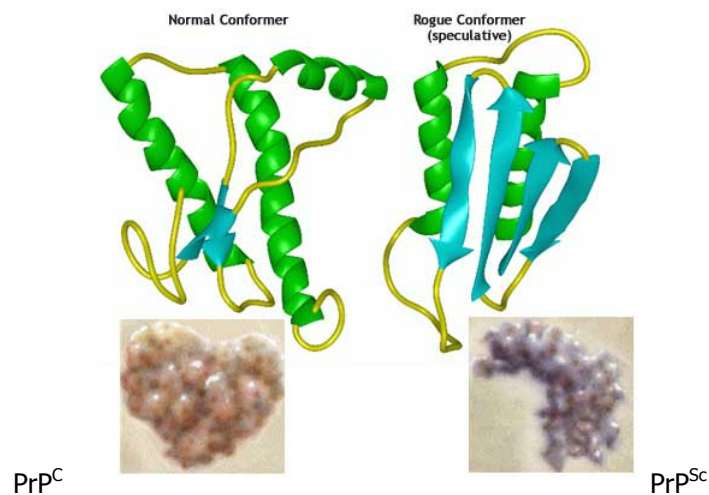


## Variant Creutzfeldt-Jakob disease

**The Infective agent:** Bovine Spongiform Encephalopathy (BSE), variant CJD and transmissible spongiform encephalopathies in general are prion diseases, caused by aggregates of misfolded prion protein.

First hypothesized by Prusiner in 1982, as the cause of scrapie (1), prions are unconventional transmissible infectious agents composed largely or exclusively of misfolded prion protein ( $\text{PrP}^{\text{Sc}}$ ), which produces the disease by propagating the abnormal conformation to the normal cellular prion protein ( $\text{PrP}^{\text{C}}$ ). The conversion from normal prion protein to abnormal prion protein form proceeds as a chain-reaction and leads to a higher content of specific forms of protein (beta sheet forms). Aggregates of  $\text{PrP}^{\text{Sc}}$  proteins are responsible for brain damage leading to the characteristic signs and symptoms of the disease (2).



**Figure 1. Conformation of normal and abnormal prion protein.** Copyright ©2008 BioQUEST Curriculum Consortium, All Rights Reserved. (<http://www.bioquest.org/index.php>)

Forms of human prion disease include sporadic, variant, inherited and iatrogenic (transmitted through certain medical procedures) CJD. Experimental evidence indicates that the prion strain responsible for the BSE epizootic in cows is also responsible for the vCJD cases in humans (3) and is different from the causative agent in other TSEs and sporadic CJD.

**Transmission:** Most reported vCJD cases appear to have been infected through the consumption of cattle products contaminated with the agent of BSE. In three cases, reported in the UK, the mode of transmission is thought to have been through receipt of a blood transfusion derived from an asymptomatic, but infected donor.

Variant CJD has been transmitted experimentally to different animal species, including wild type mice, transgenic mice and non-human primates (4)

During infection with prion diseases, infectious titres of prion protein are present in peripheral tissues (particularly lymphoid organs and spleen) before a progressive rise in brain titres finally results in clinical disease. Subclinical or carrier states may have major public health implications for public health, particularly regarding potential iatrogenic transmission from apparently healthy persons (5)

