RESTRICTED POLICY

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UPDATE ON DEVELOPMENTS FOR PRE-CLINICAL DIAGNOSIS OF vCJD, AND PROTECTION OF THE BLOOD SUPPLY

Issue

1. The development of an accurate and sensitive ante-mortem test for pre-clinical or sub-clinical vCJD is crucial to protect the blood supply and prevent transmission of vCJD through organ and tissue donation or through surgery. When the first generation ante-mortem screening tests arrive on the market we expect that there will be significant pressure on the NHS and the national blood services to implement them. This submission provides an update on the development of ante-mortem tests, and notes current and anticipated pressures on funding. It also draws your attention to the development of technologies that may reduce vCJD infectivity levels in donated blood (prion reduction technologies).

2. The policy branch continues to work closely with colleagues from S&Q Analytical Team and RDD on these issues.

Financial Implications

3. This submission highlights three areas of activity on vCJD that have financial implications, none of which is currently funded. The area of immediate relevance to DH budgets is continued funding for the National Tonsil Archive (para 7), a research study, which is essential to improve confidence in our estimate of prevalence of vCJD infection in the UK population. RDD is currently negotiating the details of a contract to finish the collection of tonsils with the HPA. Furthermore the HPA has set up an independent group to advise on the analysis of the archive, but funds to support this analysis have not yet been identified.

4. The two other areas that are the subjects of this submission, also have financial implications for the UK blood services, and possibly for DH. These are funding for evaluation and implementation of a blood-screening test for vCJD, and possibly also for implementation of technology to reduce prion-associated infectivity in blood (para 17). Our expert advisory committee (SEAC, Spongiform Encephalopathy Advisory Committee) is providing technical advice on the evaluation of prion reduction technologies. Our best estimate of a likely timeframe for Ministerial decision on funding evaluation/implementation of both these technologies is six months for prion reduction filters and twelve months for a screening test. A decision is also likely to be necessary on whether introduction of one of these measures alone will suffice, or whether some combination may be required.

Recommendation

5. You are invited to note current developments and the pressure on DH budgets. A further submission on current and future pressures on the CJD research budget will follow shortly. Separately, we shall also provide updates on development of prion reduction technologies and screening tests, including our handling plans for implementation.

Current issues

6. An update on key current issues is given below. Further background is at Annex A.

National Tonsil Archive

7. We do not have robust data on people in the UK who might have pre-clinical vCJD, or whether there is a non-symptomatic carrier state. The purpose of the National Tonsil Archive is to help us obtain a statistically significant estimate of the prevalence of vCJD infection. The initial phase has gone well with over 30,000 tonsils collected. The collection must be completed (collection of a further 70,000 samples is planned). Meanwhile, the testing methodology must be agreed, in order for testing to begin. A Steering Group has been established to determine

the tests that will be carried out on the samples. A recent progress report is at Annex B.

Research and development

8. A confirmed diagnosis of vCJD in living patients presenting with clinical symptoms is highly specific and sensitive but is invasive. For this reason, diagnosis is generally not confirmed until after death by post-mortem testing. No ante-mortem diagnostic or screening test for pre-clinical or sub-clinical disease is available.

9. The significant support given by UK public funders (about £40m, of which DH has contributed about £10m) is now beginning to bear fruit. Further information is at Annex C. Some of this research has significantly stimulated academic and commercial activity in developing ante-mortem tests.

10. Current pressure on the CJD research budget means that no new research in this area can be commissioned until 2007, even though several proposals, supported by peer review, have been considered by DH and would merit funding.

Evaluation of commercial blood screening tests

11. During this year the National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU) has received applications from nine commercial companies for tissues from vCJD patients. Most of these companies have carried out significant proof-of-principle studies and four now require human material, usually blood or serum, to evaluate their products. As this material is in short supply DH has reconstituted the CJD Tissue Management Group (chaired by Dame Ingrid Allen) to oversee the allocation of this material, and this group will report within the next few weeks. (The remit of the group is at Annex D.) Recently , our expert advisory committee, MSBTO (Microbiological Safety of Blood, Tissues and Organs for Transplantation) has supported a proposal by the National Institute for Biological Standards and Control (NIBSC) to establish a collection of animal and human samples suitable for the evaluation of vCJD blood screening tests.

