



SEAC EPIDEMIOLOGY SUBGROUP POSITION STATEMENT ON THE vCJD EPIDEMIC

Issue

1. SEAC asked the SEAC Epidemiology Subgroup to reassess the nature and future profile of the vCJD epidemic, taking into account new research and the possibility of human to human infection. SEAC identified a number of issues for the Subgroup to consider (see Annex 1).

Background

2. Incidence of vCJD has declined over the past 5 years in the UK^{1,a}. Projections based on the case data suggest the number of additional cases of vCJD arising from the consumption of BSE-infected material might be relatively small (less than 100)². However, findings from a retrospective survey of appendix and tonsil tissue from operations carried out between 1995 and 2000 on individuals predominantly (83%) in the age range 10-30 years suggest that the number of infected individuals may be greater than projections based on backcalculation from vCJD cases³. Furthermore, research in animal models suggests it is possible that a proportion of infections may remain at a subclinical level or develop into clinical disease over a longer time scale⁴⁻⁷. Although all vCJD cases tested to date (about 85% of cases) have been of the M/M genotype at the polymorphic codon 129 of the human prion protein gene, the effect of other genotypes on the susceptibility to, infectiousness of, and phenotype of, vCJD is uncertain. To date, three cases of red blood cell transfusion associated transmission of vCJD have been identified⁸⁻⁹. It is possible that secondary infection via other medical procedures may occur, though this has not yet been described, and under some theoretical scenarios, this could give rise to a self-sustaining secondary epidemic.

^a Number of deaths from vCJD in the UK in the years 1999 to 2005: 15 (1999), 28 (2000), 20 (2001), 17 (2002), 18 (2003), 9 (2004), 5 (2005) and 5 (as at 22 November 2006).

3. To address the SEAC request, the Subgroup met twice in 2005 to consider data on the epidemiology of the disease, predictions about the epidemic based on infectious disease models and relevant published and unpublished research. A position statement produced on the basis of these discussions has been revised following further discussions in 2006. The Subgroup will keep the statement under review in light of emerging scientific or medical information that improves understanding of the epidemiology of vCJD.

General observations

4. It is currently not possible to answer in full the questions set by SEAC due to continued uncertainty about key characteristics of the vCJD epidemic, in particular: the prevalence and distribution of primary and secondary infection in the UK population and incubation periods of the primary and secondary disease. Although infectious disease models provide a very useful means to test hypotheses about the potential evolution of the epidemic under different scenarios, firm conclusions about the epidemic depend on *the acquisition of better estimates of the prevalence, age and genotype distribution of infection based on population studies*. Continued surveillance to identify new cases of vCJD, with pathological and genetic analysis of suspect cases at autopsy, will also provide valuable information to understand better the epidemic, in particular: trends in the incidence of vCJD, the age and genotype distribution of those who develop vCJD and identification of possible routes of secondary transmission (e.g. maternal or related to invasive medical procedures).

Influence of age on infection

5. Evidence to inform assessment of the variation in the incidence and prevalence of infection with age is presently limited to data from vCJD cases and the retrospective survey of appendix and tonsil tissue³. The age distribution of vCJD cases has remained relatively stable since the start of the epidemic. To date cases of vCJD have been described predominantly in young adults (median age at death of 28 years). This is likely to be due to a combination of age-related differentials in dietary exposure to BSE and in susceptibility to the disease. Modelling studies based on the assumption that the vCJD epidemic is best defined by age-related differentials in exposure to BSE and susceptibility to vCJD together with an incubation period which is not age-related and a time window of dietary BSE exposure related directly to the observed BSE epidemic, which appears to be the most likely scenario, have

produced broadly similar results¹¹⁻¹³. These studies suggest that age-related susceptibility / exposure was greatest in the 10-20 year old age range, lower in early childhood and much lower later in adult life. However, although this profile may be expected to be reflected in the incidence of primary infections leading to disease, it is derived from data on vCJD cases. Thus, it is possible that it may not apply to infections in the non-M/M population and to infections that remain at a subclinical level (see later). Correlations between profiles of age-related susceptibility to prion diseases and development of gut-associated lymphoid tissue, a proposed site of systemic entry of prion agents, in sheep, cattle and humans suggest a plausible biological mechanism for age-related susceptibility to oral infection¹⁴.

