



# postnote

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## v-CJD IN THE FUTURE

**Variant Creutzfeldt Jakob disease (v-CJD) was first defined in the UK in 1996. It is widely assumed that v-CJD is caused by eating BSE-infected food. If so, the number of people potentially at risk of contracting the disease could be very large. However, there is considerable uncertainty over the likely future scale of the outbreak; it is not clear whether the 100 or so cases observed to date merely represent the 'tip of the iceberg', or whether the number affected has already peaked and is likely to tail off. This briefing outlines the main factors that will influence the number of future cases, considers models that estimate the total number of deaths, and discusses the policy implications.**

### What is v-CJD?

CJD has long been known as a rare, fatal, degenerative brain disease in humans. As outlined in the box opposite, it is one of a class of diseases known as transmissible spongiform encephalopathies (TSEs) that are also found in sheep (scrapie) and cattle (BSE). Prior to 1995, three types of CJD were known:

- an inherited form that runs in families (on average 2-3 UK cases per year);
- a sporadic form of unknown cause that struck at random and was responsible for the majority (some 40-50 per year) of UK cases;
- and an acquired form, arising from medical procedures involving tissue originating from people with CJD.

In the wake of the BSE epidemic the National CJD Surveillance Unit (NCJDSU) at Edinburgh University was set up in 1990 to monitor CJD in the UK. It spotted the first cases of a new form of the disease in 1995. This v-CJD shares some clinical symptoms with other types of CJD but varies in other respects:

- the early clinical symptoms of v-CJD are usually psychiatric or behavioural (particularly depression);
- v-CJD affects younger people (average age of death is ~29 years, compared to 65 years for sporadic CJD);

### TSEs and prions

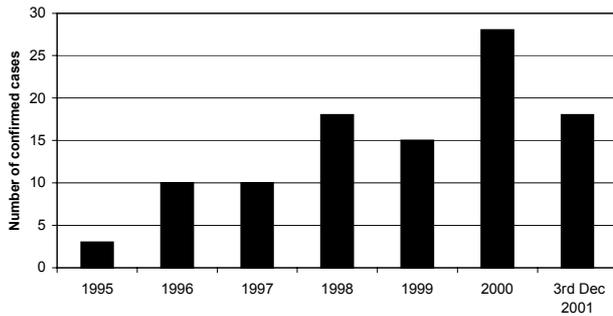
TSEs are fatal degenerative brain diseases characterised by a rapidly progressive dementia and by the spongy appearance of brain tissue examined after death. They affect many species, with common examples including BSE in cattle, scrapie in sheep and CJD in humans. Each of these can arise in subtly different forms known as strains.

TSEs were assumed to be caused by viruses, but no such agent has ever been isolated from infected tissue, nor has any immunological response to such an agent been detected in affected species. Also the agents responsible for TSEs show resistance to treatments that would normally be expected to inactivate viruses. More recent research suggests the agents may be misshapen 'prions' – proteins normally found in the brain and elsewhere. It is thought that such prions are infectious because they can distort the normal form of the prion protein into the misshapen form, producing a chain reaction that propagates the disease and generates new infectious material. This prion hypothesis is widely accepted as it accounts for most of the characteristics of TSEs as well as the observed resistance to anti-viral measures. However, there is on-going debate over whether prions can account for the variations between different strains of each disease.

- the duration of v-CJD disease is longer (up to 2 years between onset and death) than sporadic CJD (typically less than 6 months);
- v-CJD varies from other forms of CJD in that the abnormal prion protein can be detected outside the brain in lymphoid tissue and in the nervous system.

These differences - along with certain investigations such as EEG (electroencephalogram) and MRI (magnetic resonance imaging) scans - allow doctors to make provisional diagnoses of v-CJD. However, final confirmation is usually only obtained once the patient has died, when sections of the brain are examined under the microscope to determine whether they show the unique appearance of v-CJD. Confirmation before death can be obtained in exceptional circumstances by examining brain biopsies.

## Trends in confirmed v-CJD cases in the UK



Source: National CJD Surveillance Unit, University of Edinburgh

## v-CJD cases to date

Up to 3<sup>rd</sup> December 2001 there had been 103 confirmed (by *post mortem* examination) cases of v-CJD in the UK. There has been an overall upward trend in confirmed cases since 1995 (see figure). Figures for 2001 are available only up to December 3<sup>rd</sup> and may yet increase as post mortem results become available. As discussed below, cases confirmed to date reveal several features that may shed some light on the most important factors influencing the initiation and progression of v-CJD.