12. Several companies are making good progress toward formal validation and CE marking of a blood-screening test, assisted by the DH CJD Tissue Management Group. Our current assessment is that it is likely that a CE-marked blood-screening test will be on the market in late 2006 or early 2007.

13. However, it is possible that the current products may fail the evaluation process and therefore continued support for research in diagnostic development is needed.

Work by the national blood services in preparation for the introduction of screening tests

14. We understand that the blood services will soon be prepared to rapidly evaluate a commercial screening test when it arrives. DH convened an independent advisory group under the auspices of MSBTO to help the blood transfusion services prepare should a test become available. The group, chaired by Professor Don Jeffries, has reported. A particular concern is that unless the test has very high specificity, most positives found will in fact be "false" – this would lead both to unnecessary shortage of blood and the need to tell large numbers of donors why their blood could not be used. For this reason, it was felt that no screening test should be introduced unless a reliable confirmatory test was also available.

15. The National Blood Services have nearly completed their preparatory work, which concentrates on the key need to establish the specificity of potential tests. This will establish a validated cohort of fractionated blood donations from a geographically representative sample of the UK population against which to evaluate commercial screening tests. It is also intended to provide a control cohort from a non-vCJD country such as the USA. In addition the National Institute of Biologocal Standards and Control have set up a working group to determine which material would be the most suitable to quality control screening tests when they become available.

Prion reduction technology

16. Technologies for the removal of prion infectivity from blood (over and above that achieved by existing leucodepletion methods) are also under development. Two companies are reporting considerable progress: one has already obtained CE marking for its prion reduction filter, although recent data indicate that the efficacy of the CE-marked product is poorer than than the prototype product, and this will likely extend the time needed for the UK and Irish blood services to evaluate the product. Both companies' methods are likely to be applicable to transfusions of red cells in the first instance, rather than platelets or fresh frozen plasma. The UK (and Irish) Blood Services are actively engaged in a programme to evaluate these methods in terms of (a) safety, (b) levels of prion removal and (c) therapeutic efficacy of the processed blood. SEAC has recently advised on the conduct of these studies, and has emphasised the importance of efficacy studies that independently replicate those already undertaken by the manufacturers, and also the need to use animal models that mimic the human response as closely as possible. Analysts from DH Standards and Quality Analytical Team are assisting with analyses of risk reduction, and in providing indications of cost-effectiveness as the necessary information becomes available. The Department is also

being kept up to date with developments via periodic reports to MSBTO. A separate submission will follow on this.

Ethical considerations

17. Although it is almost universally recognised that it is important to develop a non-invasive test that can detect individuals who are infected with CJD but not displaying clinical symptoms, opinion on how to use such a test is divided. Consequently, the HPA, with advice from the Nuffield Council for Bioethics, organised a workshop earlier this year to debate ethical issues related to CJD diagnosis. CMO has recently agreed that HPA be asked to consult more widely on the report's recommendations.

Handling issues

18. Advice on handling will be included in the submissions which will follow on prion reduction technologies and introduction of screening tests.

Conclusion

19. You are invited to note current developments, and current and future pressures.

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Annexes

Annex A	Further background
Annex B	Recent report of the National Tonsil Archive
Annex C	Research summary
Annex D	Remit of the DH CJD Tissue management group.

Annex A

Update on developments for pre-clinical diagnosis of CJD

Further background on recent developments

In the past few years, a number of events have stimulated academic and commercial activity in this field, the most important of which are listed below.