6. Given these uncertainties, for those born before 1996, it is not possible to predict with confidence the relative risks of infection of different age groups in the population. However, it is almost surely the case that, due to the BSE control measures introduced in the UK, dietary exposure of the post-1996 birth cohorts would be very much lower or even negligible compared with older birth cohorts. Children now aged 10 years or less are at the lowest risk of having been infected by dietary exposure to the BSE agent. Furthermore, despite relatively large dietary exposure to BSE¹¹, only two cases of vCJD have been observed in the pre-1940 birth cohort and one of these is attributed to blood transfusion associated transmission⁹. This strongly suggests that adults over 67 years of age are at relatively low risk of developing primary vCJD, assuming there has been no major under ascertainment of the disease in the elderly.
7. If it is assumed that susceptibility to primary vCJD infection is greatest among those aged 10-20 years, it would be predicted that individuals in the 1970-1980 birth cohorts, given the peak in dietary BSE exposure around 1990, are at the greatest risk of being infected. However, as discussed above this hypothetical profile of age-related susceptibility to dietary BSE infection may not apply to the non-M/M population or to infections that remain at a subclinical level. Given the decline in the BSE epidemic, the 1990-1995 birth cohorts are at a much smaller risk, and this risk lowers progressively with year of birth. A continuing lack of vCJD cases in the post-1990 birth cohort¹⁵ will provide reassurance about the validity of this hypothesis.

Influence of genotype on infection

8. In the appendix and tonsil survey, three specimens were found with evidence of vCJD infection. The finding that two of these are

from persons of the V/V genotype suggests individuals of this genotype are susceptible to infection from BSE¹⁶. Those of the M/V genotype may also be susceptible to infection, based on the report of a case of probable blood transfusion associated transmission of vCJD in a individual of this genotype⁹.

9. Polymorphisms at codon 129 of the human prion protein gene influence susceptibility to, and the incubation period of, human prion diseases¹⁷⁻²⁰. 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 M/M genotype^{19,21}. 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 M/V and V/V genotypes might arise, although they can be expected to be proportionately fewer in number and possibly appear over a long time scale²¹. Projections from an infectious disease model suggest that, in the unlikely situation that other genotypes are equally susceptible to clinical disease, the total number of cases arising through dietary exposure to BSE may increase up to three-fold compared with current estimates for the M/M genotype².
10. It is not possible to predict the clinical phenotype of vCJD cases in non-M/M genotypes, should they arise. However, evidence from fatal familial insomnia and sporadic CJD indicates that codon 129 genotype does affect clinical phenotype^{22,23}. In addition, experiments in transgenic mice expressing human forms of the prion protein gene suggest that the neuropathological phenotype of vCJD may be influenced by genotype^{7,20}.

Subclinical carriers of infection

11. Experimental studies in mice suggest primary prion infections may remain at a subclinical level²⁰ but on secondary transmission may result in clinical disease^{4,5}. Thus, asymptomatic animals can be subclinical carriers of infection. The reason that infection in some animals remains at a subclinical level while clinical disease develops in others is not fully understood. The potential existence of subclinical carriers of vCJD may explain the apparent discrepancy between prevalence estimates of primary vCJD infection based on the appendix and tonsil survey and those based on the vCJD case data. Projections suggest the number of subclinical carriers could be of the order of several thousand². There are currently no data to allow the possible age and genotype distribution of subclinical carriers of infection to be determined.

Additional data to understand the epidemic better (see table)

