

**UK FUNDERS' TSE RESEARCH STRATEGY WORKSHOP 2011**  
**1<sup>st</sup>/2<sup>nd</sup> September 2011**

**REPORT**



This workshop was organised by the UK TSE Joint Funders Group to discuss the research required to minimise any future risk to the UK from TSEs. The workshop was chaired by Professor Chris Bostock and was attended by 40 leading UK TSE researchers, including specialists in epidemiology, cell biology, biochemistry, animal diseases, human and animal pathology, genetics, neurology and veterinary medicine.

This report records the views of these researchers which will now be considered by the funding bodies.

## **Programme**

The workshop was organised in four separate sessions each focussed around a particular TSE risk. Each session was led by a different chair and comprised a number of presentations followed by an open discussion, as follows.

### **Session 1: vCJD in the population: now and in the future**

Chair: Professor Richard Knight

Presentations:

Professor Bob Will and Professor Noel Gill: Variant CJD surveillance: what we know, what we don't know and what we hope to know

Dr Peter Bennett and Dr Stephen Dobra: Assessing the risks of secondary vCJD transmission: recent developments, key gaps in knowledge and research priorities

Dr Phil Minor: Test Development: progress, problems and assessment

### **Session 2: A new TSE in food animals or humans**

Chair: Professor Jean Manson

Presentations:

Professor Jean Manson: Defining a new TSE strain

Dr Rona Barron: Assessing the zoonotic potential of a new TSE strain

### **Session 3: BSE – a problem of the past?**

Chair: Professor Hugh Perry

Presentations:

Mr Patrick Burke: BSE in cattle – the latest update

Dr Jim Hope: Case control study on BARBs and atypical BSEs

### **Session 4: Summary and future directions**

Chair: Professor Roger Morris

Presentations:

Professor Richard Knight: Key points from Session 1

Professor Jean Manson: Key points from Session 2

Professor Hugh Perry: Key points from Session 3

## **Chair's Introduction**

This UK Funders' TSE Research Strategy Workshop, 2011, took place 25 years after VLA's identification in 1986 of BSE as a new disease of cattle. During this period there were over 180,000 confirmed cases of BSE in the UK with an annual peak of 37,000 clinical cases in 1992. By 2010, however, the annual number of confirmed cases in the UK had reduced to 11, due largely to the effectiveness of the control measures that were introduced and which were based on information gained from the research and surveillance programmes. This success has led to the widespread view amongst policy makers that the BSE epidemic in the UK is all but over, with the current debate largely focussing on when we will see our last case or whether there will be a continuing small annual incidence of a hypothetical "spontaneous" BSE. There is, however, ongoing concern about the significance of the results when atypical H- and L- forms of BSE and BSE-like strains are inoculated into small ruminants.

With the emergence of BSE came the possibility that it might have the potential to transmit to humans and the realisation that this eventuality could only be identified by a coordinated approach to national surveillance for CJD. This led to the creation of the NCJDRSU and the precautionary action was vindicated in 1996 with the Surveillance Unit's first reported cases of a new variant form of CJD, which was subsequently shown to be caused by infection with BSE. The epidemic of vCJD has so far followed a similar shaped curve to that of BSE, albeit shifted by some 8 years with, thankfully, very many fewer cases. The peak of 28 deaths was in 2000, but had dropped to 3 cases in each of 2009 and 2010. With vCJD there remain several key uncertainties related to this extended tail, (length of incubation, true prevalence in different age populations, possible effects of different prion genotypes etc.) all of which were discussed during the Workshop.

At the time of the Workshop the financial cost of the BSE epidemic to the UK Government was estimated at over £5billion, about 10% of which, £500million, had so far been spent on research. Initially the main focus of research was on BSE as an animal TSE, but, following the emergence of vCJD in 1996 and the realisation that BSE is transmissible to humans, a much larger annual spend on research was triggered.

