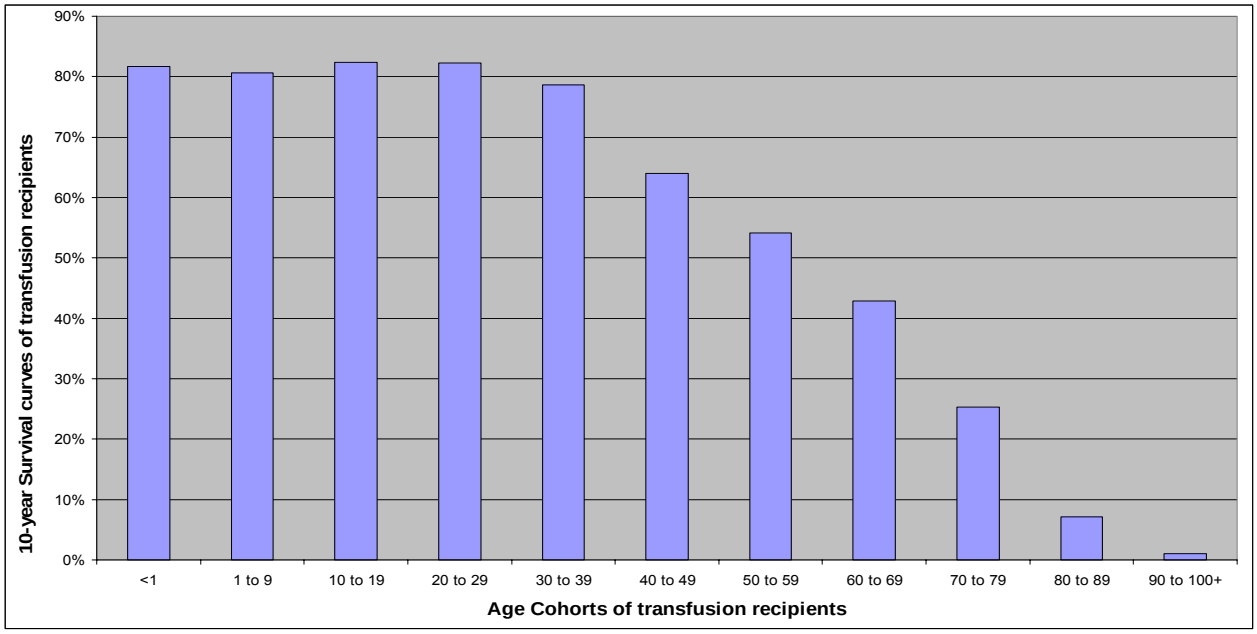


Table A1.2. Post-transfusion survival by age at transfusion.

Age groups of recipients of RBC	recipients aged under 39 years	40-49 year old recipients	50-59 year old recipients	60-69 year old recipients	70- 99 year old recipients	80- 89 year old recipients	recipients aged over 90 years
Post transfusion survival rates in 10 years	~ 80 %	64%	54%	43%	25%	7%	1%

ANNEX A2: TRANSFUSION-RELATED vCJD INFECTIONS AND FOLLOW-UP OF RECIPIENTS

Direct evidence that human blood can transmit vCJD infection comes from four detected donor-recipient linkages, all involving non-leucodepleted Red Cells sourced from donors subsequently found to have had vCJD. Three of these transmissions led to clinical vCJD cases - all in MM recipients, two being linked to the same infected donor (Llewelyn, Hewitt, Knights *et al*, 2004; Wroe, Pal, Siddique *et al* 2006). The fourth recipient, an MV heterozygote, died from unrelated causes, but post mortem examination revealed abnormal prion protein in the spleen and lymph nodes (Peden *et al*, 2004).

The Transfusion Medicine Epidemiology Review (TMER) study (Hewitt, Llewelyn and Will, 2002; Llewelyn, Hewitt, Knight *et al*, 2004) tracks donations from donors subsequently found to have vCJD, and matches these to diagnoses of vCJD in recipients, or to their death from other causes. The transmissions referred to were detected in this way. The first such match occurred in 2003, relating to a donation given and transfused in 1996. Donations associated with transmission were given up to 3.5 years prior to onset of symptoms in the donor. The table below summarises the relevant chronology.

Table A2.1: Timing of detected vCJD transmissions

	Year of transfusion	Onset of vCJD in donor	Onset of vCJD in recipient	Death of recipient
1996	Case 1			
1997	Case 2 Case 3			
1998				
1999	sub-clinical	Case 1 Case2 Case 3		
2000		sub-clinical		
2001				
2002			Case 1	
2003				Case 1
2004				sub-clinical
2005			Case 2	
2006			Case 3	Case 2
2007				Case 3

More broadly, the TMER study provides information on all detected instances in which patients have received blood components from a donor who developed vCJD. To date, there have been 66 known recipients of “implicated” components, originating from 18 donors. The transfusions took place over the period 1982-2004, most between 1996 and 2002. Some of the recipients survived (or are surviving) for significant periods with no symptoms of vCJD. In summary:

- 18 are still alive (as of April 21st 2011)
- 16 survived (or have survived) at least 10 years without symptoms of vCJD – the longest period being over 24 years (albeit following a transfusion in 1987)
- 26 survived at least 7 years without symptoms
- 33 survived at least 5 years without symptoms, including the 3 who went on to develop clinical vCJD
- 37 survived at least 3 years without symptoms of vCJD

Although there has been some follow-up of this group (Gillies, Chohan, Llewelyn *et al*, 2009), it has not been possible to obtain any prion-informative tissue at autopsy from any of those who have died of unrelated causes, apart from the one "pre-clinical case" already noted. Information on genotype is available for only a few of the group.

In more detail, the following table (using data kindly supplied by Dr Pat Hewitt and Jan Mackenzie of NHSBT) summarises the current evidence with regard to all 66 donations, listed in order of transfusion date. The NCJDSU dates the onset as the first appearance of symptoms in donors and affected recipients: these are given by year and month only here to avoid identifying individuals. Note that although most donations had been given before the onset clinical illness in the donor, seven were given shortly *after* the first signs of clinical illness. Although the donor passed the normal medical checks at the time of blood donation, in retrospect the first symptoms (which can be quite non-specific, such as insomnia or depression) were present prior to the donation.

Successive columns in the table show the onset of symptoms in the donor, the time of transfusion, the interval between these two dates, the component transfused, the current fate of the recipient, and the symptom-free survival period from transfusion. This period is calculated as being:

- to date for these still alive,
- to death for those dying of other causes and
- *to onset of symptoms* for those who developed clinical vCJD (i.e. 6.5, 7.8 and 8.3 yrs, as distinct from periods from transfusion to death, which were 7.6, 8.7 and 9.3 years)

In addition to the three clinical, and one sub-clinical case, information on genotype is available for seven recipients.[29]

[29] Information on these genotypes was kindly provided for the sub-group by Dr Simon Mead of the National Prion Unit: however, details have been omitted here to avoid possible identification of individual patients. For similar reasons, deaths are shown by year only.

Table A2.2: Information on recipients of “implicated” blood components

DONOR	TRANSFUSION			RECIPIENT		
vCJD onset	date	time before donor onset (yrs)	Component	Fate		symptom-free survival [yrs]
1997	1981	15.9	Red cells	dead	1996	14.3
1996	1984	11.7	Whole Blood	dead	2003	18.6
2003	1987	15.9	Red cells	alive		24.1
1994	1989	4.9	Red cells	dead	1989	0.3
1994	1990	4.6	Red cells	dead	1991	1.0
2001	1990	11.6	Red cells	dead	1990	0.6
1998	1990	7.8	Red cells	dead	1990	0.01
2001	1991	10.6	Red cells	dead	1992	1.6
2001	1992	9.7	Red cells	dead	1992	0.02
2001	1992	9.3	Red cells	dead	2000	7.5
1996	1993	3.9	Red cells	alive		18.3
2001	1993	8.2	Red cells	dead	2008	14.4
2001	1994	7.8	Red cells	dead	2000	6.5
1996	1995	1.3	Red cells	alive		16.3
2001	1995	6.8	Red cells	dead	2011	16.0
1996	1995	0.6	Red cells	dead	1995	0.26
1996	1995	1.3	Red cells (BCD)	dead	1995	0.01
1996	1995	0.6	Plasma cryo-depleted	alive		15.6
1996	1996	0.6	Cryoprecipitate	dead	1996	0.01
1999	1996	3.4	Red cells	dead **vCJD**	2003	**6.5**
2002	1996	5.8	Red cells	alive		15.0
1996	1996	0.5	Red cells (BCD)	dead	2001	4.7
1999	1996	2.6	Platelets (pooled)	dead	2005	8.3
1999	1996	2.6	Red cells	dead	1997	0.4
2002	1997	4.8	Platelets	dead	1999	2.7
2002	1997	4.8	Red cells	dead	1997	0.23
1999	1997	1.7	Red cells	dead **vCJD**	2006	**7.8**
2002	1997	4.1	Red cells	alive		13.4
1999	1997	1.4	Red cells	dead **vCJD**	2007	**8.3**
1999	1998	1.4	FFP	dead	1998	0.00
2002	1998	4.6	Red cells	dead	2010	12.7
1999	1998	1.1	Red cells	dead	2004	6.5
1999	1998	1.1	FFP	dead	1999	1.0
1999	1998	0.8	Whole Blood	dead	1999	0.6
2001	1998	2.7	Red cells	dead	2001	2.5
1999	1998	0.4	Red cells	alive		12.3
2002	1999	2.8	Red cells (l’depleted)	dead	2000	1.2
2000	1999	1.5	Red cells	dead **sub-clin vCJD**	2004	5.0
1999	1999	- 0.1	FFP	dead	2003	3.7
2001	1999	1.5	Red cells (l’depleted)	dead	2000	0.2
2001	2000	1.7	Red cells (l’depleted)	dead	2003	3.5

2001	2000	1.1	Red cells (l'depleted)	dead	2000	0.5	
2000	2000	0.4	Red cells (l'depleted)	dead	2005	4.8	
2004	2000	3.7	Red cells (l'depleted)	alive		10.9	
2001	2000	0.8	Red cells (l'depleted)	dead	2000	0.4	
2001	2000	1.3	Red cells (l'depleted)	dead	2000	0.14	
2001	2000	0.4	Red cells (l'depleted)	alive		10.5	
2004	2000	3.1	Red cells (l'depleted)	alive		10.3	
2001	2001	0.8	Red cells (l'depleted)	alive		10.2	
2001	2001	0.1	Red cells (l'depleted)	dead	2001	0.12	
2001	2001	-0.2	Red cells (l'depleted)	alive		9.9	
2004	2001	2.7	Red cells (l'depleted)	alive		9.9	
2001	2001	-0.5	FFP (l'depleted)	dead	2001	0.02	
2004	2001	2.2	Red cells (l'depleted)	alive		9.4	
2004	2002	2.6	Red cells (l'depleted)	dead	2002	0.09	
2001	2002	-0.4	Red cells (l'depleted)	alive		9.1	
2004	2002	1.8	Red cells (l'depleted))	dead	2009	7.7	
2004	2002	1.6	Red cells (l'depleted)	dead	2004	1.9	
2004	2002	1.6	Red cells (l'depleted)	alive		8.8	
2004	2003	0.9	Red cells (l'depleted)	dead	2003	0.38	
2004	2003	0.6	FFP (l'depleted)	dead	2003	0.04	
2004	2003	0.6	Red cells (l'depleted)	alive		7.8	
2004	2004	0.0	Red cells (l'depleted)	dead	2005	1.2	
2004	2004	-0.4	Red cells (l'depleted)	alive		6.8	
2004	2004	0.2	Red cells (l'depleted)	dead	2010	6.3	
2004	2004	-0.7	Red cells (l'depleted)	dead	2006	1.5	
2004	2004	-0.7	Red cells (l'depleted)	dead	2005	0.55	

Some of the rows in this table provide no relevant evidence on vCJD transmissibility, because the recipient died within 3 years of transfusion. In addition, the first two rows refer to transfusions that took place in 1981 and 1984, before the peak in exposure to BSE, and well before one might reasonably expect infectivity in blood to have become apparent. Omitting these rows (indicated by shaded entries in column) leads to the reduced table below, showing the most relevant 35 entries.

