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<p>一般的名称</p>	<p>白血球除去人赤血球浮遊液</p>		<p>研究報告の公表状況</p>		<p>Seitz R, von Auer F, Blümel J, Burger R, Buschmann A, Dietz K, Heiden M, Hitzler WE, Klamm H, Kreil T, Kretzschmar H, Nubling M, Offergeld R, Pauli G, Schottstedt V, Volkers P, Zerr I. Biologicals. 2007 Jun;35(2):79-97. Epub 2007 Feb 21.</p>	<p>公表国</p>
<p>販売名(企業名)</p>	<p>白血球除去赤血球「日赤」(日本赤十字社) 照射白血球除去赤血球「日赤」(日本赤十字社)</p>				<p>ドイツ</p>	
<p>研究報告の概要</p>	<p>○vCJDが血液供給へ及ぼす影響 変異型クロイツフェルトヤコブ病(vCJD)は、現状では剖検によってのみ確定診断が可能で、不治の神経変性疾患である。現在までの罹患者約200名のほとんどは、感染牛肉が広く食物環に入り込んだ英国在住者である。英国の3症例によってvCJDが輸血により感染する可能性が示された。BSEおよびvCJDは英国以外の複数の国に広がっているため、異なる国及び地域に特異的な評価を実施することが賢明であると思われる。本レビューは、当該リスクの評価及び予防的手段の検討においてドイツで採用された方法を説明するものである。これは、ウシの飼料連鎖およびヒトの食物環から、汚染物質が確実にかつ恒久的に除去できることの基本前提をとるものである。一方でこのモデルは輸血を介したvCJDの伝播が永続化するような可能性があるかどうかという疑問を新たにもたらす。しかし、実際の集団データを基にしたモデル計算は、そのようなことはないであろうことを示唆した。また、輸血経験者を供血者から排除することは、輸血の安全性向上にはほとんど寄与しないが、血液供給には多大な影響を及ぼすと考えられた。したがって、ドイツでは輸血経験者の排除は推奨されなかった。</p>					<p>使用上の注意記載状況・ その他参考事項等</p> <p>白血球除去赤血球「日赤」 照射白血球除去赤血球「日赤」</p> <p>血液を介するウイルス、細菌、原虫等の感染 vCJD等の伝播のリスク</p>
	<p>報告企業の意見</p>	<p>今後の対応</p>				
<p>ドイツにおいて、vCJDが血液供給へ及ぼす影響について実際の集団データを基にモデル計算を行ったところ、輸血を介した伝播がvCJDを永続化するような可能性はなく、輸血経験者を供血者から排除しても輸血の安全性向上にはほとんど寄与しないが、血液供給には多大な影響を及ぼすと考えられたとの報告である。</p>			<p>日本赤十字社は、輸血感染症防止のため輸血歴のあるドナーを無期限に献血延期としている。vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より英国滞在歴1日以上の方からの献血を制限している。さらに、血液製剤の保存前白血球除去を導入し、平成19年1月16日には全ての輸血用血液への保存前白血球除去の導入が完了した。今後もCJD等プリオン病に関する新たな知見及び情報の収集に努める。</p>			

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Review

Impact of vCJD on blood supply

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Abstract

Variant Creutzfeldt–Jakob disease (vCJD) is an at present inevitably lethal neurodegenerative disease which can only be diagnosed definitely post mortem. The majority of the approximately 200 victims to date have resided in the UK where most contaminated beef materials entered the food chain. Three cases in the UK demonstrated that vCJD can be transmitted by blood transfusion. Since BSE and vCJD have spread to several countries outside the UK, it appears advisable that specific risk assessments be carried out in different countries and geographic areas. This review explains the approach adopted by Germany in assessing the risk and considering precautionary measures. A fundamental premise is that the feeding chain of cattle and the food chain have been successfully and permanently cleared from contaminated material. This raises the question of whether transmissions via blood transfusions could have the potential to perpetuate vCJD in mankind. A model calculation based on actual population data showed, however, that this would not be the case. Moreover, an exclusion of transfusion recipients from blood donation would add very little to the safety of blood transfusions, but would have a considerable impact on blood supply. Therefore, an exclusion of transfusion recipients was not recommended in Germany. © 2007 The International Association for Biologicals. Published by Elsevier Ltd. All rights reserved.