- The DH-funded retrospective analysis of tonsil and appendix tissue revealed three positive samples, suggesting that several thousand members of the UK population could be clinically silent carriers of infectious prions.
- These findings gave weight to the assumption that a self-sustaining epidemic could arise, fuelled by transmissions through blood transfusions, and contaminated surgical equipment and organ and tissue transplantation.
- Experimental confirmation that current procedures are inadequate to ensure the complete inactivation of infectious prions attached to surgical instruments, especially those used in neurosurgery.
- Experiments on experimental blood transfusions in sheep, and the announcement that at least 2 cases of vCJD had almost certainly arisen through the transfusion of contaminated blood, powerfully demonstrated that transmission by blood transfusion was no longer a just a theoretical possibility.
- Recent reports of vCJD occurring Eire, France, Portugal, Saudi Arabia, Italy and Japan have demonstrated that the threat of iatrogenic transmission of vCJD is not limited to the UK.

ANNEX B

Monthly update on the National Anonymous Tonsil Archive - Phase Two to the end July 2005

The duration of the National Anonymous Tonsil Archive (NATA) Phase Two contract is 23 months in total, from 1st October 2003 to 31st August 2005. The aim of this phase of NATA is to establish a workable model for the collection, transport, processing and storage of tonsil specimens that can be scaled up to produce an archive of 100,000 irreversibly anonymised tonsil specimens that are suitable for studying the prevalence of detectable PrP^{Sc}. The specific objectives of phase two are as follows:

- To recruit and establish, over a period of the first six months, an initial functioning network of approximately 20 centres harvesting tonsil specimens.
- To establish a functioning infrastructure that will transport tonsil specimens within defined time and temperature constraints from harvesting centres to a central processing facility.
- To establish a central specimen processing facility capable of receiving, processing and archiving tonsil specimens.
- To recruit and establish a further 40 collection centres before the end of this phase of the project.

The tonsil archive is now receiving from hospitals throughout England almost 300 tonsil pairs per week (figure 1) and the total number of tonsil pairs received at the end of July 2005 was 13,678 (figure 2). The total number of tonsil pairs received during July was 1,321 compared with 1,178 during June 2005. A further 3,000 tonsil pairs have been received from the National Prion Clinic at St Mary's Hospital, although these specimens have not been processed and entered onto the database. The number of collection forms that have been completed but no tonsil tissue collected is 721 (493 due to patient objection and 228 due to clinical pathology being requested). Most of the tonsil specimens have been sent from participating hospitals to the TSE laboratory in Colindale within 72 hours (figure 3). The age range of donors of the tonsil specimens to the archive can be seen in figure 4. We expect the number of tonsils received in Colindale each week to increase, as some of the hospitals that have been visited by the Scientific Coordinator should commence tonsil collection for NATA within the next couple of months.

Figure 1 Number of pairs of tonsils collected for NATA fortnightly from January 2004 - July 2005

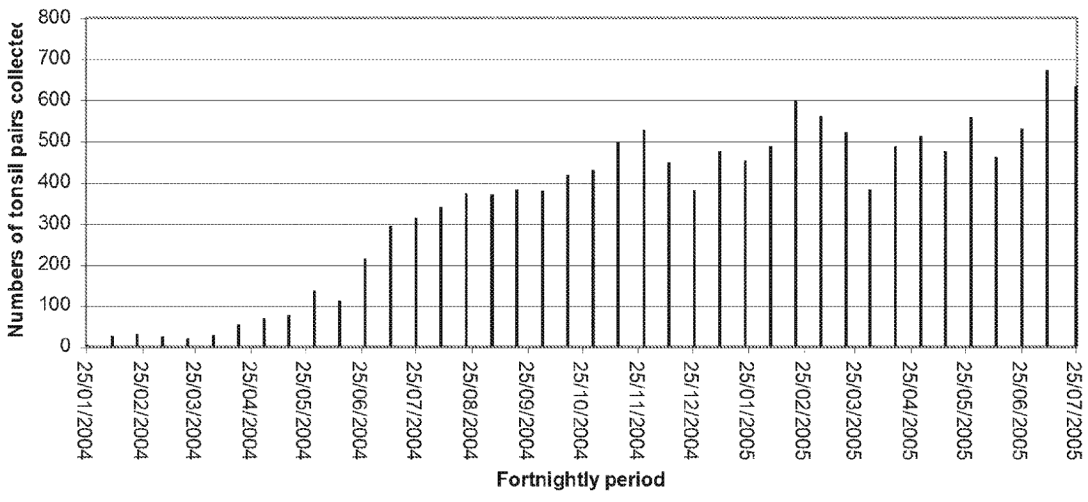


Figure 2 Cumulative number of tonsil pairs collected for NATA fortnightly from January 2004-July 2005