Table A2.4: Recipients of “implicated” blood components (reduced set)

DONOR	TRANSFUSION			RECIPIENT			
donor onset	date	time before donor onset (yrs)	Component	Fate		symptom-free survival [yrs]	
2003	1987	15.9	Red cells	alive		24.1	
2001	1992	9.3	Red cells	dead	2000	7.5	
1996	1993	3.9	Red cells	alive		18.3	
2001	1993	8.2	Red cells	dead	2008	14.4	
2001	1994	7.8	Red cells	dead	2000	6.5	
1996	1995	1.3	Red cells	alive		16.3	
2001	1995	6.8	Red cells	dead	2011	16.0	
1996	1995	0.6	Plasma cryo-depleted	alive		15.6	
1999	1996	3.4	Red cells	dead **vCJD**	2003	**6.5**	
2002	1996	5.8	Red cells	alive		15.0	
1996	1996	0.5	Red cells (BCD)	dead	2001	4.7	
1999	1996	2.6	Platelets (pooled)	dead	2005	8.3	
1999	1997	1.7	Red cells	dead **vCJD**	2006	**7.8**	
2002	1997	4.1	Red cells	alive		13.4	
1999	1997	1.4	Red cells	dead **vCJD**	2007	**8.3**	
2002	1998	4.6	Red cells	dead	2010	12.7	
1999	1998	1.1	Red cells	dead	2004	6.5	
1999	1998	0.4	Red cells	alive		12.3	
2000	1999	1.5	Red cells	dead **sub-clin vCJD**	2004	5.0	
1999	1999	- 0.1	FFP	dead	2003	3.7	
2001	2000	1.7	Red cells (l’depleted)	dead	2003	3.5	
2000	2000	0.4	Red cells (l’depleted)	dead	2005	4.8	
2004	2000	3.7	Red cells (l’depleted)	alive		10.9	
2001	2000	0.44	Red cells (l’depleted)	alive		10.5	
2004	2000	3.1	Red cells (l’depleted)	alive		10.3	
2001	2001	0.8	Red cells (l’depleted)	alive		10.2	
2001	2001	- 0.2	Red cells (l’depleted)	alive		9.9	
2004	2001	2.7	Red cells (l’depleted)	alive		9.9	
2004	2001	2.2	Red cells (l’depleted)	alive		9.4	
2001	2002	- 0.4	Red cells (l’depleted)	alive		9.1	
2004	2002	1.8	Red cells (l’depleted)	dead	2009	7.7	
2004	2002	1.6	Red cells (l’depleted)	alive		8.8	
2004	2003	0.6	Red cells (l’depleted)	alive		7.8	
2004	2004	- 0.4	Red cells (l’depleted)	alive		6.8	
2004	2004	0.2	Red cells (l’depleted)	dead	2010	6.3	

Commentary

There has been some follow-up of this group (Gillies, Chohan, Llewelyn et al, 2009), and more recently autopsy tissue has been obtained from four who died of other causes (in addition to the one "sub-clinical transmission" already noted). Although investigations have to be completed, none of these four is thought to show evidence of prion infection.[30]

Information on genotype is available for only 11 recipients in total, which further limits the conclusions tat can be drawn from survival data. However, one might reasonably expect 40% (i.e. about 10) of the 26 recipients surviving at 7 years to be MMs: it is noteworthy that three of these have so far developed clinical vCJD.

Confining attention to those transfused between 1994 (a plausible timing for onset of substantial infectivity in blood) and introduction of leucodepletion in 1999, 15 recipients have survived more than three years, of whom three developed vCJD. Of the remaining 12, one showed signs of sub-clinical infection. As against this, there have been some quite lengthy symptom-free survival periods, including four of over 12 years. Although it is arguably too early to take the observed cases as an indication of final clinical attack rate (even amongst MMs) these data do suggest that the probability of transmission – at least via non-leucodepleted red cell units – is substantial.

[30] (September 2011) The information about the four other recipients has been added subsequent to the ACDP Subgroup meeting.

ANNEX A3: POPULATION PREVALENCE OF INFECTION & INFECTIVITY

Tissue surveys

One way of investigating sub-clinical vCJD infection within the population is to search for abnormal prion protein in stored or fresh tissue samples. The best-known of such studies was the retrospective survey carried out by Hilton *et al* (2004). Using Immunohistochemistry (IHC), this found 3 positive appendices in approximately 12,000 tested. This suggests a prevalence of the order of 1 in 4,000, with Confidence Intervals ranging from 1 in 1,200 to 1 in 20,000. All three were found in patients born between 1961 and 1985. All have been genotyped, one being MM, the other two VV (Ironside, Bishop, Connelly *et al*, 2006)

The National Anonymous Tonsil Archive (NATA) was set up as a large-scale prospective study, with the eventual aim of collecting and testing 100,000 tonsil pairs from patients in different age cohorts (1961-1985, 1986-1990 and 1991-1995). Over 80,000 samples have been tested to date, using dual EIA followed-up by Western Blotting of any doubtful samples. No positives have been found by this method – a finding that provoked a good deal of discussion as to consistency or otherwise with the Hilton survey. More recently, however, further tests were carried out on 10,000 of the tonsil samples, this time using IHC. After exhaustive examination, a single sample (also taken from the 1961-85 cohort) was found to be positive in one follicle (de Marco *et al*, 2010).

The interpretation of this finding was discussed by SEAC in March 2010, and the consensus was that this single IHC result should be regarded as a “true positive” for presence of abnormal prion protein, notwithstanding the negative EIA results. This would suggest a prevalence of the order of 1 in 10,000 for this cohort, a figure fully consistent with the Hilton *et al* finding.

Although informative modelling work on age-related susceptibility and exposure to primary vCJD infection had been done (Cooper and Bird, 2003; Boelle, Cesbron and Valleron, 2004), these surveys provide little information on other cohorts. The Hilton *et al* study tested very few samples from other groups. Although the NATA study has tested large numbers from 1986-1990 and 1991-1995 with negative results to date, all these are from EIA / Western Blotting. There has been no retesting of these samples using IHC, nor is any such study planned. Given SEAC advice that the positive IHC result in the 1961-85 cohort effectively “trumped” the negative EIA findings, the status of the negative EIA results for the other cohorts in the NATA study is unclear.

Until very recently, these had been the only positive samples found, so it was possible that prevalence of abnormal protein might be essentially confined to this 1961-85 cohort (which also contains a high proportion of clinical vCJD cases. However, a further study is currently in train, in which 30,000 appendices are to be tested by IHC. The rationale for this study is reproduced at the end of this annex. First results confirm the Hilton *et al* survey for the 1961-85 cohort, while throwing doubt on any supposed differential between this and the1941-60 cohort.

Prevalence "of what"?

Whilst tissue surveys provide an important way of exploring prevalence of prion infection, it is important to be clear as to what "prevalence" is being investigated. As recognised by SEAC at its meeting in March 2010, prevalence of abnormal prion protein in *any* tissue is only a proxy measure for either of the two factors of practical concern. These are the number of people expected to develop prion disease and the number of people who are *infective* – in particular, the number whose blood might be infective.

Arguably, the prevalence *of infective donors* may be very different to the prevalence of PrP^{Sc} in any given tissue – even in any given age cohort. There is no direct evidence to link presence of PrP^{Sc} in any given tissue - whether tonsils, appendix or spleen - with infectivity in human blood. At an individual level, the presence of PrP^{Sc} in one site cannot reliably be inferred from its presence in another, even after the onset of vCJD (e.g. HPA studies of samples taken from clinical cases, in preparation). Nor does the same tissue necessarily test consistently, as demonstrated by the "IHC-positive" tonsil sample in the NATA survey, which tested negative by IHC in other follicles. Nor is presence of detectable PrP^{Sc} necessarily a good predictor of infectivity (e.g. Barron *et al*., 2007).

There is thus no direct evidence to show that blood from a donor testing "positive" in an appendix survey would infect recipients: though this has been used as a working assumption (hence the weight given to the Hilton *et al* result). Conversely, there is no guarantee that an individual whose blood was infective would test positive on a tonsil survey such as NATA. In other words, the blood of someone with a "negative" tonsil assay result might still transmit infection - a point explored in sensitivity analysis for the Ghani and Garske model (*op cit*).

In short, there are many different definitions of "prevalence": the prevalence of abnormal prion protein in different tissues may well be different, and none of them necessarily reflects the number of clinical cases to be expected, or the risk of passing on infection by any given route.

Implications and alternatives

A key question, therefore, is whether scenarios for the prevalence of infective blood donors need be consistent with tissue survey results, or whether it is more appropriate to estimate it separately.

If consistency with tonsil and appendix surveys *is* required, this can be interpreted in at least two ways:

- by requiring the *general* prevalence of infective donors to fall within the Confidence Intervals associated with the surveys (e.g. the range of roughly 1 in 1,200 to 1 in 20,000 associated with the Hilton study);
- by requiring this *only* for donors in the birth cohort from which the tissue samples were taken (e.g. the above range applied to the Hilton cohort only).

Previous DH risk assessments have taken the former approach, in view of the uncertainties involved. Although this might have appeared over-precautionary, the latest appendix survey appears – provisionally – to suggest that prevalence is indeed relatively constant across cohorts.

A quite different approach to estimating prevalence would be to work backward from the observed number of clinical cases. Though still providing no direct evidence on blood-borne infectivity, this starts from individuals in whom clinical disease developed – at least some of whose blood *has* been found to be infective. Two such what-if" scenarios can be outlined as follows.

- From the known clinical case numbers, suppose that at least 172 individuals were infected with vCJD by the food-borne route[31], and with exposure to infective material probably peaking at or about 1988-91. All those genotyped have been MMs. Given the recent case numbers, it would be surprising if the number of MMs who were infected and susceptible to clinical disease exceeded 200. (This allows for cases still to come and a small number of intercurrent deaths or missed diagnoses.) Suppose hypothetically that *only* these individuals had infective blood. In that extreme scenario, the number of infective individuals in the whole population would have reached a maximum of 200, before declining to a very small number of survivors – perhaps of the order of 30. The chance of any of these 30 donating blood being small, it is thus *conceivable* that the current and future risk of further transmissions is close to zero.

- Alternatively, suppose that a similar proportion of non-MM individuals were infected in the primary outbreak. This would comprise a group of about 300 further individuals, most still alive now. Lack of identified clinical cases in this group – with one possible recent exception (Kaksi, Mead, Hyare *et al*, 2009) - would have inhibited blood-borne transmissions being detected by the TMER study. A few of this group would by now have died of other causes. In conjunction with the few surviving MMs, there would now be about 300 infective individuals in the population. Most would be of an age that would allow them to donate blood. Given that this portion of the UK population is of the order of 35m, this would amount to a prevalence of roughly 1 in 100,000 donors infective. If blood sourced from them infected the recipients for certain, then transfusion of around 3 million units of components would have led to transmissions of the order of 30 *per year*. Arguments presented in the main text suggest that after ten years, such a rate of infection would result in about 3 clinical vCJD cases per year.

