



## IMPLICATIONS OF RECENT RESEARCH ON MODELS OF THE vCJD EPIDEMIC

### ISSUE

1. Recent horizon scanning identified the hypothetical risk of a secondary epidemic of vCJD as a result of lateral transfer of the BSE prion between individuals (for example through blood transfusion) a key issue to assess. In addition, DH requested that SEAC considers the implications of recent research on models of the profile of the vCJD epidemic. These two issues are related.

### BACKGROUND

2. Trends in the incidence of BSE in cattle show that the control measures introduced to prevent recycling of mammalian meat and bone meal have resulted in dramatic decline in the number of cases of the disease<sup>1</sup>. Control measures have also been introduced which significantly limit the potential risk of primary infection of humans from consumption of food contaminated with the BSE agent.
3. Recent numbers of vCJD cases show a decline in the incidence of vCJD<sup>2</sup>. To date, all the affected individuals have been found to be methionine homozygous (M/M) at codon 129 of the prion protein (PrP) gene, suggesting that this PrP genotype may be relatively susceptible to vCJD compared with other PrP genotypes.
4. Projections of the profile of the vCJD epidemic based on data from the BSE and vCJD epidemics, together with assumptions on parameters such as vCJD phenotype and incubation period, have suggested that the numbers of vCJD cases will be relatively small<sup>3</sup>. However, a number of recent experimental and

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<sup>1</sup> BSE Update. Item 2 SEAC 84 minutes.

<sup>2</sup> vCJD Update. Item 3 SEAC 84 minutes.

<sup>3</sup> e.g. Ghani *et al.* Updated projections of future vCJD deaths in the UK. *BMC Infect Dis.* 2003 3, 4.

epidemiological research findings suggest that the profile of the epidemic may be more complex. For example:

- A survey to detect abnormal prion protein (PrP) in tonsil and appendix<sup>4</sup> has indicated that the prevalence of infection may be higher than suggested by the number of clinical vCJD cases.
  - A case of probable blood transfusion associated transmission of vCJD was found to be heterozygous (M/V) at codon 129 of the PrP gene raising the possibility that genotypes other than M/M may also be susceptible to infection. However, the patient was asymptomatic for vCJD before dying of an unrelated cause<sup>5</sup>.
  - Findings from a study of transgenic mouse models expressing human forms of the PrP gene<sup>6</sup> suggest that the PrP genotype may strongly influence the clinical phenotype of BSE and vCJD infection.
  - An analysis of the age distribution of vCJD cases suggests that susceptibility to vCJD could be related to age, with a higher susceptibility to vCJD in younger people<sup>7</sup>.
5. The potential for secondary (human to human) infection as a result of medical procedures (e.g. use of contaminated surgical/dental instruments, blood transfusions and tissue transplants) is a further factor that may influence the profile of the vCJD epidemic.

## **SEAC CONSIDERATION**

6. SEAC has considered the profile of the vCJD epidemic on numerous occasions and has also considered the potential for secondary infections as a result of medical procedures or maternal transmission. However, in light of new information about the prevalence of the disease as well as the possible relationships between age and susceptibility and PrP genotype and disease phenotype, DH has asked the committee to reassess

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<sup>4</sup> Hilton *et al.* Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *J Pathol.* 2004 203, 733-739.

<sup>5</sup> SEAC statement on the second presumed case of blood transfusion-associated infection with vCJD. (2004)

<sup>6</sup> Wadsworth *et al.* Human prion protein with valine 129 prevents expression of variant CJD phenotype. *Science.* 2004 306, 1793-1796.

<sup>7</sup> Boelle *et al.* Epidemiological evidence of higher susceptibility to vCJD in the young. *BMC Infect Dis.* 2004 4, 26.

current models of the profile of the vCJD epidemic and consider the possible impact of secondary infections on the epidemic.

7. The SEAC CJD epidemiology subgroup has recently been disbanded and will be reconvened as the SEAC epidemiology subgroup with new terms of reference to cover both the animal and human epidemiology of prion diseases. The new terms of reference for the subgroup are:

*To report to SEAC on the significance of emerging and published epidemiological data about human and animal TSEs, and on such specific epidemiological questions as SEAC refers to it for advice.*

8. Detailed epidemiological analyses, together with new modelling work, will be required to address this issue comprehensively. Thus, it is envisaged that SEAC could task the reconvened SEAC epidemiology subgroup to address the request and report back to the committee at a later date.
9. To inform the subgroup considerations, SEAC is asked to consider the issues and identify key questions for the subgroup to address. A list of possible key and subsidiary questions is given at the end of this paper. DH has agreed to consider support for some modelling work.
10. To facilitate consideration of the key issues and questions by SEAC, a number of experts have been invited to make presentations to the committee and some of the key pieces of research are also provided in annexes as below:
  - the most recent data on the clinical profile of vCJD and sCJD cases, projections of the course of the vCJD epidemic and an estimation of the risk of primary infection (see Annex 1).
  - information on genotype-phenotype relationships from transgenic mouse models and the Kuru epidemic (see Annex 2).
  - research on measures to reduce potential vCJD transmission through the use of surgical instruments (Annex 3).
  - models of age-related susceptibility to infection (Annex 4).
11. Note that parts of Annexes 3 and 4 have not been circulated outside the committee as these annexes contain new scientific data that have

not yet been published in a scientific journal. However, the content can be discussed by the committee in the public meeting.

## **ADVICE SOUGHT FROM THE COMMITTEE**

12. The committee is asked to:

- agree that the reconvened SEAC epidemiology subgroup be tasked with a detailed consideration of the issues identified.
- suggest possible sources of additional information that could inform the subgroup's considerations.
- develop key questions for the subgroup to consider to enable it to address the issues identified.

13. Suggested key and subsidiary questions are as follows:

Q1 What are the implications of recent research for current models of the vCJD epidemic?

(a) Do recent data on age- and genotype-related effects alter the predicted profile of the vCJD epidemic and the potential number of infective carriers?

(b) Are there likely to be 'carriers' of infectivity who do not develop clinical vCJD within their lifetime, or who present with clinical features not currently recognised as vCJD, and if so, what are the limits on the possible prevalence / age distribution / genotype of such individuals?

Q2 What new evidence would lead SEAC to believe that the size of the vCJD epidemic is likely to be larger or smaller than current estimates (i.e. what new data would lead SEAC to believe that current estimates may be incorrect)?

(a) Are the current and expected data from population level studies (i.e. tonsil and appendix and other tissue surveys) sufficient to enable estimation of the age / genotype distribution of infection, and what further information would help inform predictions of the profile of the vCJD epidemic?

(b) What are the information barriers to determining the potential risks to public health from carriers of vCJD infectivity?

Q3 Is there a significant risk of a self-sustaining human vCJD epidemic through secondary transmission of BSE between humans?

(a) What are the relative risks of secondary transmission through medical procedures (transfusion, transplantation, surgery)?

(b) Taking all these potential routes of transmission and their interactions into account, how likely is a self-sustaining epidemic?

(c) If a self-sustaining epidemic is possible, what factors determine its scale?

Q4 What are the key points at which modification of practice could significantly reduce the risk of a self-sustaining epidemic?