



## Summary of SEAC's discussion on the second presumed case of blood transfusion-associated infection with vCJD

### Background

1. The Department of Health sought advice from the committee on a presumed second instance of blood transfusion-associated transmission of the variant Creutzfeldt-Jakob disease (vCJD) agent. The first case of probable blood transfusion-associated transmission of vCJD<sup>1</sup> was considered by SEAC in February 2004.
2. The National CJD Surveillance Unit (NCJDSU) had investigated this second patient after death, as the patient was a known recipient of blood from a donor incubating vCJD. Patient confidentiality and medico-legal issues surrounding the patient at the time of reporting required that the issue was considered in the reserved session of the meeting.
3. The elderly patient died in 2004, showed no clinical signs of vCJD at the time of death, which was from an unrelated cause. The patient had received a single unit of non-leucodepleted blood in 1999 that had been donated by an individual who was confirmed in 2001 as a definite vCJD case. The donor's disease onset was in 2000.
4. The NCJDSU had investigated the neuropathology, accumulation of prion protein and PrP<sup>res</sup> in autopsied tissues in the case. The PRPN genotype had also been determined. The following details were reported:
  - No evidence of a spongiform encephalopathy in an examination of brain material.
  - Immunohistochemical detection of prion protein accumulation in the spleen and in a cervical lymph node. PrP<sup>res</sup> was detected by high sensitivity western blotting in the spleen.
  - No accumulation of prion protein was detected in multiple regions of the central nervous system, tonsils, appendix, large intestine, skeletal muscle or thymus.
  - Glycotype profile of PrP<sup>res</sup> in spleen was the same as has been found in clinical cases of vCJD.

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<sup>1</sup> Llewelyn CA, Hewitt PE, Knight RS, Amar K, Cousens S, Mackenzie J, Will RG. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet*. 2004 Feb 7;363(9407):417-21.

- Histological pattern of PrP accumulation in the spleen and the lymph node is similar to that in two appendixes reported by Hilton *et al* (2004)<sup>2</sup>.
  - Methionine/valine heterozygosity at codon 129 of PrP gene (PRNP).
5. SEAC was informed that the findings suggested that this might be a preclinical or subclinical case of iatrogenic vCJD associated with blood transfusion. However, UK residency of the patient meant that oral exposure to the BSE agent could not be excluded as a possible cause of infection. Statistical analysis suggested it was extremely unlikely that two cases of infection with the vCJD agent would have been detected by chance in recipients of blood from pre-onset vCJD cases, even if the prevalence of prion protein accumulation in spleen tissue in the UK population was substantially larger than suggested by studies on appendix and tonsil tissue from persons without clinical vCJD.
  6. The Department of Health (DH) asked SEAC to assess the data available on this case, and to advise on the implications this finding may have on the risk associated with blood, and on any additional concerns for public health.

### Summary of SEAC's discussion

7. SEAC agreed that the western blot results and glycoctype profile suggested it was unlikely that the infection was preclinical sporadic CJD (sCJD). The committee noted that a single study by Glatzel *et al* (2003) had reported PrP<sup>res</sup> in the spleen of sCJD clinical cases. However, the levels of PrP<sup>res</sup> present in sCJD cases were low and detected in patients with a lengthy clinical illness from sporadic CJD.
8. The committee agreed that the statistical analysis suggested that the presence of PrP<sup>res</sup> in the case was attributable to a vCJD infection acquired via blood transfusion rather than a primary infection resulting from a food borne exposure.
9. SEAC agreed that this second patient with apparent vCJD infection added to the evidence that the vCJD agent can be transmitted by blood. However the committee noted that in this instance, although vCJD infection appeared to have been transmitted, it was not known if clinical vCJD would have developed if the patient had lived longer.
10. SEAC agreed that this case added support to its view on the risk associated with blood transfusion. The finding was consistent with there being a substantial risk associated with receipt of non-leucodepleted blood from a donor incubating vCJD. The extent to which leucodepletion reduces that risk is not known.
11. The committee agreed that it should be a public health priority for all recipients of blood (leucodepleted or not) from donors incubating vCJD to be subject to the kind of careful post-mortem examination that had been possible in this case. This would help to quantify the nature and magnitude of the risks of transmission

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<sup>2</sup> Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Ritchie D, Penney M, Hegazy D, Ironside JW. Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *Journal of Pathology*: 203 (3).733-739. Published Online: 21 May 2004

of the vCJD agent through blood [donated by preclinical cases of vCJD]. The committee re-iterated the continuing importance of the Transfusion Medicine Epidemiology Review (TMER) to identify vCJD cases who have been donors and the recipients of such donations.

12. SEAC noted that the detection of PrP<sup>res</sup> in lymphoreticular tissues of vCJD cases and the presence of infection in the spleen of this case was compatible with the lymphoreticular system being involved in the early spread of infection before entering the CNS. SEAC agreed that the detection of prion protein in the spleen but not in the tonsil of the case has implications for the national anonymous tonsil archive. The SEAC chair agreed to refer this finding to the DH/MRC steering group overseeing the archive.
13. SEAC noted that the patient was heterozygous at codon 129 of the PRNP gene and that this was the first time infection with the vCJD agent had been reported in an individual not methionine homozygous. This indicated that genotypes other than the methionine homozygous were susceptible to infection with the vCJD agent. Uncertainties remain as to the relative susceptibility of heterozygotes to food borne (or other) infection or the possible outcomes of infection. The committee agreed that the similarities between the western blot band analysis and PrP<sup>res</sup> glycoprofile seen in this case and in cases of vCJD who were methionine homozygous was reassuring with respect to the ability to make the diagnosis of vCJD in those of genotypes other than methionine homozygous.
14. SEAC stated that, in the interests of public health, this case demonstrates the importance of both in life and in death surveillance of recipients of blood products derived from blood donations from individuals subsequently found to be infected with the vCJD agent. The committee also noted that this case highlighted the importance of obtaining autopsies in such patients and, more generally, the committee reiterated the concern that it had expressed previously, that a mechanism was needed to increase the autopsy rate amongst the UK population to reduce the possibility that cases of vCJD were being missed.
15. SEAC emphasised the importance of the DH-funded sheep transfusion study which is designed to investigate the infectivity of different blood fractions taken from sheep experimentally infected with BSE by transfusing them into ARQ homozygous sheep. The committee noted that the two presumed human cases of blood transfusion-associated vCJD infection indicated the potential infectivity of transfused blood. However, current technology is unable to quantify the levels of infectivity in blood and a rapid diagnostic test remained a key research priority.

**SEAC**  
**16<sup>th</sup> July 2004**