This second example illustrates how even a very low prevalence of infective donors would generate more than enough transmissions to account for the observed number of transfusion-associated cases. Such scenarios would be inconsistent with tissue survey results only if abnormal prion protein in appendix or tonsil is taken as indicating that blood would be infectious. If there is evidence to suggest that per-unit infectivity is high, and that a high proportion of recipients would be susceptible to clinical vCJD, then the most plausible explanation for the

[31] As of April 2011, there have been 175 probable or confirmed UK cases, from which we remove the 3 presumed to be blood-borne.

small number of cases seen may turn out to be a much lower prevalence of infective donors.

Appendix

A plan for investigating vCJD prevalence by the IHC testing of appendix samples

Peter Grove and Peter Bennett
Health Protection Analytical Team
Department of Health
(Produced 2008: updated Feb 2010)

Introduction

Knowledge of the prevalence of sub-clinical vCJD is important for two reasons in the assessment of the risk of secondary transmission. Most obviously, its value sets the current level of risk of infection by secondary routes such as dental surgery and blood transfusion. Less obviously, but arguably of greater significance, prevalence estimates much above “a few in 100,000” support an epidemiology with long lived carriers, greatly increasing the probability of a self-sustaining secondary epidemic.

Evidence for an epidemiologically -significant number of carriers comes entirely from three positive samples in a study of ~12,000 archived appendix samples (Hilton et. al. 2004). SEAC advice is that these should be considered as true positives, and therefore there is no need for a strict repetition of the Hilton study. SEAC have also indicated some preference for appendix testing over the testing of tonsil tissue as in the current NATA study. The latter study has now tested over 80,000 tonsil pairs by EIA (including 16,000 from the cohort covered by Hilton et al): all have tested negative by EIA. However, one of 10,000 samples re-tested by IHC has given a positive result in one follicle. Extensive further testing of this sample has produced negative results.

Current SEAC advice is that the best estimate of prevalence is provided by using the Hilton et. al. result alone. Although a hypothesis based on a single experiment cannot be considered definitive, current advice is that finding further negative results in appendices would only “dilute” the three positives reported in the Hilton study, rather than raising any question as to their validity. If so, one would need to test a few hundred thousand further appendix samples to be able to establish a true prevalence below the level at which carriers are important. With current IHC testing capacity of ~10,000 tests per year it would take decades to bring the estimates of prevalence down to the critical level, even if the true prevalence was very low.

One option is to invest in an (at least) order of magnitude increase in IHC testing capacity. This would allow a definitive result in two to three years. Given the current capacity of ~10,000 tests per year, only about 30,000 appendix samples could be tested in this period. However, the remainder of this note discusses what could be learnt from testing this limited (from the statistical viewpoint) number of samples. For the purposes of this discussion, we assume that both tonsil and

appendix surveys provide (necessarily imperfect) indicators of a single “true” prevalence of sub-clinical infection.

If prevalence is in fact low (a few per 100,000), testing another 30,000 samples could still not lead to an estimate of much below 1/10,000. (Even if all the additional samples tested negative, one would then be in a position of having three positives out of ~ 40,000.) This would not lead to a significant qualitative change in the estimated risk of a self-sustaining epidemic but would affect the quantitative details of the risk assessments. The “worst case” prevalence scenario (the 1 in 1,400 upper confidence interval from the Hilton study) would be significantly reduced.

This assumes that the new results would simply be added to the existing results, as SEAC currently imply. Nevertheless, if true prevalence was in the Hilton range, the chance of not getting any positives in a further 30,000 samples would be very low (<5% for 1/10,000). Faced with such a result SEAC *might* wish to reconsider its view of the three positive samples.

If prevalence is much greater than 1/10,000, there is a high chance of obtaining a number of positives. If several positives were found, this would increase our confidence that our current estimates of risk (~ 1/4000) had a solid foundation. Finding *any* positives would allow a reduction in the uncertainty of the prevalence estimate (by ~50%).

HPA advice suggests that the testing of stored archived samples will be easier to organise than the collection of fresh appendix samples. While the intention is merely to look for positives this is no impediment. However, if positives are found, there arises the subsidiary question of whether they could be ‘false’ in the sense of not being indicative of vCJD infection. To investigate this possibility more fully, fresh tissue samples are required. If positives were found in the archived samples, moving over to fresh samples and testing up to 30k such samples should allow at least one sample to be verified as a true or false positive.

Testing plan

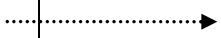
A testing plan for 30K appendix samples is attached in diagrammatic form. The plan itself (drawn up in Summer 2008) was based on the following assumptions:

- SEAC continues to prefer Hilton appendix study to NATA estimates of prevalence.
- Further appendix testing is seen as a means of increasing the sample size – and hence accuracy - of the Hilton study rather than as a repetition to test the validity of the original.
- NATA prevalence estimates remain much smaller than those from the Hilton study.
- No NATA samples tested by IHC are positive (*note*: this now needs reconsideration).
- IHC testing capacity remains at ~15,000 tests per year with a yield of ~2/3 successful tests.

- The post-mortem study under investigation will not have produced definitive results confirming or contradicting those of the Hilton study in the next three years.

The diagram begins at the top with our current knowledge based on the Hilton study. It envisaged that testing of up to 30k stored samples could begin in September 2008 (though the timeline can obviously be updated). The possible end points were as follows:

- If no positives were found, SEAC would be asked to consider the results three years later, in September 2011.
- If positives were found, then preparations would be made to collect fresh samples.
    - If further true positives were then found, and once more than 30k samples (both stored and archived) had been tested, a new prevalence estimate would be produced combining the Hilton and new results.
    - Conversely, if an initial positive from fresh tissue was shown to be a false positive on further testing, then the Hilton results could no longer be considered definitive and the best estimate would then become that of the (by then completed) NATA study.

<table>
<tr><td colspan="5">Current Knowledge
Hilton et. al.: 1/15,000 to 1/1,500 M.L.E = 1/4,000</td></tr>
<tr><td>Date</td><td colspan="2">Fixed stored appendix samples</td><td colspan="2">Fresh appendix samples</td></tr>
<tr><td>September 2008</td><td colspan="2">Begin IHC testing of up to 30k samples</td><td colspan="2"></td></tr>
<tr><td rowspan="3">  </td><td rowspan="3">No positives</td><td>On finding positive</td><td colspan="2">  </td></tr>
<tr><td>Test 10k (or remaining) stored samples</td><td colspan="2">Prepare collection and analysis of fresh samples</td></tr>
<tr><td>  </td><td colspan="2">Begin analysis of fresh samples up to 30k</td></tr>
<tr><td rowspan="2">
September 2011</td><td>On 30k STOP</td><td></td><td>On True positive and 30k total STOP</td><td rowspan="2">On False Positive (up to 30k by 2014) STOP</td></tr>
<tr><td colspan="2">Ask for SEAC opinion</td><td>Use new</td></tr>
</table>

		combined estimate	
	Test to 100k?	[redacted]	Use NATA estimate

ANNEX A4: INFECTIVITY IN BLOOD AND BLOOD COMPONENTS

Introduction

Given a starting scenario for the infectivity in a donated unit of whole blood, and proportions associated with white cells and plasma, we then need to track how much infectivity would be retained in a given component for transfusion, given its estimated white cell and plasma content. These may vary according to the method of manufacture, and white cell content will be greatly reduced – though not entirely eliminated – by leucodepletion.

The estimated infectivity per-unit can then be used to estimate the probability of transmitting the infection. Some infectivity scenarios suggest that transfused components would carry many infectious doses – more than enough to infect "for certain". In that case, the precise dose is much less important. What *is* important to appreciate is that starting from such a scenario, very significant reductions in infectivity would be required to produce any reduction in the risk of transmitting infection. Removing, say, half the infectivity would not halve the expected number of transmissions, but rather leave the number unchanged.

This annex sets out a methodology for quantifying the infectivity present in blood components, per unit transfused. It illustrates how this is done for the existing "high" and "low" infectivity scenarios, and presents sensitivity analysis showing how transmission risks would vary if other assumptions were used. We then explore how varying assumptions used would affect the probability that a single unit of either RBC or FFP from an infected donor would cause infection in a susceptible recipient. This probability is calculated using a Poisson or a linear dose-response model, as explained further below.

Calculation of infectious dose per unit

Existing scenarios start from levels of infectivity reported in rodent studies. These vary from 1 to 300 i.c. infectious dose per ml of blood, and suggest that efficiency of transmission by the i.v. route is between 10% and 100% of that of the i.c. route[32].

The "high" and "low" scenarios for human transmission take infected whole blood to carry 30 i.v. ID/ml and 0.1 i.v. ID/ml, respectively. (For brevity, all titres are quoted in i.v. terms in what follows.)

The volume of a whole blood single unit donation is 464 ml, and therefore the infectivity in a whole blood donation is 46.4 ID ("Low" infectivity scenario) or 13,920 ID (High).

It is suggested from the animal models that roughly half the infectivity is associated with white blood cells (WBC)[33]. Reflecting this, the existing baseline assumptions are that:

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[32] SEAC Position Statement from 2006

[33] Gregori *et al* (2004). Further unpublished data from the VA Medical Centre, University of Maryland, Baltimore presented to SEAC by Dr. R Rohwer showed that leucodepletion of pooled blood of hamsters with clinical hamster scrapie removed from 42% to 75% of infectivity. by depleting the blood of WBC.

- 50% of the infectivity of whole blood resides within the plasma, the remaining 50% being associated with WBC;
- the total infectivity in any component (per unit, as transfused) is the sum of the that arising from the residual plasma and the residual WBC;
- these contributions are proportional to the volume of plasma present and WBC count, respectively;

A whole blood donation typically contains 269 ml plasma and 2469 x 10^6 WBC (Krailadsiri P, Seghtchian J, Williamson L, 2001), and an equal split in the infectivity per unit implies that plasma and WBC would each be associated with 23.2 ID (Low scenario) or 6,960 ID (High). Then the specific infectivity in plasma is 0.086 ID/ml (Low) or 26 ID/ml (High) and that in WBC is 0.0094 ID or 2.8 ID per million cells.

To calculate ID/unit of any component, we multiply the residual plasma volume and WBC counts by these estimated titres. The results for Red Blood Cell and FFP units are shown in the table below.

For example, a non-leucodepleted RBC unit is assumed to contain almost all the WBC present in the original donation. The volume of residual plasma depends on the manufacturing process. For “Top/Top” (T/T) processing, this is typically 21 ml per unit.

- In the “Low” infectivity scenario, the infectivity associated with WBC would therefore be 23.2 ID (as in the original whole blood donation). Adding plasma-associated infectivity of 21 x 0.086 = 1.81 ID gives 25 ID per unit.
- In the “High” infectivity scenario, the unit would contain 6960 ID associated with WBC and 21 x 26 = 543 ID associated with plasma, or 7,503 (rounded to 7,500) ID per unit.

By comparison, Red Cell units produced by Bottom and Top (BAT) processing contain about half the residual plasma (10.5 ml) and lower WBC counts. Even without leucodepletion, the infectivity per unit is therefore substantially less, though still large in absolute terms. For FFP, the large bulk of per-unit infectivity comes from the plasma itself, with a smaller additional contribution from WBC.

