

SEAC104/3

VCJD TRANSMISSION VIA BLOOD COMPONENTS: CAN A MORE PLAUSIBLE RANGE OF SCENARIOS BE ESTABLISHED?

ISSUE

1. The Department of Health (DH) uses a wide range of possible scenarios for blood borne transmission of vCJD, to support risk management. However, a number of those scenarios over-predict the number of clinical cases of vCJD that have resulted so far from blood-borne transmission. DH analysts have drafted the paper attached at Annex A, which assesses the possibility of revising these scenarios so as to be more consistent with the available “positive” and “negative” evidence on human transmission, as well as with the findings of animal studies.
2. DH would like SEAC’s advice on the establishment of a more plausible range of scenarios. SEAC is asked to consider:
 - Acknowledging the crude nature of the calculations offered, have any major factors been misrepresented or overlooked?
 - Are members aware of any more sophisticated analysis that addresses the consistency of blood-borne transmission scenarios with observed case numbers?
 - Given the apparent consistency problem, can the existing range of inputs on infectivity, prevalence of infective donors and susceptibility to disease be reconciled with the data by invoking plausible further hypotheses - and if so, what are they?
 - If not, should some of the existing input ranges now be regarded as implausible - singly or in combination - and if so, which?
 - Should additional scenarios now be regarded as plausible - and if so, how should the current input ranges be extended?
 - Can the Committee suggest any further lines of investigation that could be implemented relatively quickly, and could throw further light on the numbers of vCJD cases likely to result from blood-borne transmission?

THE DH SCENARIOS

3. The current scenarios are based on three main inputs:
 - the prevalence of infective donors;
 - vCJD infectivity (levels and timing) in blood components; and
 - susceptibility of recipients to clinical disease.
4. Eight scenarios, using combinations of “high” and “low” values for each of these parameters, are currently used for planning purposes. These input ranges have each been based on the available published evidence and SEAC advice as detailed below. The resulting scenarios cover a very large range.
5. However, it is becoming increasingly problematic to reconcile this wide range of scenarios with the small number of clinical vCJD cases that have been attributed to blood-borne infection. To date there have been three such cases and one case of sub-clinical infection in a patient who died of unrelated causes.
5. The incubation periods for the three clinical cases of blood borne transmission that have occurred to date were 5, 6.5 and 7.8 years, therefore sufficient time has passed for further clinical cases to have emerged in patients who have been exposed to implicated blood.
6. There is thus accumulating “negative evidence” that may warrant reassessment of the potential number of vCJD cases that could be caused by blood transfusion. The attached paper considers the arguments relevant to such a reassessment.

PREVIOUS SEAC CONSIDERATION

7. SEAC provided advice on the sub-clinical prevalence of vCJD in its 2008 position statement ¹. This concluded that it would be prudent to consider that the estimate provided by the Hilton *et al* study of 1 in 4,000, provides a reasonable, pragmatic and precautionary working scenario for the prevalence of subclinical infections. However, the Hilton data have wide ranges of uncertainty and a statistical confidence interval of between 1 in 1,400 and 1 in 20,000. The current DH scenarios use this study to estimate the possible prevalence of *infective blood donors*, taking “high” and “low” figures of 1 in 4,000 and 1 in 20,000 respectively.

¹ Position Statement on Prevalence of Subclinical variant Creutzfeldt Jakob Disease Infections

8. The SEAC 2006 Position Statement on TSE Infectivity in Blood ² considered a range of data from animal studies, and concluded that:

The available data show that blood is infectious during the preclinical stage of vCJD. Although the precise time in the incubation period of vCJD at which blood becomes infectious is unclear, data from animal models suggests it may be infectious from at least, if not before, the middle of the incubation period. The source of infectivity in blood is not understood. Data from rodent studies suggests that infectivity in whole blood is around 10 ID/mL and that it mostly resides in the plasma and white blood cell components with infectivity associated with white blood cells substantially depleted by extensive washing. However, additional information from other animal models is required to assess whether these findings may be closely representative of vCJD infectivity in human blood.

9. More recent studies by Houston *et al* (2000 & 2008) have shown that scrapie and BSE can be transmitted to sheep by transfusion of whole blood taken from symptom free donor sheep. Houston *et al* (2008) gave transmission rates of 36% for BSE and 43% for scrapie. A proportion of BSE-infected transfusion recipients (3 of 8) survived for up to 7 years without showing clinical signs of disease. The majority of transmissions resulted from blood collected from donors at more than 50% of the estimated incubation period. The high transmission rates and relatively short and consistent incubation periods in clinically positive recipients suggest that infectivity titres in blood were substantial and/or that blood transfusion is an efficient method of transmission.^{3, 4}
10. The most recent (unpublished) data from sheep studies at the Roslin Institute presented to SEAC 103 shows ⁵:
- All components of blood can facilitate transmission of BSE-associated infectivity following transfusion.

³ Position Statement on TSE Infectivity in Blood, July 2006, <http://www.seac.gov.uk/statements/statement0806.htm>.

³ Houston F, McCutcheon S, Goldmann W, Chong A, Foster J, Sisó S, González L, Jeffrey M, Hunter N, Prion diseases are efficiently transmitted by blood transfusion in sheep, *Blood*. 2008 Dec 1;112(12):4369.

⁴ Houston F, Foster JD, Chong A, Hunter N, Bostock CJ, Transmission of BSE by blood transfusion in sheep, *Lancet* 2000, Sep 16, 356 (9234): 999-1000

⁵ Minutes, SEAC 103, 24 November 2009.

- Irrespective of volume, plasma content and white cell content of component transfused, similar incubation times were observed in recipients.
 - Transmission was observed as early as 30% way through the incubation period as well as asymptomatic transmissions.
11. The current DH scenarios use a range of figures from 0.1 to 30 ID/mL, with roughly half this infectivity being associated with white cells, and half with plasma.
12. With regard to the susceptibility of recipients of infected blood to vCJD, the 2006 SEAC Epidemiology Subgroup Position Statement on the vCJD Epidemic, concluded that:
- “..... polymorphisms at codon 129 of the human prion protein gene influence susceptibility to, and/or the incubation period of, human prion diseases. Observations of kuru suggest that individuals of non-M/M genotypes are generally less susceptible to this disease and have longer incubation periods than individuals of the MM genotype. On the basis that these general characteristics are a valid model for vCJD infection, it seems reasonable to assume that vCJD cases in individuals of the MV and VV genotypes might arise, although they can be expected to be proportionately fewer in number and possibly appear over a long time scale”.⁶

ADVICE SOUGHT FROM SEAC

13. SEAC is asked to consider:
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 - Are members aware of any more sophisticated analysis that addresses the consistency of blood-borne transmission scenarios with observed case numbers?
 - Given the apparent consistency problem, can the existing range of inputs on infectivity, prevalence of infective donors and susceptibility to disease be reconciled with the data by invoking plausible further hypotheses - and if so, what are they?
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⁶ SEAC Epidemiology Subgroup Position Statement on the vCJD Epidemic, 2006, <http://www.seac.gov.uk/statements/statement0806.htm>.

- Should additional scenarios now be regarded as plausible - and if so, how should the current input ranges be extended?
- Can the Committee suggest any further lines of investigation that could be implemented relatively quickly, and could throw further light on the numbers of vCJD cases likely to result from blood-borne transmission?