



SEAC EPIDEMIOLOGY SUBGROUP POSITION STATEMENT ON THE vCJD EPIDEMIC

ISSUE

1. To consider the SEAC Epidemiology Subgroup position statement on the vCJD epidemic.

BACKGROUND

2. SEAC tasked the SEAC Epidemiology Subgroup to consider the nature and future profile of the vCJD epidemic, taking into account new research and the possibility of human to human transmission. The Subgroup was also asked to consider the likelihood of a self-sustaining epidemic. A number of questions were set by SEAC.
3. The SEAC Epidemiology Subgroup met on 11th May and 13th September 2005 to consider the SEAC request. A position statement based on the Subgroup's considerations has been produced. Due to continued uncertainty about key characteristics of the vCJD epidemic, the Subgroup considered it is currently not possible for it to answer in full the questions set by SEAC. It was considered that firm conclusions about the epidemic can only be drawn by the acquisition of better estimates of the prevalence, age and genotype distribution of infection based on population studies. Therefore, additional programmes to provide such data together with their feasibility were considered.
4. It is intended that the Subgroup will keep the statement under review in light of emerging scientific or medical information that improves understanding of the epidemiology of vCJD. The statement that includes the questions set by SEAC is at Annex 1. The membership and terms of reference of the Subgroup are at Annex 2.

ADVICE SOUGHT FROM THE COMMITTEE

5. The committee is invited to comment on the position statement.



Position statement from the SEAC Epidemiology Subgroup



Membership and terms of reference of the SEAC Epidemiology Subgroup

Membership

Professor Graham Medley – Chair (University of Warwick)
Professor Sheila Bird (MRC Biostatistics Unit)
Mr Gareth Davies (Independent Veterinary Epidemiologist)
Dr Azra Ghani (London School of Hygiene & Tropical Medicine)
Professor Noel Gill (Health Protection Agency)
Professor Peter Smith (London School of Hygiene & Tropical Medicine)¹
Dr Hester Ward (National CJD Surveillance Unit)
Professor John Wilesmith (Defra)

Observers

Dr Peter Bennett (DH)
Mr Patrick Burke (Defra)
Dr Peter Christie (Scottish Executive)
Dr Alistair Douglas (DARDNI)
Dr Peter Grove (DH)
Mr Alan Harvey (FSA)
Dr Irene Hill (FSA)
Mrs Eileen Lawrence (DH)
Miss Kate Richards (SEAC Secretary)
Dr John Stephenson (DH)
Dr Marc Turner (UK Blood Service)

Secretariat

Dr Tom Barlow (Secretary, SEAC Secretariat)
Dr Neil Ebenezer (SEAC Secretariat, 13/09/05 meeting)
Dr Vivien Lund (SEAC Secretariat, 11/05/05 meeting)

Terms of reference

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.

¹ Professor Smith was unable to attend the meetings to discuss the SEAC request.



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 4 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 cases suggest³. Furthermore, research in animal models suggests it is possible that a proportion of infections may not develop into clinical disease, or do so over a longer time scale, and remain at a subclinical level⁴⁻⁷. 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. The finding of an asymptomatic case of probable blood transfusion associated transmission of vCJD of the M/V genotype⁸ suggests individuals of this genotype are also susceptible to secondary transmission by the intravenous route. It is possible that secondary infection via medical procedures may give rise to additional infections and potentially enable 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) and 3 (end September 2005).

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. This initial position statement has been produced on the basis of these discussions. It is intended that 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, firm conclusions about the epidemic can only be drawn *by 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 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. Direct evidence to inform assessment of the influence of age on the prevalence of infection 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. 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 susceptibility to vCJD together with a constant incubation period 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 results⁹⁻¹¹. 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 might be expected to be reflected in

the prevalence 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 or to infections that remain at a subclinical level (see later).

6. Given these uncertainties, it is not possible to predict with confidence the relative risk that age groups are infected for all age groups of 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 9 years old and younger would, therefore, very clearly be at the lowest risk of primary infection. Furthermore, despite relatively large dietary exposure to BSE⁹, only a single case has been observed in the pre-1940 birth cohort. This strongly suggests that adults over 66 years of age are at relatively low risk of developing primary vCJD, assuming there is no major under ascertainment of the disease in the elderly.
7. If it is assumed that susceptibility to primary vCJD infection (in terms of infections that lead to disease and infections that remain at a subclinical level) was greatest within the 10-20 year age range, it would be predicted that individuals in the 1965-1985 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 primary vCJD 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 cohort will provide reassurance about the validity of this hypothesis.

Influence of genotype on infection

8. There is an indication that non-M/M genotypes are susceptible to vCJD infection from the case of probable blood transfusion associated transmission of vCJD of the M/V genotype⁸. In addition, atypical immunohistochemical results from two of the three positive appendix samples in the appendix and tonsil survey may also be an indicator of infection in non-M/M genotypes³.
9. Polymorphisms at codon 129 of the human prion protein gene influence susceptibility to, and the incubation of period of, human prion diseases¹²⁻¹⁴. 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 genotype¹⁴. On the basis that these general characteristics are a valid model for vCJD infection, it seems reasonable to assume that primary and secondary 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 scale. Recent projections from an infectious disease model suggest that, in the unlikely situation that other genotypes are equally susceptible to clinical disease, the number of future primary cases may increase up to five-fold compared with current estimates for future cases of 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 affects clinical phenotype^{15,16}. Experiments in transgenic mice expressing human forms of the prion protein gene suggest that the neuropathological phenotype of vCJD is influenced by genotype⁷.