Not included in the £500million “research” spend is the majority of the considerable cost of surveillance for both animal and human TSEs. At the time of the Workshop DH was spending about £5million annually on CJD surveillance at HPA and NCJDRSU and Defra some £8million on BSE and scrapie testing. Some projects to analyse data generated by surveillance, so critical to an understanding of these diseases, are part of the research spend.

Annual funding for TSE research has declined from its peak of around £36million in 2000, but there remain significant sums of money available for TSE research over the next 5 to 10 years, with £20million scheduled to have been spent in 2011. The objective of this Workshop was to review the current state of knowledge of TSEs and identify ongoing gaps in knowledge and needs for future research and surveillance to help guide future research funding priorities; these are summarised in Annexes A, B, C and D. From these it is clear that many key questions and issues of both strategic and basic scientific importance remain to be addressed.

Chris Bostock

## **Session 1: vCJD in the population: now and in the future**

This session was chaired by Professor Richard Knight from the National CJD Research and Surveillance Unit (NCJDRSU). Presentations were heard from Professor Bob Will from the NCJDRSU, Mr Stephen Dobra from the Health Protection Analytical Team at the Department of Health and Dr Phil Minor from National Institute for Biological Standards and Control (NIBSC). The speakers addressed clinical and subclinical surveillance, the use of modeling and risk assessment to inform policy of transmission rates of vCJD through blood and blood products and refine estimates of prevalence and test development respectively.

The Department of Health funds research on vCJD to inform DH Policy on risk management. This approach has been developed in order to reduce the spread of vCJD in the population in the face of uncertainty on the prevalence of infection in the population, the lack of a test and many unanswered questions on the fundamental biology of the agent remaining. Thus the key priorities in research have been surveillance, decontamination of prions from surgical and medical instruments, fundamental science that underpins understanding transmission and infectivity and test development.

The question for this session of the workshop was whether the current strategy remains fit for purpose now and into the future.

### **DISCUSSION**

#### **1. Human Surveillance**

1.1. The current strategy of research funding of vCJD was considered appropriate.

Surveillance was a priority and should continue in the face of remaining uncertainty in incubation times and phenotypic expression of vCJD.

1.2. Surveillance of the elderly, particularly those developing dementia was viewed as a weak point in the current surveillance strategy. Significant hurdles to implementation existed in this cohort due to failure of many dementia patients to be investigated by a neurologist, poor autopsy rates and examination of the brain tissue. It was recognized that this issue was part of the wider problem of increasing prevalence of dementia / Alzheimer's disease in the population. Thus to address vCJD surveillance in this cohort, an innovative, simple and cost effective approach would have to be developed that was linked with the wider public health concerns in the ageing population. Apart from the logistic hurdles to surveillance, further

difficulties to implementing surveillance were likely to occur with clinical identification due to potential changes in phenotype and the presence of concomitant diseases. A diagnostic test would greatly facilitate surveillance in this age cohort.

- 1.3. Further access to material for surveillance was potentially via the Brain Banks that currently have a high profile and priority through the focus of dementia research. However, difficulties in recruitment of volunteers, logistics and unwillingness of medical staff to broach the issue with family of contribution to this valuable resource, makes this avenue of access to brain tissue difficult. Access for vCJD research and surveillance would need to be linked with dementia research and awareness campaigns.
- 1.4. Prevalence studies in the population were seen as essential to establishing measures to control the disease. The past and current appendix surveys had and were continuing to inform Policy. However, to understand the results and the apparent discrepancy between prevalence estimates and the numbers of clinical cases arising through blood transmission, estimates of prevalence in a presumed negative population were needed. Appendix tissue could be sourced from countries that did not have vCJD or from old archived tissues in the UK collected prior to the emergence of BSE.
- 1.5. The discrepancy between the results of the Hilton appendix prevalence study and the absence of clinical cases arising in patients receiving multiple transfusions of blood and blood products, raised the potential for the existence of immunological protective mechanisms. It was suggested that this was an area that could be explored in order to interpret the prevalence studies in context with the relative “absence” of clinical cases.
- 1.6. The *highly-transfused* cohort forms a key sentinel group for the emergence of vCJD. The continued monitoring of these patients may also lead to greater understanding of any immunological protective response.