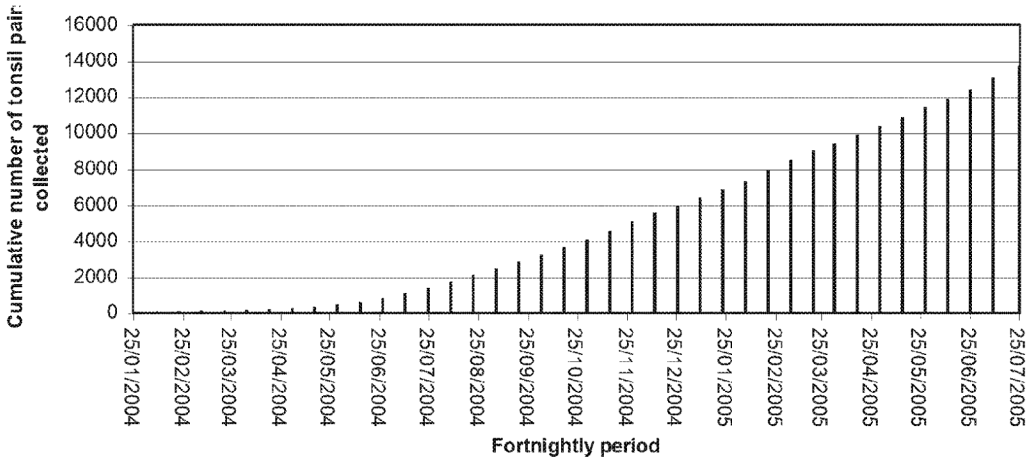
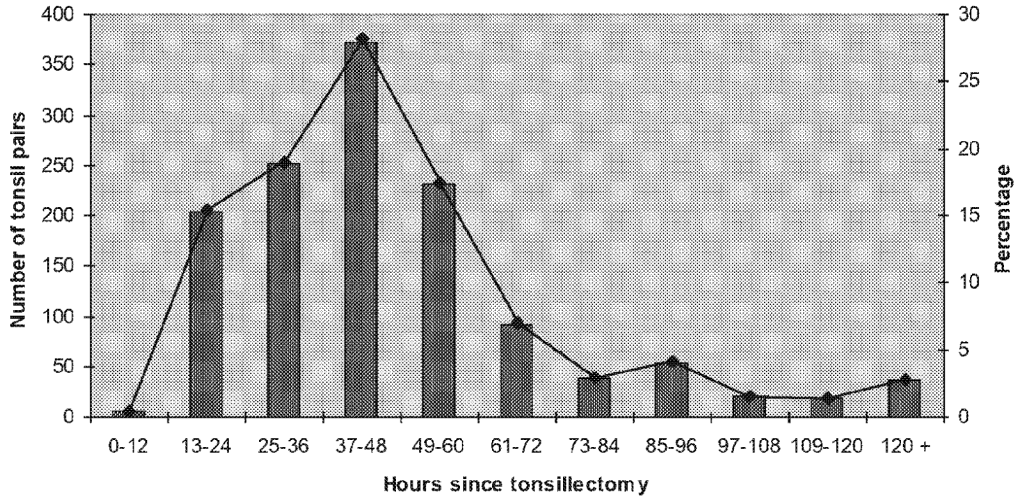


Figure 3 : Time between tonsillectomy and delivery: July 2005



Out of the 100 hospitals that perform over 200 tonsillectomies per year in England, the number that have been recruited and are currently sending tonsil pairs to NATA on a regular basis is 66. A further 45 hospitals have had a recruitment visit but have not begun collecting tonsils yet. Most of these hospitals should be starting to collect tonsils within the next few months.