## Geographical distribution

### Clusters

Clusters of cases in a particular location may occur by chance, or may indicate a common source of exposure. The more cases in the cluster, the less likely it is to occur by chance. Of the 100 or so v-CJD cases to date, 5 have occurred within 5km of each other in North Leicestershire (the so-called Queniborough cluster); it is highly unlikely that such a cluster could have occurred by chance<sup>1</sup>. An investigation in April 2001 (see box opposite) concluded that 4 of the 5 cases might be linked to beef bought at 2 local butchers, although the link remains unproven.

Three further cases of v-CJD have been linked to a South Yorkshire village (Armthorpe). It is not regarded as a cluster at present as it is possible (but not very likely) that the grouping of these cases occurred by chance. Just one further case emerging in this area would greatly increase the likelihood of it being a cluster with a common cause, and greatly diminish the chances of it being a random grouping. A study of meat supply in the area in the 1980s found no evidence of the practices identified as potential risk factors in Queniborough.

### North/south distribution

The NCJDSU has highlighted a north-south divide in the incidence of v-CJD cases in the UK. It noted that the number of v-CJD cases per million population is nearly twice as high in northern England and Scotland (1.14 cases per million population aged 10 and over) as it is in the Midlands, Wales and southern England (0.67). One possible (but as yet unproven) explanation for this could be regional variations in diet – it is possible that the northern diet included more of the food products assumed to be higher risk (e.g. burgers, sausages, etc. containing mechanically recovered meat - MRM) than that in the south.

## The Queniborough cluster of v-CJD cases

The cluster of v-CJD disease in the North Leicestershire area was first recognised in July 2000. Between August 1996 and January 1999 five people developed symptoms that were later recognised as v-CJD; all have since died. All lived within 5 km of each other in the Wreake and Soar Valley area from 1980 until 1991. Leicestershire Health Authority commissioned an investigation in July 2000, which reported in April 2001. The study investigated a number of proposed links between the cases, and enabled a number of possible causes to be ruled out as extremely unlikely. These include: high-risk surgical procedures/blood transfusions; immunisation; occupational exposure; baby foods or school meals; and injections, cuts or animal bites.

Instead, the study found a very strong association between people who developed v-CJD and the consumption of beef from one of two butcher's shops. It suggested several reasons why beef from these shops might be contaminated with high levels of the agent that causes BSE:

- the cattle were fed meat and bone meal from a very early age and thus had a high potential for exposure to BSE contaminated feed;
- the cattle were a breed that were slow to fatten and thus were slaughtered later than usual (~3 years);
- the slaughtering and butchering processes employed increased the risk of cross-contamination of meat with brain material.

While the study showed a strong association between beef from the two butchers and the development of v-CJD this does not constitute proof of cause and effect. The study estimated that the incubation period of the disease was 10-16 years. However some have questioned the methods used in the study, pointing out that they may introduce substantial sources of bias.

## Age distribution

One feature of v-CJD that distinguishes it from sporadic CJD is that the majority of cases are young (see figure, page 3). There are three possible explanations for this:

- younger people may have been more exposed to BSE-infected food products during the 1980s;
- younger people might be more susceptible to infection from a given exposure in the first place;
- the incubation period might vary with age, with the disease taking less time to progress in younger people.

It is not known which of these is most likely to account for the observed age distribution, although mathematical models (discussed later) suggest this could not have arisen from an age-dependent incubation period alone.

## Genetic susceptibility

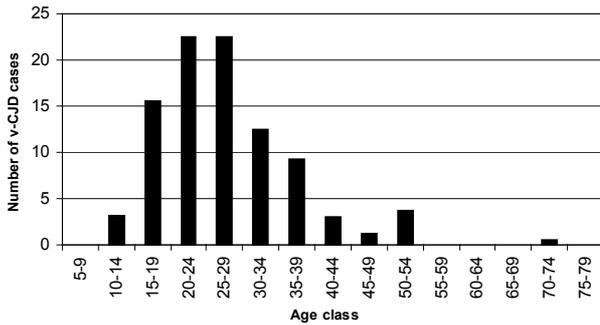
All v-CJD victims to date share a common genetic profile; only ~40% of the UK population have this profile. It is thus possible that only this 40% are susceptible to the disease. However, it is possible that the remaining 60% of the population are also susceptible to v-CJD, but that it takes longer for clinical signs to appear.

## Modelling the future progress of v-CJD

### Key areas of uncertainty

It is assumed that v-CJD is a consequence of exposure to BSE-infected material from cattle. However, uncertainties remain in key areas, as discussed below.