Leucodepleted components have WBC counts that are lower by several orders (empirically, 0.34 x 10^6 and 0.26 x 10^6 for RBC (T/T) and RBC (BAT), respectively[4]). This means that the *relative* contribution to per-unit infectivity is small compared to that from residual plasma, and in the scenarios considered here, per-unit infectivity is essentially proportional to the volume of plasma present.

Nevertheless, it is noteworthy that in high-infectivity scenarios, leucodepletion leaves behind *some* appreciable White Cell-associated infectivity. For example, the 0.34 x 10^6 White Cells remaining in a Top/Top unit would be associated with approximately 0.7 ID. On its own, this would lead to a significant risk of transmitting

infection, though in these calculations it is “swamped” by the 441 ID associated with residual plasma content.[34]

Table A4.1: Total infectious dose for RBC and FFP, per unit transfused.

	Residual Plasma Volume, ml	Low Infectivity scenario	High Infectivity scenario	Comments
Blood components without leucodepletion				
RBC (T/T)	21 ml	25 ID/unit	7,500 ID/unit	WBC mean count is 2469 x10^6. Total infectivity is a sum of the infectivity arising from residual plasma and WBC.
RBC (BAT)	10.5 ml	6.3 ID/unit	1,870 ID/unit	WBC mean count is 569 x 10^6. Total infectivity is a sum of the infectivity arising from residual plasma and WBC.
FFP	220ml	19 ID/unit	5,718 ID/unit	WBC mean count is 9 x 10^6. Total infectivity is a sum of the infectivity arising from plasma and residual WBC.
Blood components post leucodepletion				
RBC (T/T)	21 ml	1.8 ID/unit	545 ID/unit	Infectivity in residual WBC is small compared to that of plasma in these scenarios.
RBC (BAT)	10.5 ml	0.9 ID/unit	271 ID/unit	
FFP	220 ml	19 ID/unit	5,695 ID/unit	

Probability of infection given an infected unit

The probability transmitting infection can be calculated using two different dose-response models: Poisson or linear. The former assumes that a minimal infectious dose (ID) is needed to transmit the infection: the chance of transmission thus depends on the probability of at least one ID being present. The linear dose response model is a continuous model, in which an ID_{50} is defined as the dose needed to infect 50% of recipients. The probability of infection is then proportional to the dose received, up to a limit of 2 ID_{50}, at which point infection is regarded as certain. Both models have been used in the extant literature. The Poisson is arguably more realistic, though the linear model has previously been endorsed by SEAC as a precautionary working assumption in the absence of contrary evidence. The relationship between the models is such that 1 ID_{50} in the linear model can be regarded as similar to 0.7 ID in the Poisson model.[35]

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[34] This also demonstrates that even if infectivity were wholly associated with WBC rather than plasma, leucodepletion would not be sufficient to eliminate transmission risk from Red Cell units.

[35] This can be seen by considering a hypothetical experiment. Suppose that 1000 individuals each receive 1 ml of infected component, and that 500 are infected. This corresponds to an infective titre of 1 ID_{50} per ml in the linear model.

Poisson dose-response

As shown in the table below, with this dose-response model the residual infectivity in plasma is enough to give (essentially)100% certainty of transmission to a susceptible recipient in the high infectivity scenario, for RBC or FFP, leucodepleted or not.

In the low infectivity scenario, all non-leucodepleted units still carry 100% risk of transmission. After leucodepletion, the infectivity from residual plasma gives a transmission probability of 84 % and 60 % for RBC processed using the T/T and BAT methods, respectively. The probability of transmission via infected FFP remains at 100%.

Table A4.2: Probabilities of transmission (Poisson dose-response model)

	Residual Plasma Volume	Low Infectivity scenario	High Infectivity scenario
Non-leucodepleted components			
RBC (T/T)	21 ml	100 %	100 %
RBC (BAT)	10.5 ml	100%	100 %
FFP	220 ml	100 %	100 %
Leucodepleted components			
RBC (T/T)	21 ml	84 %	100 %
RBC (BAT)	10.5 ml	60 %	100 %
FFP	220 ml	100 %	100 %

Linear dose-response model

The following table shows the equivalent probabilities calculated using the linear dose-response model, after converting IDs to ID_{50} as described previously.

If infection requires receipt of a minimum Infectious Dose (ID) as in the Poisson model, this same result is interpreted in terms of recipients having a 50% chance of receiving one ID and a 50% chance of receiving none. The probability of receiving x infectious doses is given by the Poisson law, $p(x) = m^x e^{-m}/x!$, where m is the average number of IDs per recipient. For a large number of recipients, this probability depends only on the volume transfused and not on its distribution amongst the recipients. The chance of receiving no infectious doses (x = 0) is $p(0) \equiv m^0 e^{-m}/0! = e^{-m}$. A 50% chance of infection therefore requires a value of m for which $e^{-m} = 0.5$: this is given by m = 0.693. Therefore, the expected number of infectious doses (ID) per recipient of blood corresponding to 1 ID_{50} is 0.693.

As can be seen, the only significant difference between the tables is that in the low-infectivity scenario, the probability of transmission via leucodepleted T/T- and BAT-processed RBC is 100% in the linear model, as compared to 60 % and 84 %.

Table A4.3: Transmission probabilities (linear dose-response model).

	Residual Plasma Volume	Low Infectivity scenario	High Infectivity scenario
non-leucodepleted components			
RBC (T/T)	21 ml	100 %	100 %
RBC (BAT)	10.5 ml	100 %	100 %
FFP	220 ml	100 %	100 %
leucodepleted components			
RBC (T/T)	21 ml	100 %	100 %
RBC (BAT)	10.5 ml	51 %	100 %
FFP	220 ml	100 %	100 %

Exploring alternative scenarios

The calculations offered so far refer to the scenarios used in existing DH risk assessments. We now consider the effect of varying assumptions both about the amount of infectivity in blood and about its distribution (retaining the same assumptions as before about the composition of units transfused).

Scenarios with lower infectivity

Given the results already calculated, it is of interest to consider the effect of reducing, rather than increasing, the level of infectivity in blood. In calibrating the transmission model, we are particularly interested in the risks associated with non-leucodepleted components. W*hat would be the transmission risks be, if infectivity was substantially lower than previously assumed?* The following table shows calculated transmission risks for different scenarios for Whole Blood infectivity ranging from 0.1 ID/ml (the existing “low” scenario) down to 0.001 ID/ml.

Table A4.4: Effect of varying WB infectivity on transmission risks via non-leucodepleted RBC or FFP (Poisson dose-response model)

Whole blood infectivity	probability of transmission via infected unit T/T RBC	probability of transmission via one infected unit BAT RBC	probability of transmission, via one infected unit FFP
0.1	100%	100%	100%
0.05	100%	95%	100%
0.01	92%	46%	85%
0.005	71%	27%	61%
0.001	22%	6%	17%

Substantial reductions are only seen at levels much lower than the existing "low" scenario. This is particularly marked for T/T RBC (more commonly transfused than BAT in the 1990s), where decreasing infectivity by a factor of 10 (to 0.01 ID/ml for Whole Blood) would reduce the probability of transmission by less than 10%. A 100-fold decrease is needed to reduce the resulting risk of transmission by a factor of about 5. For FFP, a 10-fold reduction in infectivity reduces the probability of transmission by just over 20%. In summary, a *very* marked reduction in infectivity is required to substantially reduce the expected number of transmissions prior to leucodepletion.

Varying the distribution of infectivity

We have assumed so far that 50% of the infectivity in whole blood is associated with WBC, and would so be largely removed by leucodepletion. However, this is not known exactly: the relevant animal models suggest a percentage lying between 40% and 75%. It is of interest to explore the effect of varying this assumption.

We therefore consider how the division of infectivity between WBC and plasma affects the transmission probability for non-leucodepleted RBC and FFP, across all possible distributions from 100% to 1% association with WBC, and for four scenarios as regards overall (Whole Blood) infectivity.

- In the existing "High Infectivity" scenario, all results remain at 100%, regardless of distribution of infectivity between plasma and WBC.
- Results for the existing "Low Infectivity" scenario, and scenarios with 10-fold and 100-fold lower infectivity are shown in the following table. (The shaded rows in each table indicate the ranges that might be seen as "plausible" in the light of animal models.)

Again, these differences only become substantial in scenarios below the current range As can be seen,

- Almost all figures in the first table remain at or close to 100%
- The extreme highlighted rows in the second table show that for a constant (0.01 ID/ml) Whole Blood infectivity, changing the proportion associated with RBC from 80% to 20% decreases the transmission probability for non-leucodepleted T/T RBC from 98% to 70%.

- A similar change in the even-lower infectivity scenario in the third table reduces the T/T RBC transmission probability from 32% to 11%.

Final comments

This Annex has provided sensitivity analysis on the infectivity present in RBC and FFP. Exploring the effect of changing inputs is important, given the multiple uncertainties involved. Nevertheless, the analysis shows that for non-leucodepleted RBC, any significant reductions in predicted transmission risks would require *very* substantial reductions in the previously-assumed infectivity of blood. Otherwise, the virtual certainty of transmission would remain, whichever dose-response model is used. The same applies for transmission via FFP with or without leucodepletion. Changing the assumed distribution of infectivity (between association with WBC and plasma) has little effect in the existing range of scenarios, but becomes significant at lower overall infectivity levels. Such scenarios can help show how transmission risks, and the benefit of leucodepletion, would vary in different circumstances.

Table A4.5: Effect of varying distribution of infectivity on probability of transmission via non-leucodepleted RBC or FFP (Poisson dose-response).

(a) Whole Blood infectivity 0.1 ID/ml (existing 'Low' scenario)

% infectivity associated with WBC	% infectivity associated with plasma	probability of infection, 1 unit T/T RBC	probability of infection, 1 unit BAT RBC	probability of infection, 1 unit FFP
99%	1%	100%	100%	42%
90%	10%	100%	100%	98%
80%	20%	100%	100%	100%
70%	30%	100%	100%	100%
60%	40%	100%	100%	100%
50%	50%	100%	100%	100%
40%	60%	100%	99%	100%
30%	70%	100%	99%	100%
20%	80%	100%	96%	100%
10%	90%	100%	93%	100%
1%	99%	98%	85%	100%

(b) Whole Blood infectivity 0.01 ID/ml

% infectivity associated with WBC	% infectivity associated with plasma	probability of infection, 1 unit T/T RBC	probability of infection, 1 unit BAT RBC	probability of infection, 1 unit FFP
99%	1%	99%	65%	5%
90%	10%	99%	62%	33%
80%	20%	98%	59%	54%
70%	30%	97%	55%	68%
60%	40%	95%	51%	78%
50%	50%	92%	46%	85%
40%	60%	87%	42%	90%
30%	70%	81%	36%	93%
20%	80%	70%	30%	95%
10%	90%	55%	24%	97%
1%	99%	33%	17%	98%

(c) Whole Blood infectivity 0.001 ID/ml

% infectivity associated with WBC	% infectivity associated with plasma	probability of infection, 1 unit T/T RBC	probability of infection, 1 unit BAT RBC	probability of infection, 1 unit FFP
99%	1%	37%	10%	1%
90%	10%	34%	9%	4%
80%	20%	32%	9%	7%
70%	30%	29%	8%	11%
60%	40%	25%	7%	14%
50%	50%	22%	6%	17%
40%	60%	19%	5%	20%
30%	70%	15%	4%	23%
20%	80%	11%	4%	26%
10%	90%	8%	3%	29%
1%	99%	4%	2%	31%

ANNEX B: MODELLING METHODOLOGY AND RESULTS

ANNEX B1: COMPARING PUBLISHED IMPERIAL MODEL RESULTS WITH PREVIOUS DH SCENARIOS

This Annex compares the projected number of clinical cases of vCJD transmitted via red blood cell transfusions, as estimated in the existing DH transmission scenarios and in the epidemiological modelling carried out by Imperial College. It provides a simple comparison of the average number of expected cases per year, treating this as roughly constant for the next 70 years. In reality, the case numbers projected by the Imperial College model vary from year to year, with a shallow peak around 2025 and a long tail to 2079, but this has been approximated to a constant rate for present purposes.