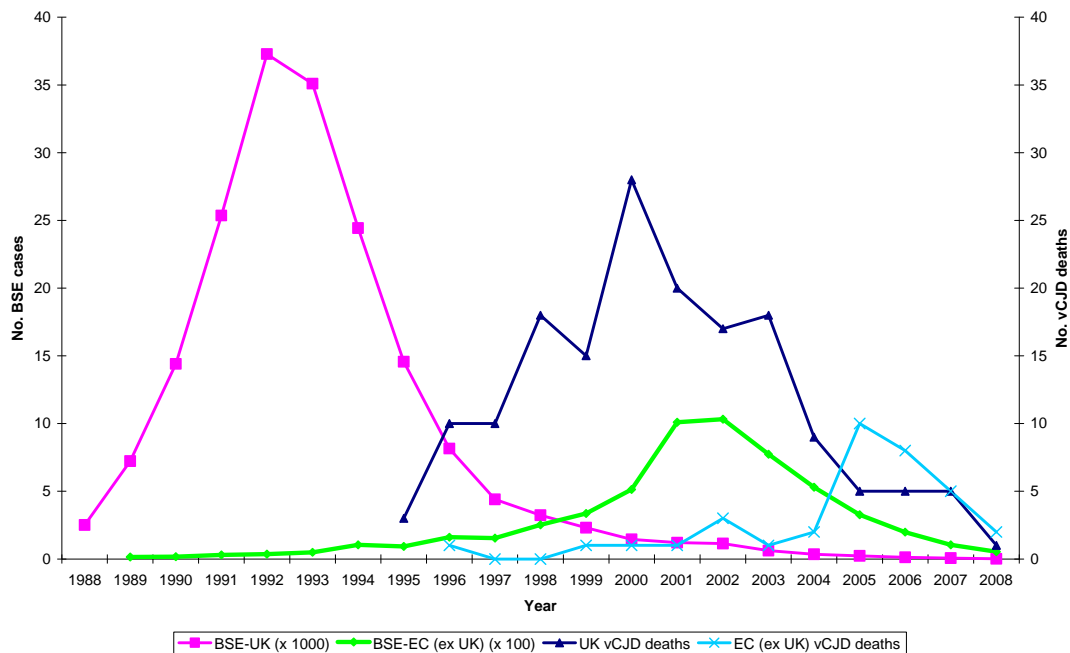
**Epidemiology:** Since 1996 and as of August 2008, a total of 209 cases of variant CJD cases have been identified from 11 countries: 167 from the United Kingdom, 23 from France, 4 from Ireland, 3 from the United States, 4 from Spain, 2 in the Netherlands, 2 in Portugal, and 1 each from Canada, Italy, Japan, and Saudi Arabia. In the UK, variant CJD has tended to affect younger individuals with an average age of onset of around 28. Sporadic CJD usually affects middle-aged and elderly individuals.

**Table 1 - Worldwide total number of cases, as of August 2008 Source: [EuroCJD](#)**

Country	Total number primary cases (Number alive)	Total number secondary cases: blood transfusion (Number alive)	Cumulative residence in UK 6 months during period 1980-1996
UK	164 (3)	3 (0)	167
France	23 (0)	-	1
Republic of Ireland	4 (0)	-	2
Italy	1 (0)	-	0
USA	3 <sup>†</sup> (0)	-	2
Canada	1 (0)	-	1
Saudi Arabia	1 (1)	-	0
Japan	1* (0)	-	0
Netherlands	2 (0)	-	0
Portugal	2 (1)	-	0
Spain	4 (0)	-	0

<sup>†</sup> the third US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the United States since late 2005. According to the US case-report, the patient was most likely infected as a child when living in Saudi Arabia. \*the case from Japan had resided in the UK for 24 days in the period 1980-1996.

**Figure 1: Number of reported BSE cases and vCJD Deaths (probable and definite) in the EU (excluding UK) and in the UK, 1988-2008. Source: EuroCJD**



In 2000 the epidemic of vCJD peaked in the UK, declining progressively with only one death in 2008 (as of 1 September 2008) (<http://www.cjd.ed.ac.uk/figures.htm>). There is a clear delay between the UK epidemic and the occurrence of cases in other EU countries, which peaked in 2005, with 10 deaths. The time period between peaks of BSE and vCJD cases in the UK is around 8 years.

**Incubation period:** The incubation period in vCJD is difficult to establish, but is estimated to be around 10 years. The incubation period in transfusion transmitted vCJD has been between 6.5 and 8 years.