12. As discussed above, knowledge of the prevalence of infection cannot be determined accurately from infectious disease models because of the uncertainties regarding the effect of genotype and age at infection and the possibility of secondary transmission from subclinical carriers of infection. Further data are required to understand better the prevalence, age and genotype distribution of both primary and secondary vCJD infection.
13. The PrP^{Sc} screening programme, due to begin in 2007, of the large number of samples under collection for the National Anonymous Tonsil Archive (NATA) will allow more accurate assessments of the prevalence and age and genotype distribution of infection. It is strongly recommended that testing of samples collected by NATA is progressed with all possible urgency.
14. However, although PrP^{Sc} tests have always proved positive in tonsils of clinical vCJD cases, there are uncertainties about the sensitivity of tonsil tests to detect subclinical infection. In addition, although tonsils are being collected from a wide age range of individuals, tonsillectomy is more commonly conducted at relatively young ages. Thus, many of the samples will be collected from individuals with relatively low dietary exposures to BSE. Additional programmes to test other tissues collected from a different age distribution of individuals would provide further data as well as assurance about the findings from NATA.
15. PrP^{Sc} testing of a range of tissues collected from autopsies would provide substantial data on the prevalence and age and genotype distribution of predominantly older age cohorts of the population. Thus, testing of samples collected at autopsy would provide valuable additional and complementary data to NATA and a combination of NATA and a post mortem tissue archive currently provides the best route to estimating the prevalence of subclinical vCJD.
16. An expert group convened by the Health Protection Agency is currently considering the implementation of a post mortem tissue archive. There is a legal requirement for consent from a close relative of the deceased or the deceased in life to collect post mortem tissues. Due to concerns that consent may be less likely to be granted and therefore, the yield of samples diminished, if test results can be attributed to individuals, collection of post mortem samples is to proceed on the basis that samples will be anonymised to prevent the subsequent identification of individuals.

However, potentially valuable information is lost by non-attributable collection and testing of post mortem samples. Attributable testing provides an opportunity to identify living persons linked to infected deceased individuals by potential routes of transmission (e.g. by blood transfusion or surgery) and to monitor the health of these individuals and request permission in life for autopsy in the event of their death. The establishment of such transmission networks would provide direct data on the transmissibility of vCJD between individuals of different genotype and by different routes of transmission. It is recommended that a study be conducted, in parallel with the post mortem archive, to assess whether attributable testing would make relatives of a deceased individual less likely to allow sample collection. Should such a study indicate that attributable testing does not appreciably reduce the yield of samples, attributable collection of post mortem samples should be seriously considered.

17. A third approach to measuring the prevalence of abnormal prion protein has been proposed in response to the recommendation of SEAC²⁴. It is suggested that samples of donated blood could be tested anonymously using a number of prototype blood tests to estimate the prevalence of subclinical vCJD in the blood donating population. As a large number of samples could be tested relatively quickly, this proposal is welcomed. However, progressing this approach will depend on the performance of prototype blood tests when applied to blinded evaluation panels. In addition, interpretation of the results will depend on the strategy employed to confirm reactive samples from initial screening tests.
18. By comparison to the surveys suggested above, surveys of residual appendectomy, splenectomy or other discarded post-operative tissues, although informative, would provide fewer data. In addition, due to the low number of donors, testing of tissues from deceased tissue / organ donors would provide insufficient data to allow meaningful estimates of the prevalence of subclinical vCJD.
19. It is also recommended that enhanced clinical surveillance in the elderly be considered. Although vCJD cases arising from primary transmission of BSE are observed mostly in young adults, there may be potential under-ascertainment of cases in the elderly, possibly due to misdiagnosis. Enhanced surveillance of this section of the population would allow this possibility to be tested. Furthermore, such enhanced surveillance would provide additional assurance that clinical cases of secondary transmission of vCJD may be detected since this section of the population is the group

most likely to have undergone invasive medical procedures and / or to have received blood transfusions. Should cases be detected in older age groups, it would be important to undertake statistical analyses to estimate the proportion of cases that might have arisen from the dietary route versus medical interventions, i.e. the proportion of disease that could have arisen from primary or secondary transmission.

20. Clinical monitoring and, with pre-mortem patient consent, post mortem vCJD tests on individuals considered to be 'at risk of vCJD for public health purposes' would help to inform assessment of secondary transmission risks. Proposals are currently being developed for blood component recipients and should be considered for all at risk groups.

Self-sustaining epidemic

21. Risk assessments of secondary transmission through surgery, blood transfusion, dentistry and bone / tissue / organ transplantation²⁵⁻²⁷ suggest that, on the basis of what is presently known, transmission via the surgical and blood routes are the most important in terms of the possible contribution to secondary transmission. This is on the basis of the relatively high number of surgical procedures and blood transfusions and estimated transmission efficiencies via these routes. The large number of dental procedures coupled with good patient survival implies that any significant risk via this route could have a major impact on the dynamics of secondary infection. However, there is a lack of data on the infectivity of tissues of the oral cavity of individuals infected with vCJD and on the efficiency of transmission via dental procedures, therefore the potential for transmissions by dental surgery is uncertain. The risk of transmission via transplantation, depending on what tissues / organs are transplanted, is thought to be relatively high but the number of procedures is relatively low. Uncertainties in key parameters in all these risk assessments remain, such as the profile of the primary epidemic, infectivity levels in tissues, transmission efficiencies via routes and the effectiveness of decontamination / infectivity reduction methods.
22. The information currently available from follow up of children born to vCJD cases cannot exclude the possibility of maternal transmission of vCJD. However, on the basis of the information available on prion diseases of humans and animals, maternal transmission of vCJD, if it occurs, is unlikely on its own to support a self-sustaining secondary epidemic.