## **2. Decontamination**

- 2.1. It was suggested that research should focus on decontamination of surgical and dental instruments. Endoscopes were also an important priority with increased colonoscopy in the older age group and high risk groups.

## **3. Modelling**

- 3.1. Estimates of secondary infections of vCJD arising from blood transfusions underpin efforts in determining future policies on vCJD on surveillance, blood safety and decontamination.
- 3.2. Modelling of blood-borne transmission shows that combining precautionary estimates and assumptions leads to an over-prediction of clinical cases to date that could have arisen from blood and blood products. However, there remain feasible scenarios in which further clinical cases associated with blood-borne transmission appear, and continue – albeit with relatively low incidence – for several decades.
- 3.3. Further refinements of models are required. Surveillance data is critical and detection of any atypical or phenotypic variations in vCJD and emergence of new prion strains are important to the development of more scenarios. Fundamental questions that would inform modeling remain such as:
  - What is the relation between subclinical state and infectivity?
  - How many infected patients go on to an infective carrier state?
  - Is there a relationship between the presence of abnormal prion and inflammation which could have resulted in an over-estimation of prevalence.

#### **4. Test development**

- 4.1. The development of a test for CJD was considered an important priority and needed to mitigate the risk of those subclinically infected with vCJD donating blood and undergoing operations without appropriate safeguards. There was little incentive for manufacturers to develop a test as the number of cases of vCJD was declining and the market for the test would mostly be the UK. A further difficulty was the fact that the prion protein was so poorly defined, making it difficult to develop a definitive test.
- 4.2. The issue of false positives (the specificity of the test) of current tests was raised in relation to “patient” management. Test sensitivity was also an issue. The diagnostic tests currently under development are only at best 70% sensitive. Further developments and tests that could improve the sensitivity and specificity were discussed but a lack of test validation prevented the use of these.
- 4.3. The question was posed as to whether it was possible to undertake rectal lymphatic tissue biopsies to identify vCJD. As tests on this tissue had not been validated, it was considered better to test the tonsil. However, the tonsil is difficult to obtain after death.

4.4. A large negative control group for test development and validation was required.

## **5. Epidemiology of vCJD**

5.1. The Chair invited participants of the workshop to discuss why the prevalence of CJD varied across the UK and why the epidemiology of the disease differed between France and the UK, with more males affected in the UK and more females affected in France, and a higher onset age in France. The different epidemiology of the disease in France was not understood. Dietary difference between the north and south may explain the differences in prevalence within the UK.

5.2. Concerns were raised about historical cases of BSE and subsequent reports of vCJD in Saudi Arabia. The potential for other countries in Asia and Africa to have cases of BSE and vCJD existed and may still emerge as cattle, meat and bone meal and beef products which may have been infected with BSE were exported before control measures were introduced in the UK.

5.3. It was stated that the number of sporadic CJD cases was rising. Participants were invited to discuss the reason for this. It was suggested that this was likely to be due to improved surveillance with more cases of sporadic CJD being detected (i.e. through MRI scans). There had been a similar increase in sporadic CJD in countries which did not have a BSE epidemic but improved their surveillance. This supported this theory and suggested that the increase in sporadic CJD was not related to the BSE outbreak.

## **6. Conclusions**

6.1. Without isolation of the agent and development of a test, management of vCJD remains confined to reducing the risk of exposure by implementation of measures such as surveillance and monitoring at risk groups and decontamination. The current strategy of focus on surveillance and decontamination was supported.

6.2. Several areas for further research were proposed:

- The addition of the elderly and those with dementia to the surveillance strategy would ensure that should prolonged incubation periods of vCJD emerge and changes in phenotype occur, vCJD would not be “hidden” beneath “dementia”. It was recognised that this would be difficult to achieve.