The existing DH scenarios are produced by combining high or low inputs for susceptibility, prevalence and infectivity:

	High	**Low**
Susceptibility	100% susceptibility	10% susceptibility
Prevalence	1 in 4,000	1 in 20,000
Infectivity	30 ID/ml	0.1 ID/ml

These are compared with two Imperial College scenarios: the median result from the full set of 1.5 million “baseline” model runs, and a variant that takes the median of the 2,000 “most likely” runs.

Table A1 sets out the case numbers in each projection, while Chart A1 shows this comparison graphically. Chart A2 focuses on the four lowest DH scenarios and compares these with the Imperial College estimates.

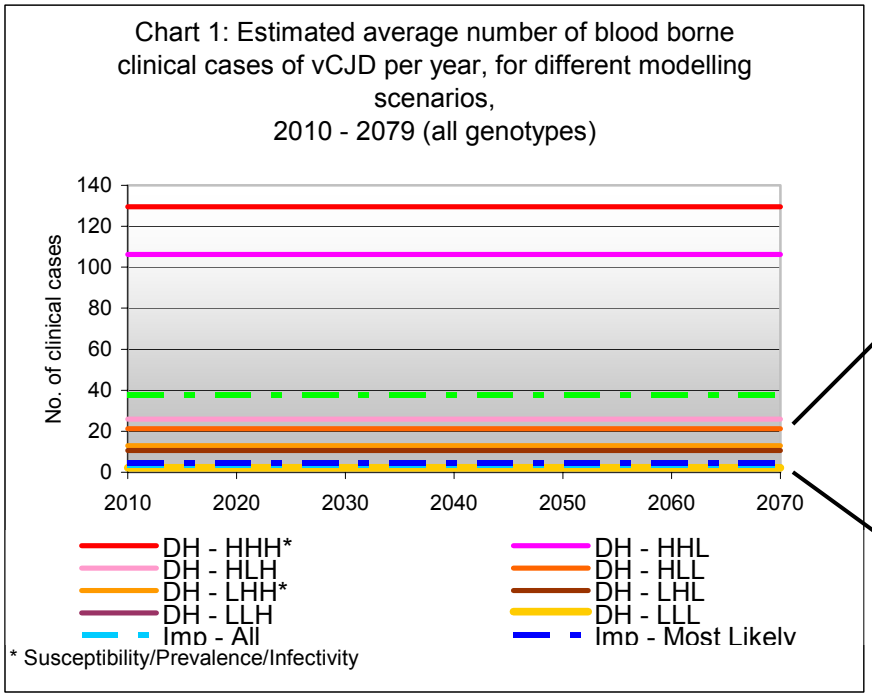
As can be seen, the Imperial College projections are positioned towards the lower end of the existing DH range, falling between the low susceptibility/low prevalence and low susceptibility/high prevalence scenarios. The upper 95% credibility interval value from the Imperial College model would give an average number of cases per year between the most pessimistic scenarios (high susceptibility/high prevalence) and the high susceptibility/low prevalence scenarios, but closer in magnitude to the less pessimistic of these.

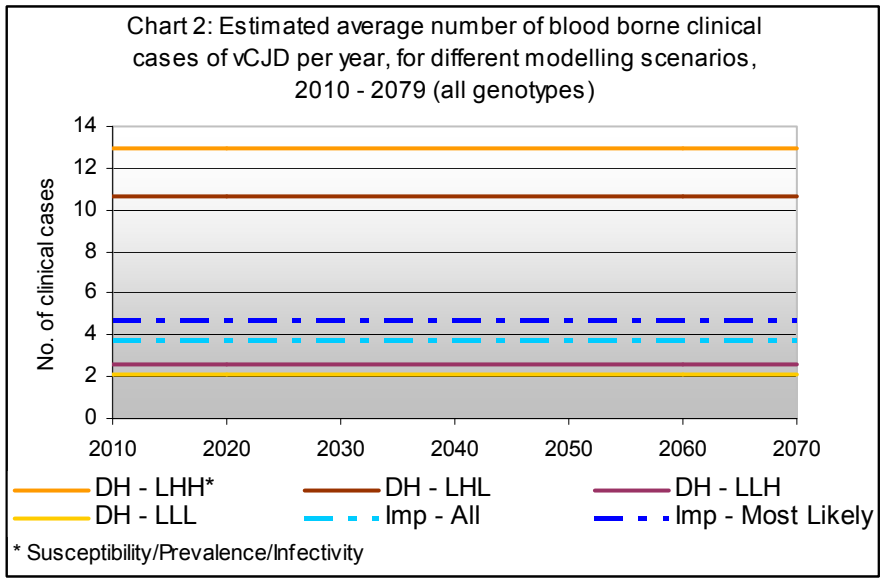
Overall, there is considerable overlap in the ranges given by the different models, but the expected number of cases in the DH worst case scenario is over 3 times the number from the 95% upper limit value from the Imperial College model.

Table 1 - Average number of clinical cases of vCJD expected, per year, from 2010 to 2079

Scenario	Average number of clinical vCJD cases transmitted via blood, per year
DH - HHH	130
DH - HHL	106
Imperial - 95% upper	***37***
DH - HLH	26
DH - HLL	21
DH - LHH	13
DH - LHL	11
Imperial – Most Likely*	***5***
Imperial – All*	***4***
DH - LLH	3
DH - LLL	2
Imperial - 95% lower	0

*Median values





ANNEX B2: DH/CORU MODEL FOR RED CELL TRANSMISSION: ILLUSTRATIVE RESULTS

Introduction

Like that produced by the Imperial College group, this model deals only with transmission via Red Cells. However, many of the same considerations apply to transfusion of other components. This Annex presents some illustrative results, refining the previous discussion of "model calibration" – the attempt to delineate a range of scenarios consistent with current evidence. In doing so, it is important to differentiate between clinical cases that – according to the model – should have been seen so far and projected cases yet to occur. It is also important to distinguish between transmissions that have already happened and those yet to do so

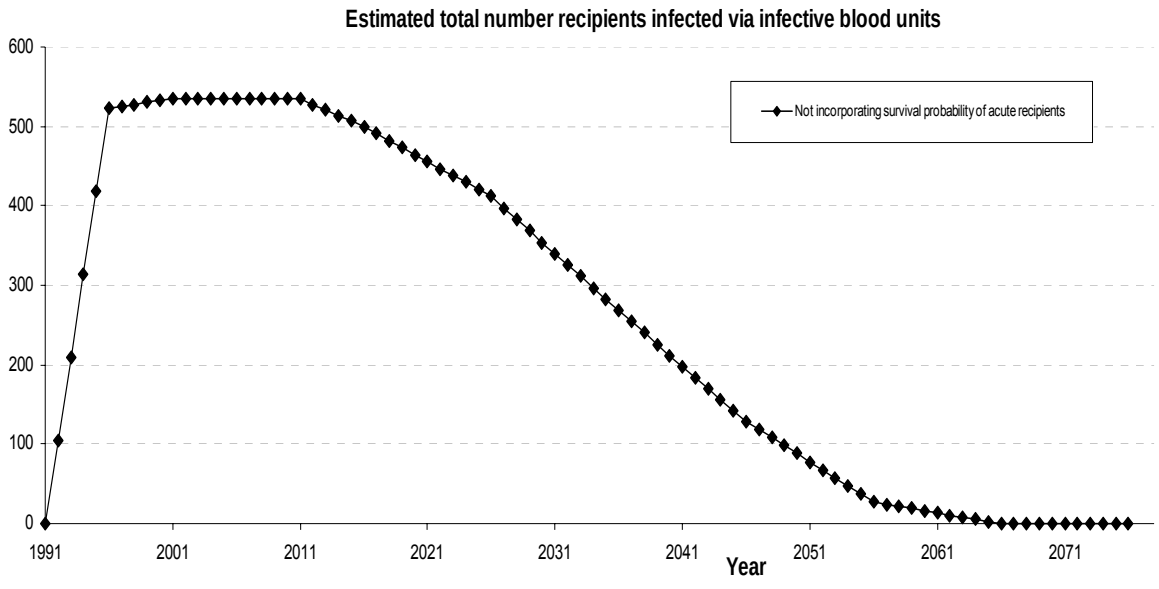
Model calibration: alternative prevalence scenarios

As noted, existing scenarios derive from the tissue survey carried out by Hilton *et al* (2004), suggesting a rough prevalence of prion infection of 1 in 4,000 (95% CI: 1 in 1,200 to 1 in 20,000). There is a received view that prevalence inputs should be "consistent with Hilton" – though as we have argued, prevalence of abnormal prion protein in tissues may not equate to prevalence of infectivity in blood. Prevalence estimates also require updating in the light of more recent evidence: we may also need to consider scenarios in which the chance of an infective unit transmitting vCJD infection is significantly less than 100% . For present purposes, however, we leave these caveats to one side, and use "Hilton prevalence" and "certain infection" inputs to illustrate the model.

(a) "Blanket 1 in 4,000"

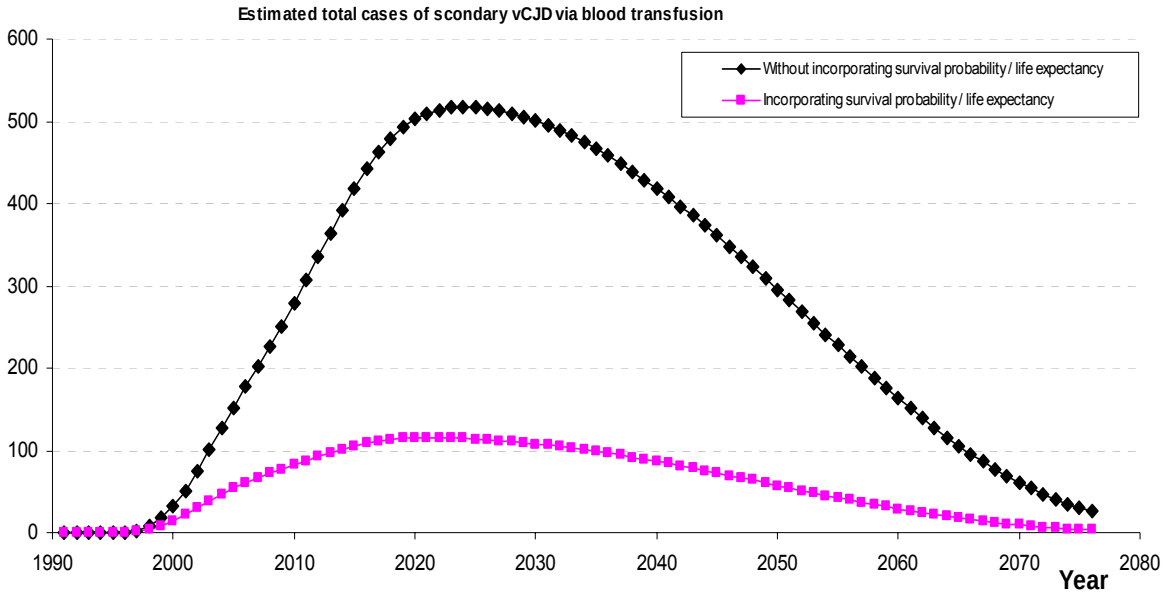
Firstly, suppose that the "central Hilton prevalence" of 1 in 4,000 applies to all age cohorts born up to 1996. This might be seen as the current DH "precautionary scenario". Assuming that primary infections occurred circa 1990 and allowing for a modest mean delay of 2 years in blood becoming infective, the model shows that a *very* large number of transmissions – over 500 per year - would have taken place from the mid-1990s onward. The rate only tails off as more donors come from amongst those born from 1996 onward.