**Clinical presentation:** Clinical descriptions of all forms of CJD have been developed by the National Creutzfeldt-Jakob Disease Surveillance Unit in the UK (<http://www.cjd.ed.ac.uk/clinfeat.htm>): Patients with vCJD have prominent early psychiatric (depression, anxiety and withdrawal) or sensory symptoms with a delayed onset of neurological abnormalities. Ataxia develops at around 6 months, and dementia and myoclonus are seen later in the illness. The disease always progress to death (6,7).

**Diagnosis:** Clinical and investigative features, which are included in the diagnosis criteria, may be indicative of the diagnosis of vCJD but are never definitive. Important diagnostic tools include:

- **EEG** shows a typical periodic pattern in many cases of sporadic CJD, but this is rarely seen in vCJD.
- **MRI** brain scan shows pulvinar high signal in 90% of cases of vCJD and basal ganglia high signal in about 70% of cases of sporadic CJD.
- **CSF14-3-3 protein** is elevated in 90% of cases of sporadic CJD and 50% of vCJD cases.

Neuropathological examination, usually after autopsy, is necessary for diagnostic confirmation and is also the definitive method for distinguishing between sporadic and variant CJD.

**Treatment:** Only palliative treatment is possible. No curative treatment is available.

**Preventive measures:** Since 1989, several control and prevention measures have been implemented in the EU with the prohibition of ruminant protein in ruminant feed and the use of certain specified bovine risk materials (SRMs) in human food in 1997. In 2001, a regulation was adopted aiming at eradication of certain TSE. As a result, the number of BSE affected cattle in the UK has declined steadily, with only 10 reported cases so far in 2008 (as of March 2008) (figure 1). The probability of food-borne exposure to prion diseases in the EU appears now to be very limited (9,10).

To date, there has been no known association between primary vCJD and occupation, medicines, immunising agents, gelatin, or surgery (including the use of catgut sutures). Nevertheless, vCJD infection has been observed in three recipients of blood transfusions from two donors who later developed the disease (13, 14, 15) and one blood recipient who died of another cause without clinical symptoms, but who at autopsy had prions in spleen and lymph nodes. The possibility of a risk has been assessed for plasma products, human organ and tissue transplants and contaminated surgical instruments or devices, but, to date, no transmission through these routes has been identified. However, prions are remarkably stable and relatively resistant to proteases, high temperatures and UV-radiation, as well as to commonly used disinfectants.

#### **Key areas of uncertainty**

The vCJD epidemic peaked in the UK in 2000 and the incidence has subsequently decreased steadily. There are, however, remaining concerns and uncertainties:

- **Genetic susceptibility:** Up to now, all tested cases of vCJD have been methionine homozygotes at codon 129 of the PrP gene (a genotype present in approximately 40% of Caucasian populations), with an estimated mean incubation period of about 10 years. If other genotypes are not completely resistant to infection but have longer incubation periods, as suggested in kuru and growth hormone-related CJD, subsequent epidemics in these genotypes may yet appear.
- **Sub-clinical forms:** Persons with latent disease undergoing neuro-surgical procedures could result in instrument contamination with a risk of secondary transmission. (5, 8). The first evidence of transmission through blood transfusion raised concerns about iatrogenic transmission and there is the possibility of pre-clinical or sub-clinical prion-associated infection in an unknown proportion of the population (12).
- **Number of humans infected:** While ascertainment of cases is probably good for young adults, it is still possible that cases of vCJD in old people are missed, because of the small proportion of those dying from dementia who undergo post mortem neuropathological examination (5)
- **Clinical features:** It is possible that the infection produces other symptoms different than those described until now for vCJD, for example in persons with genotypes other than MM at codon 129 of the prion protein gene (5,8).

## EU Surveillance for variant CJD

The surveillance of vCJD is currently performed by EuroCJD, a surveillance network for all forms of CJD (<http://www.eurocjd.ed.ac.uk/EUROINDEX.htm>). The case definitions for vCJD have been recently revised and apply to all EU countries ([link](#)).

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