- Test development was supported as it would provide a key surveillance, as well as clinical tool. However, the issues of sensitivity and specificity would need to be resolved before the introduction of any test as a surveillance tool.
- Fundamental questions such as immunological resistance to infection, infectivity and subclinical status remain. Addressing these would greatly inform modelling and predictions and hence inform Policy's risk management approach to vCJD.

## **Session 2: A new TSE in food animals or humans**

This session was chaired by Professor Jean Manson (Roslin Institute). The background for this session was set out in two presentations. Professor Manson spoke on defining new TSE strains, assessing their zoonotic potential and how they can be modified on cross species and within species transmissions. Defining carriers of disease and their ability to transmit infection, what controls the species barrier and the nature of the infectious and neurotoxic agent/s were also discussed. Dr Rona Barron (Roslin Institute) then spoke on 'Assessing the zoonotic potential of a new TSE strain'. This posed the questions 'Can we detect a new strain in the field?' and 'Can we establish if it is transmissible to humans?'. The presentation provided some answers to these questions and posed further questions for participants to discuss.

### **DISCUSSION**

#### **1. Surveillance**

- 1.1. Participants stressed the importance of human surveillance in the detection of new TSE diseases, although they cautioned that this relies on it being easily distinguishable from known human TSEs (as was the case for vCJD).
- 1.2. Many felt that animal surveillance was equally important in order to detect new TSEs, where the emphasis should be on surveying fallen stock.
- 1.3. It was felt that government was too reliant on the current tests and that there needed to be more emphasis on how a TSE that cannot be detected by these tests would be found

#### **2. Potential for transmission to humans**

- 2.1. Participants agreed that the zoonotic potential of an animal TSE should be assessed using a panel of different methods, but that there had to be agreement on how to interpret the results when different methods gave contradictory results.
- 2.2. A key question will always be determining whether there is a link between an animal TSE and a human TSE, irrespective of where it is first detected, which requires continued surveillance of both animals and humans and a range of methods to use.

#### **3. Agreed areas recommended for further funding**

- 3.1. Improved surveillance tools and tools for understanding zoonotic potential, these need to be both faster and cheaper.
- 3.2. In vivo, in vitro and cell based methods for assessing zoonotic potential should be compared to determine the best approach.
- 3.3. It is important to know more about animal atypical TSEs, including whether they are sporadic
- 3.4. Research flocks and TSE archives are important resources for the future and should be maintained, funding should be made available before these resources are lost
- 3.5. It is important to understand the disease at the molecular level
  - How does the protein misfold?
  - What is the neurotoxic agent (it was noted that this information might be useful to those studying other neurodegenerative diseases)?
  - What are the common features of TSEs?
  - What is the infectious agent? (still seen as a key unanswered question)
  - What controls the species barrier?
  - How is disease transmitted between brain cells?
  - What is the route of transmission to humans?
  - What determines individual human susceptibility?
  - What are the significant potential routes for secondary transmission between humans?

### **Session 3: BSE – a problem of the past?**

This session was chaired by Professor Hugh Perry from the University of Southampton. Presentations were heard from Mr Patrick Burke from the TSE Policy Team at the Department for Environment, Food and Rural Affairs and Dr James Hope from the Animal Health and Veterinary Laboratories Agency.

The key issues and research gaps identified by the researchers at the session and following discussion were as follows.

#### **1. The BSE epidemic**

- 1.1. The origin of the BSE epidemic will probably never be determined with certainty.
- 1.2. We do not know whether or not some of the BARB cases represent truly sporadic classical BSE. If there are spontaneous cases then BSE will never be eradicated although reducing surveillance could make it appear that BSE has been eradicated.