### Age at death of v-CJD cases (UK)



*Exposure/dose* – although the first case of BSE was recognised in 1985, the epidemic is thought to have started in the 1970s. Up to 1989, when a specified bovine offal ban was introduced, some 475,000 infected cattle may have entered the food chain. But the window of exposure may have extended beyond 1989, depending on the effectiveness of the ban and other control measures. Different meat products may have posed different levels of risk: products containing MRM are thought to have been among the most infectious as they were liable to contain fragments of spinal cord until 1995 (when use of spinal column for MRM was banned). The extent to which MRM was used within the food industry prior to 1995 is likely to be a key factor determining the number of people exposed and their level of exposure. The Food Standards Agency (FSA) announced plans in August 2001 to determine which foodstuffs contained MRM from cattle in the 1970-80s.

*Susceptibility* - as noted above, only 40% of the UK population may be genetically susceptible to v-CJD. It has also been suggested that younger people are more likely to contract the infection than the old (this is based on the observed age profile of the cases of v-CJD that have emerged to date).

*Incubation period* – the delay between infection and the appearance of clinical symptoms may be a reflection of the time taken for infectivity to be transmitted from the digestive system to the central nervous system and ultimately into the brain. The shortest possible incubation period for the cases to date is of the order of a few years (exposure declined in the late 1980s and early 1990s and the first v-CJD cases emerged in 1995). The average duration of the incubation period and how much it varies within the population and/or with age are key factors in determining the future shape of the v-CJD outbreak. For instance, if the mean incubation period is short, with little variation from person to person then most cases of v-CJD may already have emerged.

### Predictions from mathematical models

These uncertainties mean that it is very difficult to project accurately the total number of people likely to be affected. It is however possible to use mathematical models to explore a range of different assumptions about exposure/dose, susceptibility and incubation period. The general approach is to see which combination of assumptions most closely fits the observed pattern of v-CJD cases to date. These can then be used to model

patterns of infection among the population, which in turn can form the basis of projections on the likely timing and numbers of future v-CJD cases. Such models are very sensitive to the assumptions made, particularly to those concerning incubation period. The following points summarise the results of modelling to date:

- Estimates of the upper number of future cases have fallen with time. Most models agree the outbreak will peak close to 2001.
- Most estimates put the total number of expected cases between a few hundred and several thousand.
- The lowest estimates (~200 v-CJD cases) come from a model<sup>2</sup> which assumes susceptibility to infection falls dramatically after the age of 15, and uses a relatively short (~17 years) incubation period.
- Another model<sup>3</sup> looked at exposure/dose. Even where this is assumed to be high (millions of infections), the model predicts no more than a few thousand cases.
- The highest estimates<sup>4</sup> come from models that identify random scenarios to fit the observed pattern of v-CJD cases. The worst case scenario identified was when the incubation period is assumed to be about the same length as average life expectancy, which would give an upper limit of more than 130,000 cases.

An additional area of uncertainty is the possibility that BSE has spread to sheep. As discussed in more detail later, there is no evidence that this has actually occurred. A recent model<sup>5</sup> estimates that exposure to BSE-infected lamb could cause, at most, a further 50,000 cases of v-CJD. Uncertainty surrounding these estimates will diminish with time. The estimates may also be informed by measures of infectivity among human and animal populations (see below).

## v-CJD diagnosis and treatment

### The 'tonsil test'

As noted previously techniques such as MRI allied with clinical observations allow reliable classification of 'probable' v-CJD cases. A test has also been developed to detect abnormal prion protein in lymphoid tissue such as tonsils and appendixes (researchers believe that prions 'replicate' in these tissues during the incubation period). Such tests have detected abnormal protein in tissues from all v-CJD patients tested to date. The tests also suggest that the abnormal protein is more widely distributed throughout lymphoid tissue in v-CJD than it is in sporadic CJD. A version of the test is also being used in a Department of Health (DH)/Medical Research Council (MRC) survey of 18,000 samples of tonsils and appendixes removed from patients in the past 30 years or so. None of the 3,000 samples tested so far have shown detectable levels of the abnormal protein, although it is not clear how representative they are of the population at large. It is also not known at what point in the incubation period abnormal protein is detectable in these tissues (in one of the v-CJD cases, the test detected abnormal prions in the patient's appendix, removed 8 months before the first clinical symptoms emerged). The Spongiform Encephalopathies Advisory Committee (SEAC) has identified research for a diagnostic test using blood as a key priority. Public funders of TSE research issued a call in early 2001 for

research proposals to develop rapid, reliable and non-invasive diagnostic tests. This includes diagnostics to allow early identification of disease in humans and animals as well as rapid screening of human and animal populations, foodstuffs and tissues and blood used in medical procedures (see below). However, further research would be needed to validate any test.