Keywords: Bovine spongiform encephalopathy; Variant Creutzfeldt–Jakob disease; Blood supply; Risk assessment

Abbreviations: AFSSAPS, Agence Française de Sécurité Sanitaire des Produits de Santé (French medicinal products authority); BSE, bovine spongiform encephalopathy (degenerative neurological disease in cattle caused by prions); CJD, Creutzfeldt–Jakob disease (TSE disease in humans, transmissible via medicinal products (iatrogenic) or occurring sporadically); FFP, “fresh frozen plasma” (plasma for transfusion); GBR, “geographical BSE risk”: classification of countries into one of four risk classes (GBR I–IV) by the Scientific Steering Committee of the European Commission; GSS, Gerstmann–Sträussler–Scheinker syndrome (a human TSE); HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus (agent of AIDS); i.c., intracerebral; IU, infectious unit; i.v., intravenous; M, methionine; PMCA, protein misfolding cyclic amplification (method for amplification of PrP^{Sc} in vitro); PrP, prion protein; PrP^c, cellular, physiological form of the prion protein (c = cellular); PrP^{Sc}, pathological form of the prion protein (Sc = Scrapie); RBCC, red blood cell concentrate; SCMPMD, Scientific Committee on Medicinal Products and Medical Devices of the European Commission; SRM, specified risk material (bovine materials in which the BSE agent can be detected in high concentrations (brain, spinal cord etc.)); SSC, Scientific Steering Committee of the European Commission; TSE, transmissible spongiform encephalopathy (disease of the brain, generic term for neurological disorders caused by prions); UK, United Kingdom (Great Britain and Northern Ireland); V, valine; vCJD, variant Creutzfeldt–Jakob disease (human TSE caused by the BSE agent, first described in 1996).

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1. Introduction

A working group was formed in 2001 by request of the German Federal Ministry of Health that consisted of staffs from the Paul-Ehrlich-Institut, the Robert-Koch-Institut and the Federal Ministry of Health, as well as external experts. The task of this working group has been to assess the risks for the blood supply in Germany with regard to vCJD and to prepare reports outlining a strategy. The spread of bovine spongiform encephalopathy (BSE) among cattle is believed to be the origin of the problem, followed by the transition to humans via the food chain. Since the epidemiological course shows geographical differences, every country needs to assess its specific vCJD risk as a condition for developing a reasonable national blood supply strategy. The group published reports¹ in 2001 and in 2006 [1]. This review summarizes the current view of the group of the impact of vCJD on blood supply.

2. The Occurrence of BSE

Feeding of ruminant material to cattle has most probably caused the occurrence of BSE, a disease of cattle that was first diagnosed in the UK in 1986 [2]. Technological changes (pressure and temperature conditions) in the manufacture of meat and bone meal and other products are considered to be the cause for the occurrence of BSE in the UK beginning in 1985, since the inactivation of the BSE pathogen was no longer sufficiently effective [3]. This assumption is confirmed by the course of the epidemic in the UK where a decline in the number of cases was observed during the mid-1990s with a time lag representing the incubation time of 4–5 years for BSE following the ban on the feeding of meat and bone meal and the regulations on the disposal of BSE-infected animal carcasses [4] (Table 1). While in the first few years it was assumed that there was only one strain of BSE in cattle, several authors have described atypical BSE cases in the past few years [5–7]. These cases do not represent a uniform strain and are characterized by an altered molecular weight of the accumulated PrP^{Sc}, a different anatomical distribution pattern of the pathological changes and the PrP^{Sc} deposits, and partly by the occurrence of amyloid plaques. All cases of atypical BSE described so far have been found in animals older than 8 years. The cases described in France show a biochemical similarity with the cases of scrapie in sheep. Therefore, the possibility that these might be scrapie infections in cattle is discussed.

Through animal trade and trade of feeding stuff components produced from animal carcasses and slaughtering by-products (bone meal, fats for milk replacers, grieves etc.), BSE spread from the UK to other European countries and countries outside Europe (e.g. Canada, Japan, Israel). First Ireland (1989), then Switzerland (1990) and France (1991) reported cases of BSE. During the mid-1990s, Portugal (1994), the Netherlands (1997), Belgium (1997), Luxembourg (1997),

and Liechtenstein (1998) reported cases. Toward the end of the 1990s, it became clear that almost all countries with extensive exchange of goods within the European single market during the previous decade were affected by BSE. It was, therefore, not surprising that BSE was diagnosed in some cattle of Denmark, Germany, and Spain in the year 2000 and also in Austria, the Czech Republic, Finland, Greece, Italy, Slovakia, and Slovenia in 2001. Since 2002, BSE has also been diagnosed in Polish cattle. Cases of BSE in cattle imported from the UK were reported as early as the early 1990s by several European countries (Portugal 1990, Germany 1992, Denmark 1992, Italy 1994). Three BSE cases have so far occurred in the United States, of which one animal had been imported from Canada. The two indigenous cases were of the atypical BSE type of which the origin is still unknown.