Figure B2.1(a): Transmission scenario with 1 in 4,000 donors born up to 1996 infective.



To translate these transmissions of infection into projected cases, we separate recipients into MM homozygotes (40% of population) and other genotypes. For illustration, we take the mean secondary incubation period to be 10 years for MMs and 20 years for others, including both MV and VV, each subject to a Gamma distribution (α = 10, 20 yrs respectively and β = 1.0 in both cases, though this can easily be varied). If all recipients are susceptible to clinical disease, the projected clinical case numbers are as below.

Figure B2.1 (b) Projected clinical cases resulting from above transmission scenario



Clinical vCJD cases via Red Cell transfusion: 575 prior to 2011; 4477 thereafter

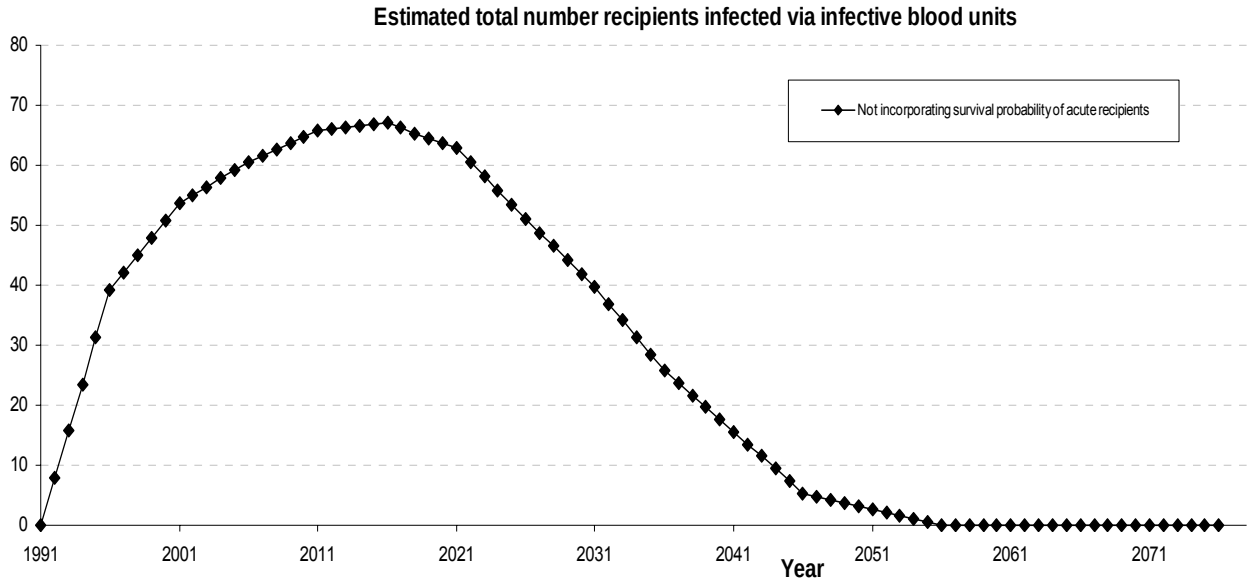
This provides a good illustration of the problem with such scenarios – that of explaining the small number of clinical cases seen to date. The model allows for limited recipient survival, with a large proportion of infected recipients dying of other causes prior to development of vCJD symptoms. But even so, the lower curve shown suggests that we would have seen of the order of 50 blood-borne clinical cases *annually* for some years, and nearly 600 to date. This is obviously unrealistic.

(b) "Minimal" Consistency with Hilton prevalence

Another way of defining consistency with the Hilton survey is to suppose only that the proportion of infected donors must reach 1 in 20,000 (the lower CI) in the 1960-85 birth cohort: it may be negligible in other cohorts. As shown below, the scale of transmission is reduced by a factor of about 10. In addition, a higher proportion of transmissions would occur later, with the annual rate only peaking in about 2015. [36]

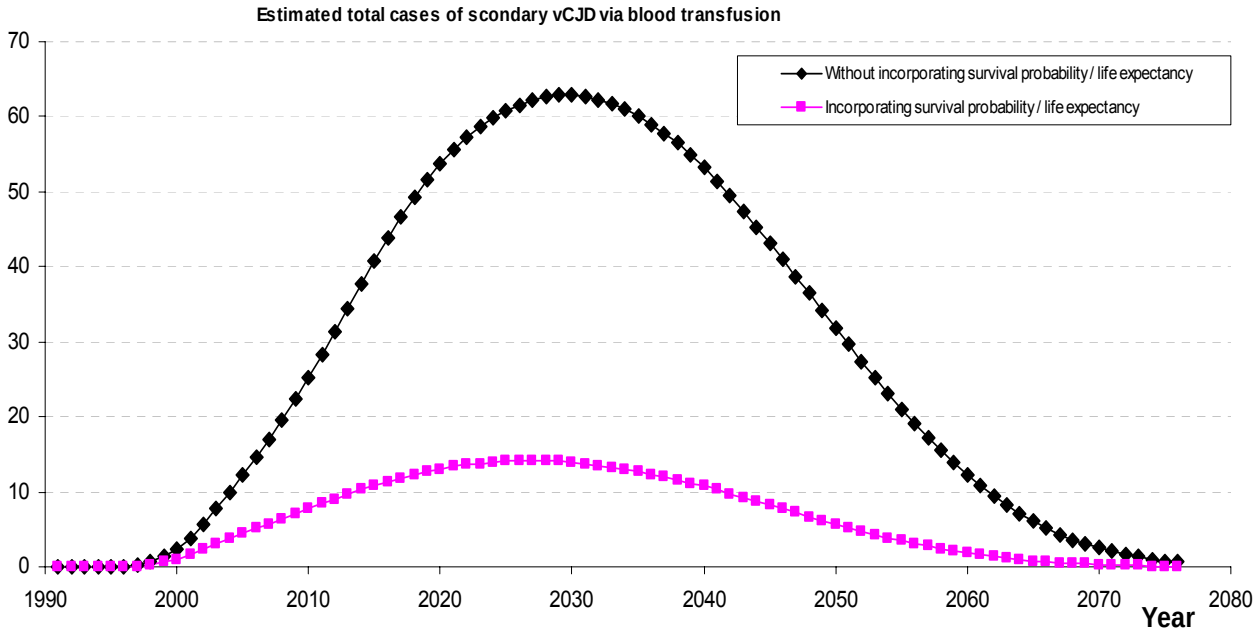
[36] By comparison, applying a 1 in 20,000 (rather than 1 in 4,000) prevalence across all cohorts born before 1996 would reduce the scale of transmission by a factor of 5, with the timing obviously unchanged.

Figure B2.2 (a): Transmission scenario with 1 in 20,000 donors born in 1960-1985 infective.



Using the same inputs for incubation periods, and retaining the assumption that all infected recipients are susceptible to clinical vCJD, the projected number of cases then appears as below. There remains significant inconsistency with the actual number of cases that might have been blood-borne.

Figure B2.2 (b): Projected clinical cases resulting from the above scenario



Clinical cases from Red Cell transfusions: 49 prior to 2011, 476 thereafter

Some further points are worth noting:

- Lengthening the mean delay from infection to blood becoming infectious reduces the inconsistency somewhat. For example, a mean delay of 6 rather than 2 years reduces number of cases expected prior to 2011 to 39, while leaving the projected number of *future* cases almost unchanged.

- Results are highly sensitive to the choice of β in the Gamma-distributions for secondary incubation periods: changing this from 1 to 1.5 reduces the projected numbers of cases markedly, to just 16 prior to 2011 and 338 thereafter. However, this is because we have increased the mean Incubation Period, so that more of those infected die of other causes. If we adjust α to maintain a constant *mean* Incubation Period, the differences become much less marked.
- The Imperial model uses a more generalised distribution for incubation periods. This is a 4-parameter function, of which the Gamma distribution is a special case. It appears that the additional degree of freedom allows the entire curve to be displaced to the right, so that the leading tail of the distribution can be reduced at will.

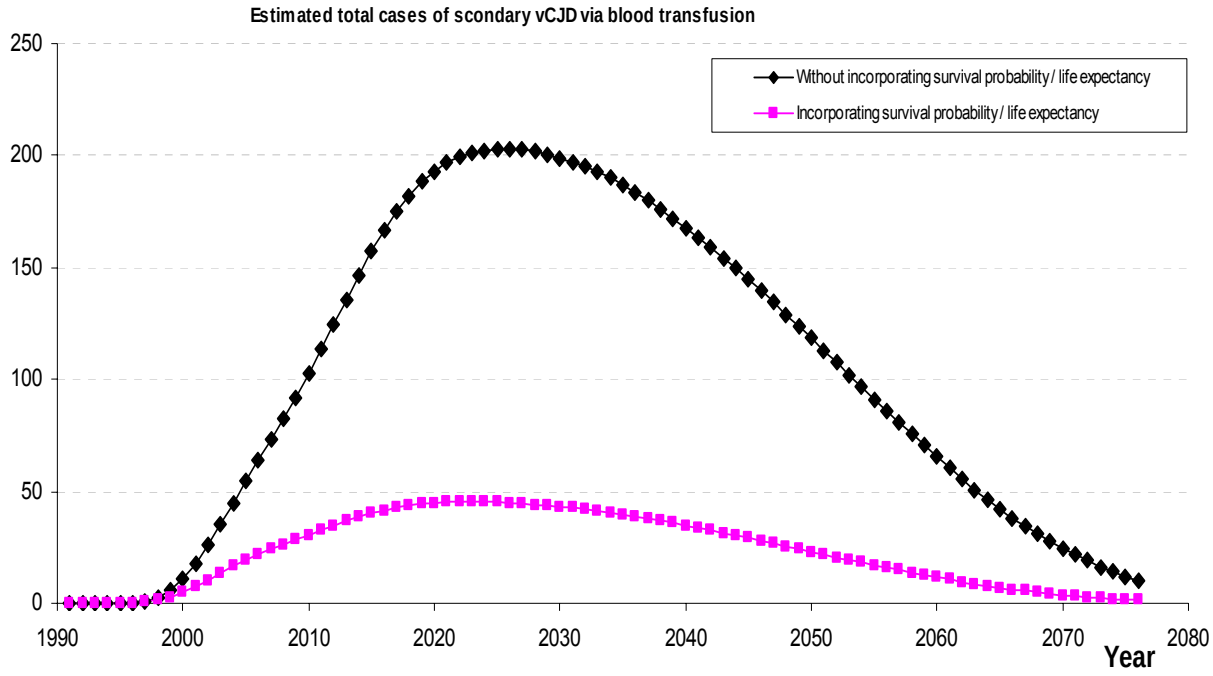
Overall, the inputs used so far generate *some* of the most important feature of the Imperial model's central scenario: that of a long wave of secondary cases, with relatively small numbers appearing each year but persisting for several decades. However, the total number of projected cases is significantly greater, and (critically) the inconsistency with case numbers seen to date remains unacceptable. **This suggests that "realistic" scenarios require prevalence of infective donors to be below 1 in 20,000 even in the "Hilton cohort" and/or susceptibility to clinical vCJD following infection to be less than 100%.**