A contract that went out for tender through the Official Journal of European Community has been awarded to a courier company, PDP Couriers, for the collection and delivery of the tonsils to the HPA. A further contract that also went out for tender has been awarded for the off-site storage of the archive. Funding has been

made available for Scottish participation in NATA and procedures for the recruitment of Scottish hospitals to the study are underway.

During the next phase of this project (Phase 3 – Final roll-out and main collection), any minor difficulties with the tonsil collection procedures within the hospitals should be ironed out and more hospitals will be sending us tonsil specimens, so the target of 500 tonsil pairs per week should be achievable. Currently approximately 50,000 tonsillectomies are performed annually in England.

Figure 4 Number of tonsillectomies by age range: January 2004 - July 2005

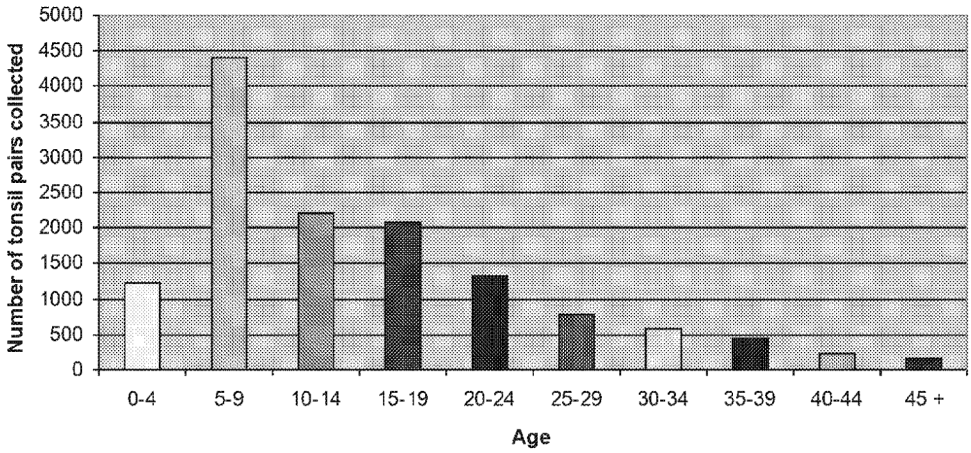


Figure 5 below shows the location of all of the hospitals currently taking part in NATA. Figure 6 shows the ratio of tonsils collected compared with the population of each Strategic Health Authority. Most of the SHA's have a ratio of less than or equal to 1:5,000.

Figure 5 Hospitals sending tonsils to NATA

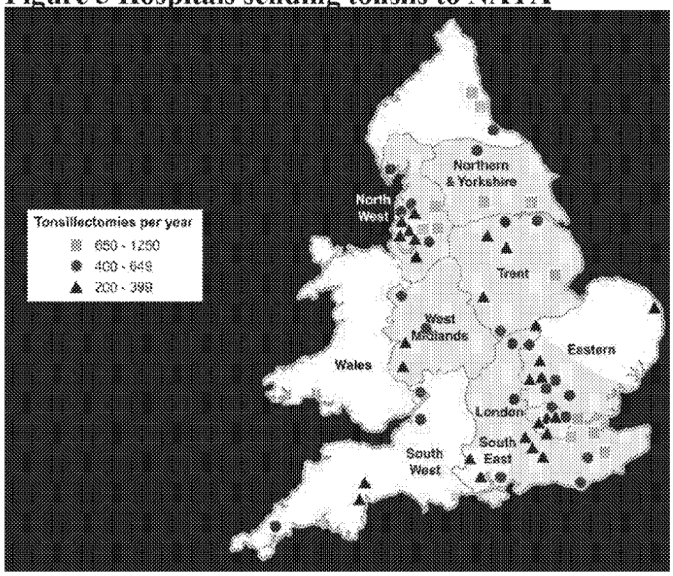
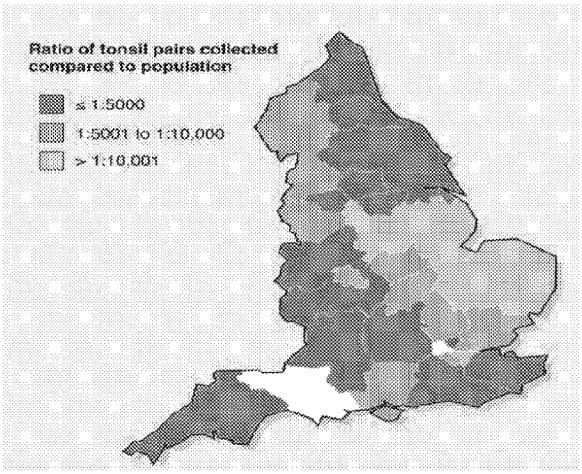