23. On the basis of current understanding, the transmission risk from the surgical route on its own could create a self-sustaining epidemic under worst case conditions of long incubation period for iatrogenic vCJD and / or a large proportion of infections entering a subclinical carrier state, and long survival times of patients following surgery. The National Institute for Health and Clinical Excellence recently issued guidance to reduce potential transmission risks via surgery by preventing the dispersion of surgical instruments used in high risk procedures (operations on the brain and posterior eye) between sets²⁸. Should tissues of the oral cavity carry appreciable vCJD infectivity, the transfer of dental tissue between patients via contaminated instruments be reasonably efficient and a subclinical carrier state exist, the dental surgery route could also support a self-sustaining epidemic. Blood borne transmission on its own is thought unlikely to result in a self-sustaining epidemic, especially given the precautionary measures already enacted (e.g. deferral of donations from blood recipients, import of plasma for fractionation and leucodepletion). In addition, interactions between routes of transmission will also make a self-sustaining epidemic more likely.
24. The likelihood of a self-sustaining epidemic cannot be quantified at present. The complexity and number of interactions between potential routes of transmission makes development of a workable model to quantify interactions within and between routes and the effect interactions might have on transmission risks very difficult. Development of a combined population level model to explore the effect of interactions between the blood and surgical routes is under consideration. This work should be supported.
25. On the basis of current risk assessments of transmission routes considered in isolation, factors such as the number of events potentially allowing transmission to occur (e.g. the total number of blood transfusions or the number of times surgical instruments are re-used), infectivity of tissues, the efficiencies of transmission and the effectiveness of decontamination / infectivity reduction methods are all, to varying extents, key influences on the likelihood of a self-sustaining epidemic arising and the rate that it might develop.
26. On the basis of current understanding, a secondary epidemic is more likely if many individuals are exposed to potentially infectious material from a single individual (e.g. through incomplete decontamination of surgical instruments) or vice versa (e.g. if blood products are pooled, exposing each recipient to multiple donors). A secondary epidemic is also generally more likely if patients who

have undergone one potentially infectious procedure are at increased risk of undergoing further procedures.

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Table of potential investigative programmes to improve understanding of the vCJD epidemic

The table outlines three areas for further investigations to improve understanding of the vCJD epidemic. Associated ethical and practical considerations are summarised. This includes: **A** Studies to provide data on the prevalence, year of birth and genotype distribution of individuals with evidence of infection (demonstrated by accumulation of PrP^{Sc} in tissues) in the population. The studies are ordered both in terms of the value of the information they could provide and their feasibility. Transmission networks providing direct data on the transmissibility of vCJD between individuals of different genotype and by different routes of transmission could be established if attributable testing was undertaken. Possible risk reduction measures might also be envisaged as a result of the identification of transmission networks. However, risk management is not within the remit of the SEAC Epidemiology Subgroup thus, such measures are not considered here. **B** Enhanced vCJD surveillance. **C** Research on transmission risks.