(c) Further consideration of prevalence

Exploring some more detailed points about prevalence provides more insight into the relative sensitivity of outputs to changes in inputs. For example:

- Suppose that the previous 1 in 20,000 prevalence of infective donors is extended to the immediate "post-Hilton" cohort born1985-1996. This would not affect modelled case numbers up to 2011 (because very few of those infected by donors in this cohort would have yet developed clinical disease). However, projected *future* cases would rise from 476 to 732.
- We can also consider relative prevalence between age groups *within* the Hilton cohort - i.e. concentrating infective individuals toward the 1961 or 1985 end. This can have a significant effect. For example, the previous scenario can be varied by keeping the assumed number of infected donors the same, but putting them entirely in either the 1961-66 or 1980-85 sub-cohort. In the former scenario, the model projects 79 cases before 2011 and 382 future cases. In the latter, the figures shift to 15 and 582 respectively.
- Prevalence of infective donors in the "pre-Hilton" (1941-60) cohort has a much greater effect on projected case numbers, and especially on those predicted to have occurred already. The example below shows a scenario with 1 in 10,000 of all donors born 1941-95 infective and 100% susceptibility. Over 100 clinical cases are "predicted" to date.

Figure B2.3: Scenario with 1 donor in 10,000 infective, all cohorts 1941-1985



Clinical cases from Red Cell transfusions: 209 prior to 2011, 1770 thereafter.

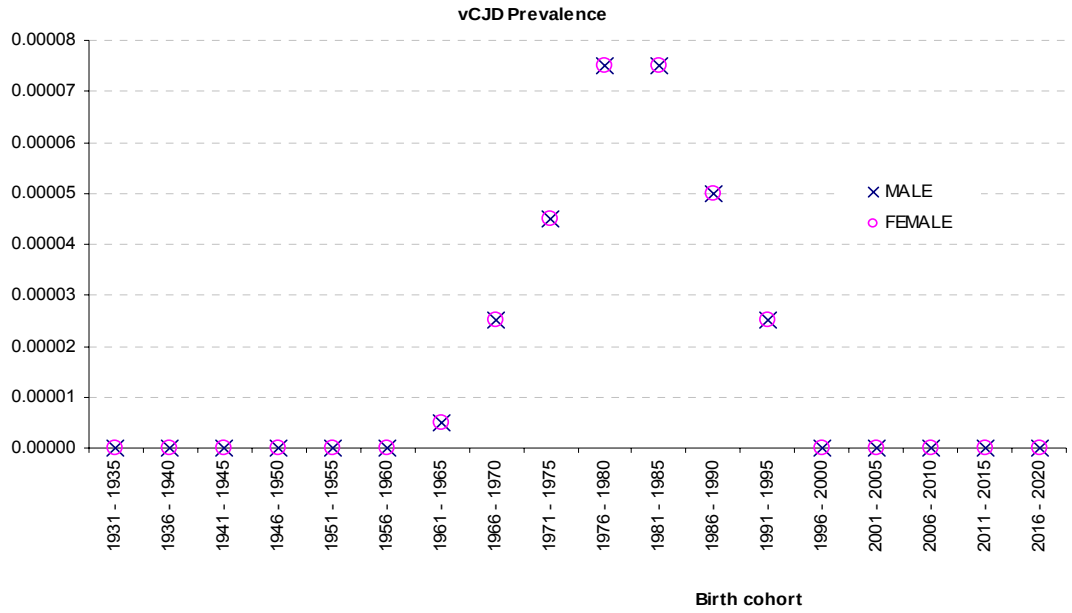
To summarise, "Realistic" scenarios therefore require:

- the prevalence of *infective* donors to be significantly below the range implied by the Hilton study of infection (even within the "Hilton" cohort) *and/or*
- the susceptibility to clinical disease of infected recipients to be significantly less than 100% *and/or*
- the transmissibility of vCJD infection via an infective unit of red cells to be significantly less than 100%.

Although of great scientific interest, the differences between these are not necessarily great in practical terms. All adjust the overall scale of case projection downward, without introducing any significant cohort / timing effects. Retaining 100% transmissibility – with the implication of onward transmission – and reducing susceptibility is more precautionary than reducing transmissibility.

Scenarios similar to published Imperial College Baseline

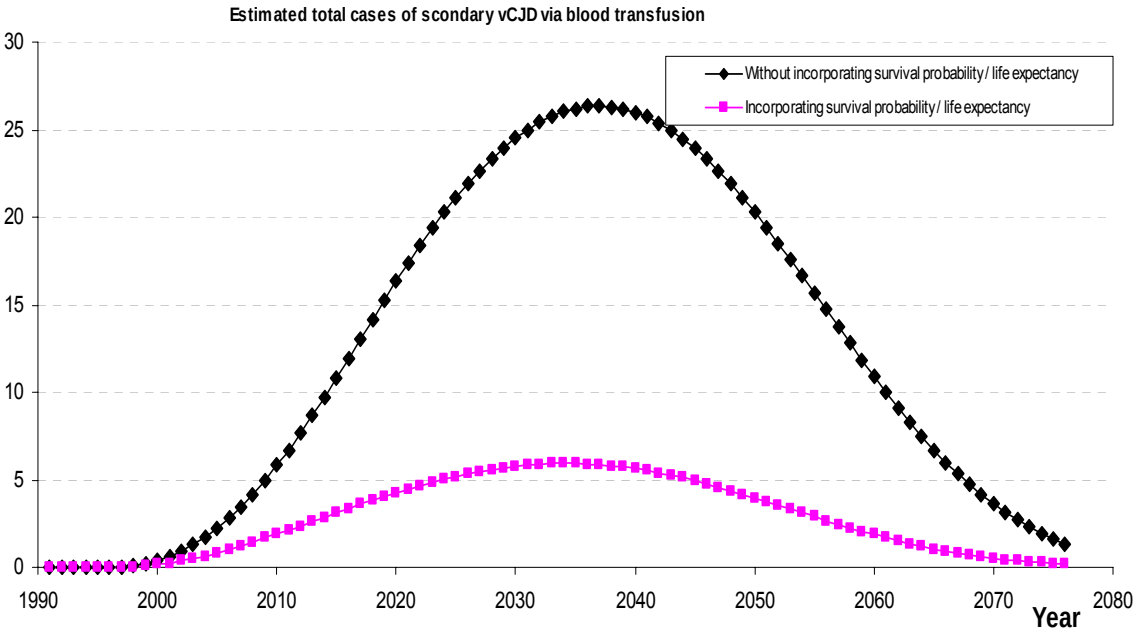
To demonstrate how this modelling method can produce results similar to the Imperial College model as published, we use a distribution of infective donors by age as shown below. This provides an overall prevalence of 1 in 20,000 for the 1960-85 cohort (at the lower end of the Hilton Confidence Interval) while avoiding discontinuities between age bands.



In addition, we assume a mean delay in onset of infectivity of 5 years from infection (with a variance of 3), and retain Gamma-distributed secondary incubation periods with $\beta = 1.0$ and $\alpha = 10$ and 20 years for MM and non-MM genotypes.

Combined with 100% susceptibility, this would produce a scenario with 29 clinical cases to date. We therefore scale down the projections by assuming a susceptibility to clinical vCJD of 35% of those infected. The resulting scenario is shown below. Its general properties are similar to the central Imperial scenario. (For comparison, this has 246 blood-borne cases in total, with a slightly later peak but otherwise very similar timing.) Scenarios of this type can be produced by many (fairly plausible) combinations of inputs.

Figure B2.4: Illustrative baseline scenario (with 35% susceptibility to clinical vCJD)



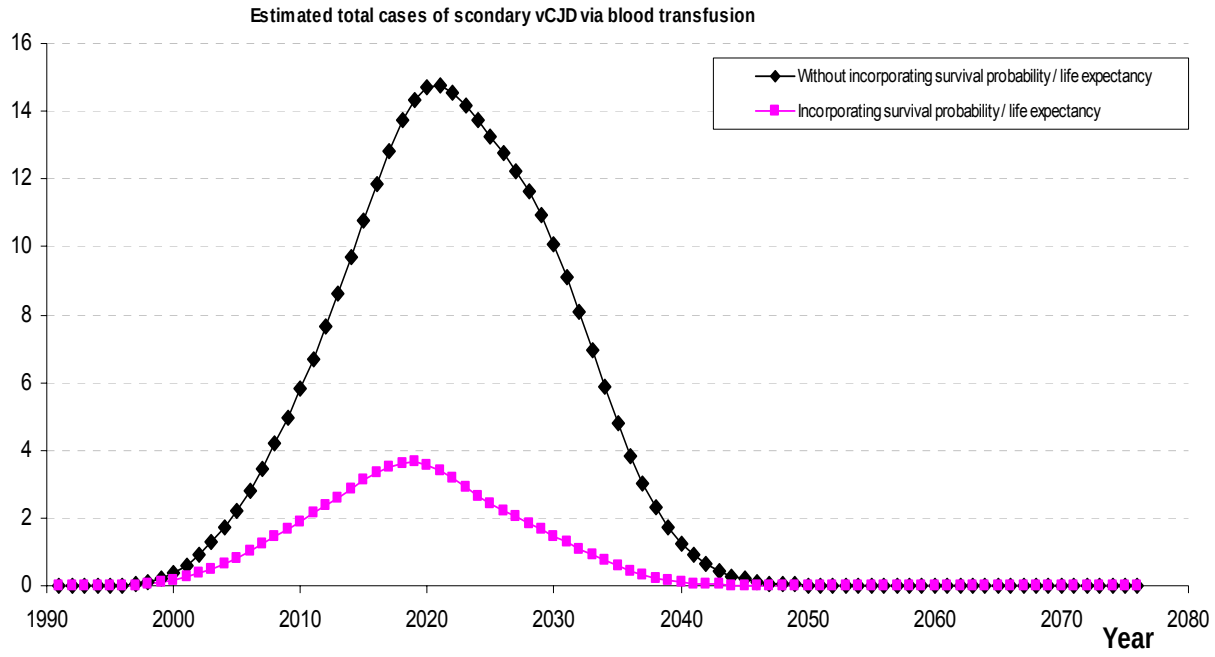
Blood-borne clinical cases: 10 prior to 2011, 231 thereafter)

Effect of stopping new transmissions

Suppose, hypothetically, that transmission could be halted very rapidly, with no new secondary infections after the end of 2011. How great would be the effect on future clinical cases, given our assumptions about incubation periods, and the number of future cases caused by infections that have already happened?

Starting from the scenario in Figure B2.4 above, Figure 5 shows the effect of "switching off" very rapidly after 2011, reducing (linearly) to zero from 2016 onward.