Figure 6 Ratio of tonsils collected to population of each Strategic Health Authority



Annex C

Cross-government activity to stimulate research into diagnostic development

1. Although all public funders of TSE-related research had always included diagnostic development as an important topic in their TSE research strategies, it has been difficult to stimulate interest from the academic and commercial communities. The unique nature of these diseases and the perception that the commercial market was likely to remain small has contributed to this situation. In addition, powerful modern techniques such as PCR and ELISA, used to detect conventional microorganisms, cannot be readily adapted to the detection of TSEs and therefore few groups have been willing to make the required substantial investments in time and resources.

2. The UK public research funders decided, through the TSE R&D Funders Co-ordination Group (Chaired by Sir John Pattison, and latterly by Professor Sally Davies), to try to address this problem by pooling their resources and influence. A meeting was held at Hinxton Hall on the Wellcome Trust Genome Campus in February 2001 and organised by the MRC. This was attended by over 100 delegates, including many researchers not currently in the field, along with a substantial number of commercial companies. Following this meeting, a call for research proposals was made under the auspices of all the public funders of TSE-related research, and co-ordinated by the MRC. Over 100 expressions of interest were received and 55 outline applications were received. A panel of reviewers with wide-ranging expertise considered these applications and invited 35 full proposals. These were peer-reviewed in the normal manner and considered during a 2-day meeting on September 20th & 21st 2001. Eventually 25 projects were funded and details placed on the MRC website.

Provision of research resources to aid diagnostic development

In addition to funding research contracts and grants, several public funders have supported the establishment and maintenance of TSE research resources. The most important of these are listed below.

- DH and the MRC support the CJD tissue bank at NCJDSU in Edinburgh.
- DH supports the CJD Resource centre at NIBSC
- BBSRC supports the TSE Resource Centre at the Institute for Animal Health.
- Defra support the TSE tissue bank at the Veterinary Laboratory Agency.

ANNEX D

Remit of the DH CJD Tissue Management Steering Group

- to ensure adequate resources for the tissue banking centres;
- to ensure that the tissue collections were managed in accordance with the MRC's[1][2] and the Royal College of Pathologists' guidelines; and to ensure ethical approval would be obtained for any research undertaken;
- to draw up guidelines to handle and manage requests for tissues, which could then be used by tissue centres on a day to day basis[3];
- to act as an independent adjudicator if competing requests from research groups were received.

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[1] The MRC's role and guidelines for MRC-funded brain banks, 1995
[2] The MRC's draft "Human Tissues and Samples for Use in Medical Research" guidelines
[3] see appendix 3, page 82 in the MRC's guidelines.

DH CJD TISSUE MANAGEMENT GROUP
MEMBERSHIP

Chairman: Professor Dame Ingrid Allen

Professor James Ironside
Professor James Lowe
Dr Philip Minor
Dr John Stephenson (DH)
Dr Iram Malik (DH)
Professor Brian Anderton
Professor John Collinge
Professor Paul Ince
Dr Richard Knight
Dr Paul Lewis
Dr Marc Turner
Professor Roy Weller
Dr Pat Hewitt (NBS)
Dr. Marc Turner (SNBTS)
Mrs Gillian Turner (Human BSE Foundation)