BLOOD-BORNE TRANSMISSION OF vCJD RE-EXAMINATION OF SCENARIOS

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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.