

### 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<sup>Sc</sup> 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 is undertaken. Possible risk reduction measures might 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.

<b>Option</b>	<b>Objectives</b>	<b>Practical / ethical considerations</b>
<b>A Prevalence and distribution of PrP<sup>Sc</sup></b> <b>1</b> PrP <sup>Sc</sup> testing of National Anonymous Tonsil Archive samples with PrP codon 129 genotyping of positive cases.	<ul style="list-style-type: none"> <li>• 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 &lt; 20 years of age]).</li> </ul>	<ul style="list-style-type: none"> <li>• Large data set obtained but sensitivity of tests to detect subclinical infection unclear.</li> <li>• Ethical approval for collection of tonsils obtained - tonsil collection underway – 35 000 tonsil pairs archived as of November 2006 (about 10 000 from the 1965 to 1985 birth cohort).</li> <li>• 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.</li> <li>• 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.</li> </ul>
<b>2</b> Post mortem PrP <sup>Sc</sup> tests of autopsy material with PrP codon 129 genotyping of positive cases.	<ul style="list-style-type: none"> <li>• 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 &gt; 45 years of age).</li> </ul>	<ul style="list-style-type: none"> <li>• Large numbers of samples from a range of tissues available for testing (e.g. brain, spleen, appendix, tonsil).</li> <li>• Consent from relative / carer of the deceased and ethical approval required.</li> <li>• Development of a collection strategy and support of coroners required.</li> <li>• Evaluation of appropriate high-throughput test method required.</li> </ul>
<b>3</b> Anonymous PrP <sup>Sc</sup> testing of donated blood.	<ul style="list-style-type: none"> <li>• Estimation of infection prevalence by year of birth of the blood donating population.</li> </ul>	<ul style="list-style-type: none"> <li>• Large number of blood samples could be tested relatively rapidly.</li> <li>• Depends on the availability of suitably evaluated blood tests.</li> </ul>

<p><b>4</b> PrP<sup>Sc</sup> tests of appendectomy or splenectomy samples with PrP codon 129 genotyping of positive cases.</p>	<ul style="list-style-type: none"> <li>• Estimation of infection prevalence by year of birth and genotype (approx. 53 000 appendectomy and 2 800 splenectomy procedures / year).</li> </ul>	<ul style="list-style-type: none"> <li>• Ethical approval required.</li> <li>• 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<sup>Sc</sup> only found in a proportion of vCJD cases tested.</li> <li>• Development of collection and testing protocol and support from surgeons required.</li> </ul>
<p><b>5</b> PrP<sup>Sc</sup> 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<sup>Sc</sup> in these tissues.</p>	<ul style="list-style-type: none"> <li>• Estimation of infection prevalence by year of birth and genotype (approx. several 100 donors / year).</li> </ul>	<ul style="list-style-type: none"> <li>• Tissues other than tonsil tested (e.g. spleen, appendix, retina) but relatively rare procedures therefore very few data produced.</li> </ul>
<p><b>5</b> PrP<sup>Sc</sup> tests on residual material captured by prion reduction filters used on donated blood.</p>	<ul style="list-style-type: none"> <li>• Estimation of infection prevalence of the blood donating population.</li> </ul>	<ul style="list-style-type: none"> <li>• Potentially many 100 000s of tests / year. However, prion reductions filters have not been evaluated and implemented as a blood safety measure.</li> <li>• Development of a method to remove and test material from filters required.</li> <li>• Support from transfusion services required.</li> </ul>
<p><b>B vCJD surveillance</b> 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"> <li>• Estimation of vCJD prevalence in population age group where definitive diagnosis may be more difficult.</li> </ul>	<ul style="list-style-type: none"> <li>• Support from neurologists / geriatricians and ethical approval required.</li> <li>• Primary vCJD presumed rare in elderly - possibly few cases.</li> <li>• Support from the brain banks required if analysis of these samples undertaken.</li> </ul>
<p><b>C Research on transmission risks</b> 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"> <li>• 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.</li> </ul>	<ul style="list-style-type: none"> <li>• Ethical approval required.</li> <li>• Development of protocols and system to track and monitor individuals classified as 'at risk of vCJD for public health purposes' are being developed.</li> </ul>