In addition to animal trade and trade with animal products, however, intrinsic national factors influenced the occurrence and spread of BSE. Since by the 1980s most EU member states had changed their animal carcass disposal methods and processed side products from abattoirs without the removal of risk materials under pressure and temperature conditions that were not sufficient for the inactivation of the BSE pathogen, this pathogen was continuously spread, thus increasing the number of BSE cases. Moreover, only passive monitoring systems based on the reporting of clinical symptoms were in place; BSE rapid tests were not yet available.

Organs and tissues of BSE infected cattle in which the pathogen has been detected are called “specified risk materials” (SRM). SRM of naturally infected animals may, especially toward the end of the incubation period and during the development of clinical BSE symptoms, contain the pathogen in very high concentrations. Using biological detection systems for the BSE pathogen, which include a species barrier, e.g. intracerebral infection into mice, 10⁵ infectious units/g SRM (brain) were determined, while a 1000-fold increased infectivity titer is assumed for transmissions within a species [8–10]. The Scientific Steering Committee (SSC) of the European Commission set up an SRM list for cattle (e.g. skull including brain and eyes, tonsils, spinal cord) (SSC 1998²), which served as a basis for various European policies for the exclusion of SRM in the food and feed chains. Since the spread of the BSE crisis in Europe, the definition of specified risk materials has been revised several times (a comprehensive overview of the European legislation can be found in Table 2 of [1]). According to the latest amendment, the tissues designated as SRM must be subjected to safe removal and must not enter the food chain. The following tissues are designated as SRM: “The skull excluding the mandible and including the brain and eyes, the vertebral column excluding the vertebrae of the tail, the spinous and transverse processes of the cervical, thoracic and lumbar vertebrae and the wings of the sacrum, but including the dorsal root ganglia, and the spinal cord of

² Scientific Steering Committee (SSC), 1998. Listing of Specified Risk Materials: a scheme for assessing relative risks to man—Opinion of the SSC adopted on 9 December 1997 (Re-edited version adopted by the SSC during its Third Plenary Session of 22–23 January 1998).

¹ The reports published by this group in German language in the years 2001 and 2006 can be found in the internet: <http://www.pei.de>.

Table 1
Number of BSE cases reported

Country	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005 ^a
Austria	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Belgium	0	0	0	0	0	0	0	0	1	6	3	9	46	38	15	11	1
Canada	0	0	0	0	1*	0	0	0	0	0	0	0	0	0	2	1	1
Czech Republic	0	0	0	0	0	0	0	0	0	0	0	0	2	2	4	7	8
Denmark	0	0	0	1*	0	0	0	0	0	0	0	1	6	3	2	1	n.d.
Finland	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	n.d.
France	0	0	5	0	1	4	3	12	6	18	31	161	274	239	137	54	n.d.
Germany	0	0	0	1*	0	3*	0	0	2*	0	0	7	125	106	54	65	32
Greece	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	n.d.
Ireland	15	14	17	18	16	19	16	73	80	83	91	149	246	333	183	126	69
Israel	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Italy	0	0	0	0	0	2*	0	0	0	0	0	0	48	38	29	7	3
Japan	0	0	0	0	0	0	0	0	0	0	0	0	3	2	4	5	7
Liechtenstein	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	n.d.
Luxembourg	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	1
The Netherlands	0	0	0	0	0	0	0	0	2	2	2	2	20	24	19	6	n.d.
Poland	0	0	0	0	0	0	0	0	0	0	0	0	0	4	5	11	18
Portugal	0	1*	1*	1*	3*	12	15	31	30	127	159	149	110	86	133	92	37
Slovakia	0	0	0	0	0	0	0	0	0	0	0	0	5	6	2	7	n.d.
Slovenia	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	2	1
Spain	0	0	0	0	0	0	0	0	0	0	0	2	82	127	167	137	75
USA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Switzerland	0	2	8	15	29	64	68	45	38	14	50	33	42	24	21	3	3
United Kingdom	7228	14407	25359	37280	35090	24438	14562	8149	4393	3235	2301	1443	1202	1144	611	343	151

Source and information on up-to-date statistics: Office International des Epizooties, as of 9 January 2006 (www.oie.int). *Cases in imported animals.