#### **2. Surveillance**

- 2.1. If controls are relaxed then continued surveillance is crucial. This includes ensuring that comparisons between countries take account of different age profiles of the national herds and the intensity of surveillance in different demographic categories in other countries.
- 2.2. Research could be done to determine if surveillance can be made more efficient at detecting novel TSEs and monitoring the end of the epidemic.
- 2.3. Mathematical modelling of the epidemics is probably as good as it will get with the given data, we would need a significantly improved/different evidence base to improve on current models.
- 2.4. Appropriate monitoring is required to determine if the epidemic will match the predicted reductions in prevalence of the models.
- 2.5. Detecting rare forms of BSE requires considerable surveillance effort. Animals with signs should be targeted, and the appropriate infrastructure is needed to detect and report such cases.

### **3. Unusual TSEs**

- 3.1. There is uncertainty in relation to how atypical BSE arose and whether its persistence in the environment poses different issues to classical scrapie or BSE.
- 3.2. There is a need for an archive of tissues to allow us to look and see whether any novel TSEs discovered in the future are new phenomena or just rare cases that occur from time to time.
- 3.3. While we can detect H and L BSE we are not sure how sensitive our methods are.
- 3.4. There is uncertainty over what risk atypical TSEs pose to humans compared with classical TSEs. There is a possible risk of transmission to humans of novel TSEs and so we need to know where and when these TSEs occur and how they relate to the quality of surveillance in different age groups of cattle in different countries.

### **4. Official Controls**

- 4.1. If feed bans are relaxed it is essential to determine if rendering can ever be 100% effective at inactivating infectivity from different TSEs.
- 4.2. The role of human behaviour in reacting to official controls and incentives relating to TSE control needs to be examined as this has not been the subject of formal research to date.
- 4.3. A watching brief is needed to track whether atypical strains could be transmitted to other animals e.g. deer herds (this is especially a concern with the growing UK deer market).
- 4.4. If a pre-mortem test was developed the researchers felt that a use for such a test would be found even if this is not apparent at present.

### **5. Basic research**

- 5.1. The largest issues relating to basic science remain our lack of understanding of the structure of the agent and the issue of what is the biological basis and significance of TSE strains.
- 5.2. We need to use cell models alongside in vivo systems as cell models alone cannot take into account the interactions of the disease with systems in the body. However,

the advantage of cell models is that they allow many hypotheses to be tested rapidly and cost effectively which can then be validated in animal models.

5.3. Research is required to understand how the agent travels from the gut to the brain, kills neurons and leads to the death of the animal.

## **Session 4: Summary and future directions**

This session was chaired by Professor Roger Morris from King's College London. Presentations were heard from Professors Richard Knight, Jean Manson and Hugh Perry, with the following key points emerging:

### **1. Surveillance**

- 1.1. This should continue in both animal and human populations.
- 1.2. Animal surveillance is required in order to rapidly detect the potential emergence of new TSEs diseases, and determine whether a disease has zoonotic potential. Animals with signs or symptoms should be targeted, with appropriate information and support provided to encourage the reporting of new BSE cases
- 1.3. Surveillance systems are not static and need to change as new evidence comes to light (for example the age limits for ruminant testing). A watching brief is also needed for the future to track whether atypical strains could be transmitted into other animals e.g. CWD in deer herds (this is especially a concern with the growing UK deer market).
- 1.4. Continued effort is needed to refine and develop new tools for detection, notably with regard to the potential for new strains, taking into account emerging research of the biological basis of TSEs
- 1.5. An important issue in human surveillance is the need to improve its effectiveness in the elderly population, where cases are harder to discern than in the young and the scale of the problem is not really understood. Given the increasing numbers of elderly with dementia, a broad-based, low cost screening tool would be needed, for example utilizing blood testing, once validated, supported by MRI

### **2. Biobanks**

- 2.1. Linked to surveillance, archived material from human vCJD cases should be harmonized in both the storage and the range of materials held. A control group is also needed. Given the emerging linkage between biological mechanisms across neurodegenerative disorders, links to other disease collections (for example through

the UK Brain Bank Network) should be encouraged, alongside increased numbers of autopsies in the various patient groups with neurodegenerative diseases.