Subclinical carriers of infection

11. Experimental studies in mice suggest primary prion infections may remain at a subclinical level but on secondary transmission 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 the vCJD case data. Recent projections to explore this possibility 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

12. As discussed above, knowledge of the prevalence of infection cannot be determined accurately from quantitative 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 2006, of the very 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 (see table). 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 asymptomatic and subclinical infection. In addition, although tonsils will be 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 (see table).
15. Principally as an infection control measure, a pilot study is underway to investigate the feasibility of testing the spleen, tonsil and / or appendix from cadaveric tissue / organ donors. Pilot studies to screen corneal and multi-organ donors are also under consideration. Although, testing of tissue from cadaveric, corneal and multi-organ donors might provide a limited amount of data, pilot studies to assess the feasibility of such testing are welcomed and encouraged.
16. PrP^{Sc} testing of a range of tissues collected from autopsies would, in principle, provide substantial data on the prevalence and age and genotype distribution of the section of the population presumed most likely to carry the majority of primary vCJD infections. However, such a programme relies heavily on consent for testing, which is a legal requirement, from the deceased (in life) or a close relative / carer. Practical and cost considerations around informed consent could have a substantial detrimental impact on the feasibility of such a programme. Nevertheless, it is recommended that serious consideration be given to testing samples collected from autopsies. By comparison, retrospective survey of residual appendectomy or splenectomy tissues, although informative, would be less useful (see table).

17. It is also recommended that enhanced clinical surveillance in the elderly be considered (see table). 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.
18. Clinical monitoring and, with 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

19. Current risk assessments of secondary transmission through surgery, blood transfusion, dentistry and bone / tissue / organ transplantation¹⁷ 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 a secondary epidemic. This is on the basis of the relatively high number of surgical procedures and blood transfusions and estimated transmission efficiencies via these routes. By comparison, the risk of transmission via dentistry per procedure is thought to be relatively low, although the number of procedures is relatively large. In contrast, 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. However, uncertainties in key parameters in the 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.
20. 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 likely to be inefficient.

21. 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 long patient survival times. The National Institute for Health and Clinical Excellence is currently conducting an assessment of precautionary measures to reduce potential transmission risks via surgery. 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). The large number of dental procedures (coupled with good patient survival) implies that any significant risk via that route could have a major impact on the dynamics of secondary infection. In addition, interactions between routes of transmission will also make a self-sustaining epidemic more likely.
22. The likelihood of a self-sustaining epidemic cannot be quantified at present. The complexity and number of interactions between potential routes of transmission make development of a workable model to quantify interactions within and between routes and the effect interactions might have on transmission risks very difficult. Work is underway to develop population level models for the surgical and blood routes with a view to developing a combined model to explore the effect of interactions between these routes. This work should continue to be supported.
23. On the basis of current risk assessments of transmission routes considered in isolation, factors such as the number of potential transmissions, 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.
24. 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 dispersion of surgical instruments between sets) 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.

SEAC Epidemiology Subgroup November 2005

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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. Possible risk reduction measures might be envisaged as a result of the additional information that the studies could provide if attributable testing was undertaken. However, there are legal barriers to attributable testing. Furthermore, 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 |
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| 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. • Evaluation of appropriate high-throughput and sensitive test method, development of testing strategy (e.g. by age group) and ethical approval for testing required. • 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 PrP ^{Sc} testing of cadaveric, corneal and multi-organ donors* as part of screening programme to establish eligibility for donation 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. several 100 cadaveric and multi-organ donors / year and several 1000 corneal donors / year). | <ul style="list-style-type: none"> • Tissues other than tonsil tested (e.g. spleen, appendix, retina) but relatively rare procedures (especially cadaveric and multi-organ donors) therefore relatively few data produced. • Consent to PrP^{Sc} tests will be included as part of protocol for consent to donation. PrP^{Sc} tests included as part of communicable disease screening to determine eligibility for donation. • Evaluation of an appropriately rapid test method is underway. • Organs from multi-organ donors are often used so quickly that PrP^{Sc} testing prior to use, to establish eligibility for donation, would be precluded. • Development of a tissue collection and testing protocol and training for staff in removal of tissues for PrP^{Sc} tests is underway. |

* Bone and breast milk donors excluded as evidence suggests undetectable levels of PrP^{Sc} in these tissues.

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| <p>3 Post mortem PrP^{Sc} tests of autopsy material, particularly of people aged 15-54 years 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 in population age group at greatest risk of infection (approx. 30 000 eligible autopsies / year). | <ul style="list-style-type: none"> • Large numbers of tests (although autopsy rates falling) on a range of tissues (e.g. brain, spleen, appendix, tonsil). • Consent from deceased (in life) or relative / carer and ethical approval required. • Evaluation of appropriate high-throughput test method required. • Development and piloting of a consent for tissue collection and tissue removal protocol and support of pathologists required. • 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>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>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?