### Research on treatment

Development of diagnostic tests to identify those at risk of v-CJD prior to the emergence of clinical symptoms raises the question of what therapeutic interventions may be possible. Research in this area covers two main strategies. First, is research into treatments to delay the spread of prions in the lymphoid tissue; studies here are focused on preventing 'replication' of the prions. Second, is research to inhibit the formation of abnormal prion protein in the brain. Researchers in the US have shown that two existing drugs (the anti-malarial quinacrine and the anti-psychotic chlorpromazine) slow formation of abnormal prion protein in mouse brain cells. A US research group has already conducted initial studies giving such treatments to CJD cases. MRC is designing a trial to evaluate the effectiveness and potential side effects of one of these drugs (quinacrine). Evaluation of this drug is only part of an ongoing UK programme of drug development for CJD treatments. A number of other potential treatments are currently being researched and may require evaluation in clinical trials in the near future.

### Other routes of infection

#### Medical interventions

Animal studies suggest that v-CJD can be acquired through transfusion of contaminated blood, although none of the human cases to date has been attributed to this route. The risks of such transmission are thought to be small: no cases of v-CJD have occurred among people with haemophilia (who may receive blood from many thousands of donors), nor are people who have received blood transfusions over-represented in the v-CJD affected population. A reliable diagnostic test could allow screening of donated blood to further reduce the risks.

Another potential source of infection is via cross-contamination from instruments previously used in certain types of surgery. Prions can survive the processes used to destroy infective agents such as bacteria and viruses on surgical instruments. Applying the 'tonsil-test' to tissues taken from v-CJD patients at *post mortem* has shown the abnormal protein to be present not only in brain and lymphoid tissue, but also in tissue from the retina and optic nerve. SEAC has assessed the risk as being greatest for operations involving central nervous system and ophthalmic tissue, followed by lymphoid tissue. It sees rigorous implementation of washing, decontamination and general hygiene procedures as the key to reducing any risk of v-CJD transmission, and considers that disposable instruments should be used for surgery only where this does not compromise patient safety. In January 2001, DH announced £200M to modernise all NHS decontamination/sterilisation facilities and introduced single-use instruments for tonsils surgery.

However, following concerns over adverse events, re-usable instruments were re-introduced for such surgery in December 2001. The DH has also set up a CJD Incidents Panel which is currently consulting on:

- advice on when potentially contaminated instruments/blood should be removed from use;
- establishing and publicising a confidential database of all people potentially exposed;
- possible public health action concerning people identified as being potentially exposed (e.g. advising them not to donate blood or organs);

#### BSE in sheep

Research has shown that sheep can be infected by eating BSE-infected material; this raises the possibility of exposure to BSE through contaminated lamb. It must be stressed that this is just a possibility – there is no evidence that sheep in the UK flock have been infected with BSE. The FSA is thus not recommending people to stop eating lamb. However, it is known that sheep were exposed to feed containing BSE-contaminated meat and bone meal during the 1980s and early 90s. Studies have thus tried to detect the BSE agent in sheep tissues. A major problem is that scrapie is endemic in the UK flock, and could mask BSE in sheep. The test currently used to differentiate between BSE and scrapie in sheep is slow: it involves injecting tissue into strains of mice and characterising the disease that develops (this can take up to 2 years). The Veterinary Laboratory Agency (VLA) and Institute for Animal Health have used this test to examine brains from scrapie-infected sheep; no evidence of BSE has been found in the 180 or so sheep tested to date. The same test has also been used to look for BSE in pooled brains, ostensibly from around 3,000 scrapie-infected sheep, although it is now thought that the brains tested originated from cows. SEAC has identified the development of a new test to rapidly distinguish between scrapie and BSE in sheep as a priority. Several such tests – including a rapid (molecular) test developed by the VLA – are currently being evaluated. FSA also sees an urgent need to develop rapid diagnostic tests to allow screening of animals for TSEs at abattoirs.

DEFRA is currently consulting on a National Plan for the long-term control and eradication of scrapie, based on a breeding programme that selects for scrapie resistance. SEAC supports the introduction of this programme but has recommended parallel research be conducted to establish whether resistant sheep can be carriers of the disease without themselves developing clinical signs. Work to address this is underway.

#### Endnotes

- 1 Investigation Report, Leicestershire Health Authority, March 2001.
- 2 Valleron et al, 2001. *Science* 294, 1726-28.
- 3 d'Aignaux et al, 2001. *Science* 294, 1729-31.
- 4 Ghani et al, 2000. *Nature* 406, 583-84.
- 5 Ferguson et al, 2002. *Nature* 413, 70.

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