- 2.2. Archived animal material could offer an insight into whether there is a sporadic version of BSE, and in conjunction with human material support fundamental research into TSE pathophysiology.

### **3. Diagnosis**

- 3.1. Diagnostic tests, in the field and under development, currently lack stringency and sensitivity, and there is a continued need for research effort in this area. Of key importance would be the validation of a less invasive and scalable screening test that would enable population prevalence studies to be undertaken. Blood tests, such as that under development at the MRC Prion Unit, showed considerable promise, but clarification was needed as to what a human test needed to achieve: does it need to identify that a person is potentially infectious, or as part of the process to determine that a person has the clinical disease.
- 3.2. A bottleneck to commercial development in the clinical arena was the unique nature of the UK problem, which effectively created a single market in the blood transfusion service. Accordingly the Government needed to clarify whether a diagnostic test would be implemented if it were developed by industry.
- 3.3. There remained a need for public funding to be directed towards basic research to develop diagnostic tests for TSEs, an area where there is little appetite from industry to develop such a test. It was noted that translational research funding streams are available to take fundamental research forward, such as the MRC DPFS and DH i4i programmes.

### **4. Epidemiological Modeling**

- 4.1. Further mathematical modeling of disease prevalence is required, and accurate scientific data is needed to feed into the models – these two factors are mutually dependent. Models will need to be continually refined and updated with new data and real life outputs
- 4.2. Some lessons may have been learnt from the BSE epidemic; however, social scientists should do work looking at human behaviour to prevent a repeat of previous mistakes. It was also of concern that commercial pressures were mounting

to relax animal control measures, which reinforced the need for continued surveillance in this area.

- 4.3. Awareness was needed regarding the risk of sub-clinical infection and secondary transmission of vCJD from blood transfusions and surgery, which could yet be a significant public health issue. As a consequence, research assessing approaches to decontamination should continue.

## **5. Disease mechanisms**

- 5.1. The workshop highlighted the need for further fundamental research is required to shed light on, for example, the nature of the TSE infective agent, the significance of strain differences as well as host genotype, how they are propagated, and which components of pathogenesis result in the clinical manifestation and death.
- 5.2. Basic understanding of the disease in both animal and human TSEs, to understand how animal material can be processed so that it is safe, and to develop effective preventive and therapeutic strategies.
- 5.3. There is a seamless join between prion disease and other neurodegenerative diseases, such as dementias. It is increasingly recognised that protein misfolding is fundamental to many neurotoxic processes, and that molecular pathways are common across clinically defined neurodegenerative disorders.
- 5.4. The development of cell models of disease can offer important insights into the disease process, and allow hypotheses to be tested rapidly and cost effectively prior to validation in animal models. Cell models may also offer significant potential for drug screening.
- 5.5. It is important not to forget the importance of scrapie as a model, where atypical scrapie has some BSE-like properties. Scrapie is a natural disease where prospective blood sampling can be undertaken, which may offer insights into TSE pathogenesis.
- 5.6. Effort should be made to ensure that important resources such as animal herds, bioresources and databases are maintained to support the research community's efforts.
- 5.7. A coordinated approach across Government Depts and the Research Councils would continue to be needed to ensure high quality research could be maintained across the full range of TSEs with the potential to impact upon human health.

## **Annex A: Additional comments from the ACDP TSE subgroups**

**The risk assessment sub group** agreed with the conclusions of the workshop, with the following additions:

- That what is needed in terms of a human diagnostic test is a simple, non-invasive test that could be used in clinical or preclinical diagnosis.
- That another important area of research is the development of potential treatment.

**The risk management sub group** agreed with the conclusions of the workshop, with the following additions:

- That large cohorts of elderly patients are being assessed for dementia and/or enrolled in clinical trials, potentially providing the opportunity to use these existing cohorts to test for vCJD. It was emphasized however that this type of surveillance study might require a different route of funding than previous/ongoing prevalence studies. They recommended that surveillance of the elderly for vCJD should be considered and raised with the parent committee (ACDP).