Figure B2.5: Scenario as in Fig B.2.4, with new transmissions rapidly reduced after 2011



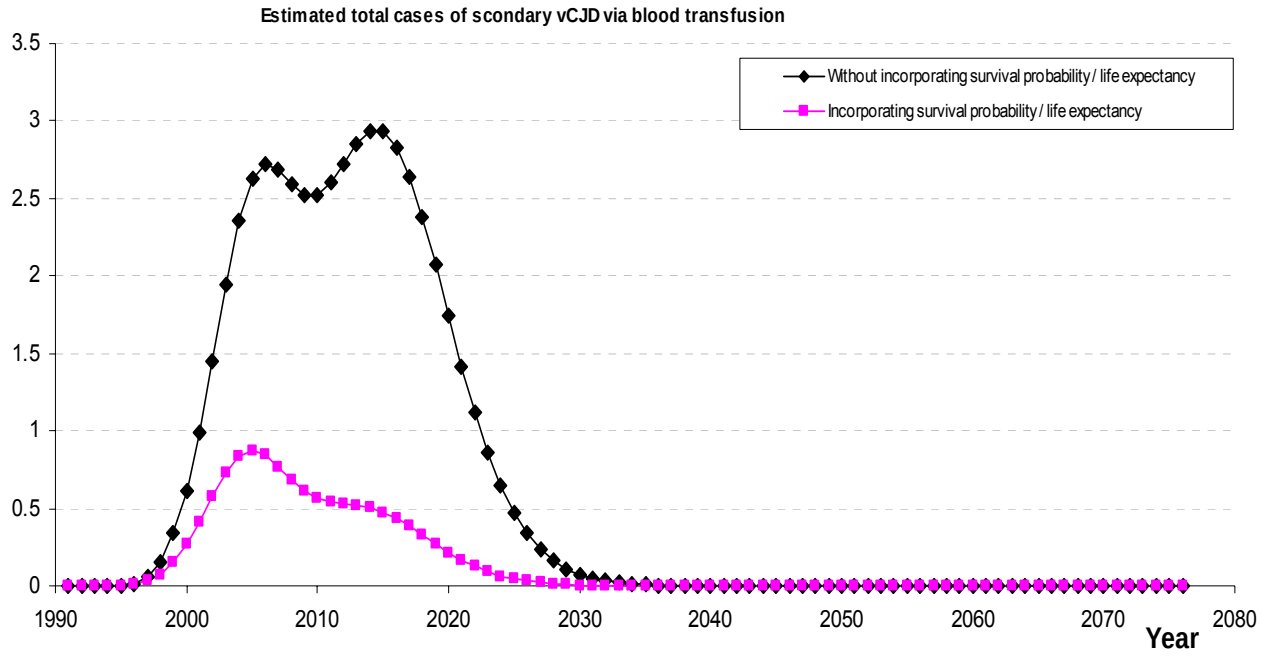
Blood-borne clinical vCJD cases: 10 prior to 2011; 61 thereafter.

As can be seen by comparison with Figure 4, it would take some years for this reduction to have a major effect on new cases, but the eventual effect would be considerable. The reduction in transmission would prevent 170 of the 231 future cases that would otherwise have happened. Although the numbers are only illustrative, the point is that a large proportion of future cases could still *in principle* be prevented. (The Imperial model supports a similar conclusion.) The figures indicate an upper bound for the effect of any putative intervention – e.g. rapid phasing-in of universal prion filtration immediately, in the "best case" of this removing virtually all infectivity.

What if leucodepletion had stopped transmissions?

Finally, we use the model to explore what would have happened had leucodepletion been completely effective in preventing new transmissions. The scenario shown below again starts with the same inputs as that in Figure B2.4, but now assumes that transmissions were reduced rapidly from 1999.

Figure B2.6: Scenario as in Fig B.2.4, but with leucodepletion effective in preventing new transmissions



Blood-borne clinical vCJD cases: 7 prior to 2011; 5 thereafter

Although the assumed effectiveness of leucodepletion is contrary to the results of animal models, it is of interest that this is the only scenario fully consistent with the human case data.

ANNEX B3: EFFECT OF AGE CUT-OFF FOR SUSCEPTIBILITY ON CASE NUMBERS

Summary

The concept of *susceptibility* refers here to the proportion of individuals infected with vCJD who might go on to develop clinical symptoms. (Amongst those who are susceptible, whether or not disease actually develops will depend on individual survival as compared with the incubation period.) The simplest possible scenarios are generated by assuming a fixed susceptibility – e.g. 100% or 10% - regardless of age. Alternatively, susceptibility may depend on age at infection. This has been considered previously in the context of primary infection (and incorporated into the Imperial College model already discussed).

Age-dependent susceptibility to disease may be a less compelling hypothesis for secondary, blood-borne infection. However, one alternative to existing scenarios is that susceptibility is age-dependent in the specific sense of infected "elderly" individuals being less likely to develop symptomatic vCJD. This is given some plausibility by a recent research using a mouse model. It is of interest to explore how great a reduction in expected case numbers might result from some "upper age cutoff" for susceptibility to disease, given both the tendency of existing models to "over-predict" case numbers and the large proportion of transfusions given to relatively elderly patients.

Although an age-dependent cutoff in susceptibility has the potential to reduce the predicted number of cases significantly, this effect is itself reduced by differentials in post-transfusion survival. Calculations allowing for both effects suggest that age thresholds of 40, 50 and 65 years at transfusion would reduce the expected number blood-borne clinical cases by roughly 75%, 60% and 30% respectively.

Clearly, these alternative scenarios lie within the existing "high" (100%) and "low" (10%) susceptibility range. It is also worth noting that the existing "low" (10%) susceptibility scenario would be reached by an age-dependent model in which susceptibility was confined to recipients aged under 20 at transfusion.

Key inputs

Recent research by Brown *et al* (2009) suggests that aged mice orally exposed or injected intracerebrally with scrapie brain homogenate have not developed clinical TSE disease during their lifespan, although they have displayed signs of TSE disease in their brains. The reduced status of follicular dendritic cells in aged mice appears significantly to impair the accumulation of TSE agent in lymphoid tissues. If so, age might present a significant barrier against the development of clinical TSE symptoms, as distinct from infection.

This raises the question of whether older human recipients of blood components might be less susceptible to developing clinical vCJD. How much difference this would make to eventual case numbers will depend not only on the age distribution of blood recipients, but on the distribution of those who survive long enough to develop the symptoms of vCJD rather than dying of other causes. To explore this question using a simple model, we consider various age "cutoffs" for susceptibility. Any such cut-off is clearly a simplification, as one would expect susceptibility to reduce progressively rather than suddenly. It is in any case difficult to judge how the definition of an "aged" mouse would translate into a human lifespan.

To illustrate the effect of a cutoff on case numbers, we consider how many patients (above and below the cut-off) are likely to survive at least 10 years from transfusion. As discussed, a significant proportion of blood-borne cases might plausibly appear within such a period, at least amongst MM homozygotes. (This assumption can be varied: longer incubation periods would obviously magnify the effect of limited post-transfusion survival).

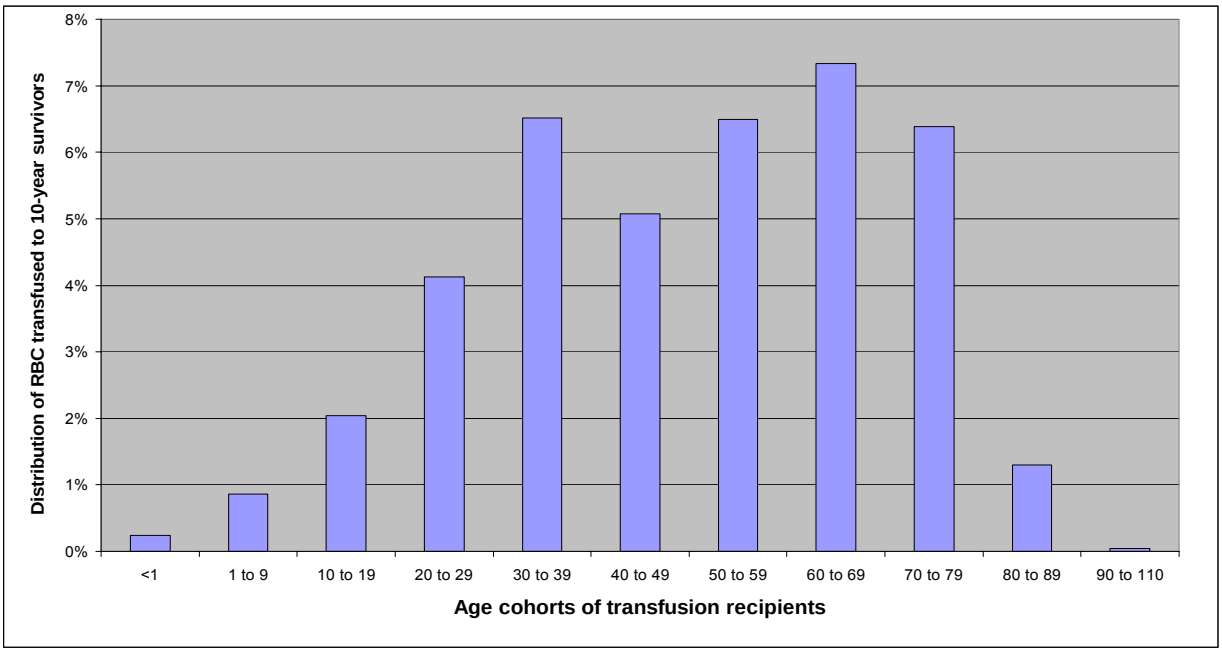
Calculations

As Red Blood Cells (RBC) are the most commonly-transfused component, we have used the data available on post-transfusion survival and age distribution of transfusion recipients of RBC. To check the plausibility of the calculated age distribution of recipients still alive after 10 years, this is also compared with that of the known recipients of implicated RBC components transfused in the interval 1998 - 2004.

- As discussed in Annex A1, the distribution of RBC units transfused to recipients is available from the Epidemiology and Survival of Transfusion Recipients (EASTR) study conducted by NHSBT in 2001/2002. This shows, for example, that recipients aged over 50 years received 75% of all RBC transfused (see Figure A1.1).
- However, estimated 10-year post-transfusion survival declines sharply by age cohort (as shown in Figure A1.2). For example, recipients in the 80-89 cohort receive 17% of all RBC units transfused but have only a 7% chance of being alive after 10 years.

Combining these two effects, we can calculate the distribution of RBC by age of recipient, *counting only expected "10-year survivors*". The result is shown in the Figure below.

Figure B4.1: Distribution of RBC transfused to 10-year survivors, by age at transfusion



We can now consider the percentage of RBC units transfused to 10-year survivors that go to recipients beyond various possible cut-off ages, e.g. aged 40, 50 and 60 years at transfusion.

Table B4.1 Proportion of RBC units transfused to 10-year survivors above age cutoffs

	Recipients aged over 40 years	**Recipients aged over 50 years**	**Recipients aged over 65 years**
Percentage of RBC transfused	65%	53%	29%

For example, amongst "10-year survivors", 53% of RBC units go to recipients aged over 50 years. **Given that exposure to vCJD infection in each age cohort is proportional to the number of units transfused,** using this age as the upper threshold for susceptibility would also reduce the expected number of vCJD cases by 53%, as compared with a fully-susceptible population. Had differential survival rates not been taken into account, the reduction would have been significantly greater, at about 75%.

In reality, these calculations are only illustrative, given that there is no direct evidence of age-dependent susceptibility in humans (at least for secondary transmission). Indeed, the spread in ages amongst the three presumed blood-borne cases seen so far tells against any strong age dependence.