Option	Objectives	Practical / ethical considerations
A Prevalence and distribution of PrP^{Sc} 1 PrP ^{Sc} testing of National Anonymous Tonsil Archive samples with PrP codon 129 genotyping of positive cases.	<ul style="list-style-type: none"> • Estimation of infection prevalence by year of birth and genotype (approx. 100 000 tonsils from operations carried out from 2003 onwards on individuals from all age groups but predominantly from younger individuals [to date approx. 70% of tonsils collected from individuals < 20 years of age]). 	<ul style="list-style-type: none"> • Large data set obtained but sensitivity of tests to detect subclinical infection unclear. • Ethical approval for collection of tonsils obtained - tonsil collection underway – 35 000 tonsil pairs archived as of November 2006 (about 10 000 from 1965 to 1985 birth cohort). • Evaluation of appropriate high-throughput and sensitive test method, development of testing strategy (e.g. by age group) and ethical approval for testing in hand – testing expected to begin early 2007. • Positive samples could be retained long-term, and genetic analysis undertaken of these stored samples and of tissue from future vCJD cases (with appropriate ethics committee approval) to determine whether they were derived from the same individual.
2 Post mortem PrP ^{Sc} tests of autopsy material with PrP codon 129 genotyping of positive cases.	<ul style="list-style-type: none"> • Estimation of infection prevalence by year of birth and genotype in population age group at greatest risk of infection (approx. 100 000 coronial autopsies / year with approx 80% of samples collected from individuals > 45 years of age). 	<ul style="list-style-type: none"> • Large numbers of samples from a range of tissues available for testing (e.g. brain, spleen, appendix, tonsil). • Consent from relative / carer of the deceased and ethical approval required. • Development of a collection strategy and support of coroners required. • Evaluation of appropriate high-throughput test method required.
3 Anonymous PrP ^{Sc} testing of donated blood.	<ul style="list-style-type: none"> • Estimation of infection prevalence by year of birth of the blood donating population. 	<ul style="list-style-type: none"> • Large number of blood samples could be tested relatively rapidly. • Testing depends on the availability of suitably evaluated blood tests.

<p>4 PrP^{Sc} tests of appendectomy or splenectomy samples with PrP codon 129 genotyping of positive cases.</p>	<ul style="list-style-type: none"> • Estimation of infection prevalence by year of birth and genotype (approx. 53 000 appendectomy and 2 800 splenectomy procedures / year). 	<ul style="list-style-type: none"> • Ethical approval required. • Tissues other than tonsil tested but most procedures conducted in an emergency – a proportion of tissues may be unsuitable for testing. Splenectomy relatively rare - few data produced. Appendix testing may underestimate infection prevalence since PrP^{Sc} only found in a proportion of vCJD cases tested. • Development of collection and testing protocol and support from surgeons required.
<p>5 PrP^{Sc} testing of deceased tissue / organ donors* as part of screening programme to establish eligibility for donation.</p> <p>* Bone and breast milk donors excluded as evidence suggests undetectable levels of PrP^{Sc} in these tissues.</p>	<ul style="list-style-type: none"> • Estimation of infection prevalence by year of birth and genotype (approx. several 100 donors / year). 	<ul style="list-style-type: none"> • Tissues other than tonsil tested (e.g. spleen, appendix, retina) but relatively rare procedures therefore very few data produced.
<p>6 PrP^{Sc} tests on residual material captured by prion reduction filters used on donated blood.</p>	<ul style="list-style-type: none"> • Estimation of infection prevalence of the blood donating population. 	<ul style="list-style-type: none"> • Potentially many 100 000s of tests / year. However, prion reductions filters have not been evaluated and implemented as a blood safety measure. • Development of an appropriate method to remove and test material from filters required but may be problematic. • Support from transfusion services required.
<p>B vCJD surveillance Enhanced clinical surveillance of neurological conditions in the elderly with the possible inclusion of survey of tissues from brain banks.</p>	<ul style="list-style-type: none"> • Estimation of vCJD prevalence in population age group where definitive diagnosis may be more difficult. 	<ul style="list-style-type: none"> • Support from neurologists / geriatricians and ethical approval required. • Primary vCJD presumed rare in elderly - possibly few cases. • Support from the brain banks required if analysis of these samples undertaken.
<p>C Research on transmission risks Enhanced database linkage of individuals classified as 'at risk of vCJD for public health purposes' to inform assessment of secondary transmission risks.</p>	<ul style="list-style-type: none"> • Follow-up individuals considered 'at risk of vCJD for public health purposes' including regular clinical assessment, blood tests and to ask for consent to post mortem analysis. 	<ul style="list-style-type: none"> • Ethical approval required. • Development of protocols and system to track and monitor individuals classified as 'at risk of vCJD for public health purposes' are being developed.

ANNEX 1

Issues SEAC asked the SEAC Epidemiology Subgroup to consider

1. 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?
2. 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?
3. 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?
4. What are the key points at which modification of practice could significantly reduce the risk of a self-sustaining epidemic?