^a Data for 2005 still incomplete. n.d., not done.

bovines aged over 12 months, and the tonsils, the intestines from the duodenum to the rectum and the mesentery of bovines of all ages; the skull including the brain and eyes, the tonsils and the spinal cord of ovine and caprine animals aged over 12 months or which have a permanent incisor erupted through the gum, and the spleen of ovine and caprine animals of all ages.” Because of the significant decrease in the number of BSE cases in the European Union, the age limit for the collection and safe removal of SRM for the spinal cord of bovine animals was raised to 24 months and a raise of the test age is being discussed.³

The SSC has developed a procedure by which the geographical BSE risk (GBR) in a member state or non-European country can be evaluated. In its opinion, published in July 2000,⁴ it laid down the following criteria for classifying one of four risk levels:

- Structure and dynamics of the bovine population,
- BSE surveillance,
- Cullings in connection with BSE cases,
- Imports of bovine animals and meat and bone meal (MBM),
- Feeding,
- Ban on the feeding of meat and bone meal (MBM bans),

- Regulations concerning specified risk material (SRM bans),
- Removal of animal carcasses.

The risk levels are defined in Table 2.

At that point in time (2000), Argentina, Australia, Chile, Norway, New Zealand, and Paraguay were classified as GBR level I, Austria, Finland, Sweden, Canada, and the United States as GBR level II, whereas the UK and Portugal were classified as GBR level IV. All other countries, including Germany, were classified as GBR level III. Germany’s classification as GBR level III caused heated discussions in Germany, since up to that time the country had been considered to be absolutely BSE free. In actuality, all countries rated into BSE level III indeed identified BSE cases in their own countries within the following months.

Since 2001, the GBR has been assessed for various other countries, e.g. candidate countries for accession to the EU. Almost all countries were classified as GBR level III, since insufficient monitoring had been carried out to guarantee satisfactory statistical safety. A number of countries evaluated in 2000 were later re-evaluated, which led to the classification of Austria, Canada, USA, Mexico and South Africa to GBR level III. In March 2003, Canada’s second BSE case was discovered (the first case was diagnosed in 1993), and in June 2005, the first BSE case was confirmed in the USA.⁵

³ See the “BSE road map” for more details, http://europa.eu.int/comm/food/food/biosafety/bse/roadmap_en.pdf

⁴ Final Opinion of the Scientific Steering Committee on the Geographical Risk of Bovine Spongiform Encephalopathy (GBR). Adopted on 6 July 2000.

⁵ The results and opinions of the Scientific Steering Committee (SSC) and the European Food Safety Authority (EFSA) can be found in http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html and <http://www.efsa.eu.int> respectively.

Table 2
GBR levels as defined by the SSC

GBR level	Presence of one or more cattle clinically or pre-clinically infected with the BSE agent in a geographical region/country
I	Highly unlikely
II	Unlikely but not excluded
III	Likely but not confirmed or confirmed, at a lower level
IV	Confirmed, at a higher level

The member states and third countries were also classified into five BSE status categories.⁶ The classification in status categories was based on criteria similar to those of the SSC. However, in this context the number of diagnosed BSE cases served as an important additional factor. Consequently, other points of combating BSE laid down in this EU regulation refer to the status category of the appropriate country, such as the required extent of the safe retrieval and removal of SRM.

Following the steady decrease of BSE cases in the UK in the past few years, the number of BSE cases reported per one million bovine animals older than 30 months has fallen below 1,000, enabling a re-evaluation of the UK. The application was given a favorable opinion by the European Food Safety Authority (EFSA), and it was suggested that the UK be classified as BSE risk status III. A change in the BSE risk status represents a significant relief for the UK regarding international trade of bovines and bovine animal products.

3. BSE in Germany

Passive BSE surveillance has been performed in Germany for years, i.e. all bovine animals that died or became clinically sick due to disorders of the central nervous system and were suspected to have suffered from BSE were examined. The brains of such animals were subjected to histopathological examination, and any samples with abnormal results were also examined for plaques of PrP^{Sc} by immunohistochemical examination and/or scrapie associated fibril (SAF) extraction with subsequent immunoblot. These examinations did not reveal any BSE cases in German cattle.

The first BSE rapid test, the Prionics Check Western blot developed by Prionics (Switzerland), became available in mid-1999. Even though the test had not yet been approved, it was already used in some European countries. A series of examinations using this BSE test for 5,000 beef cattle was carried out between March and May 1999 in North Rhine-Westphalia, Germany. All these animals showed negative results, reinforcing the hope of a BSE-free Germany.

In preparation for transposing the Commission Decision 2000/374/EC, which established random BSE monitoring of bovine animals, a few voluntary BSE examinations were carried out in cattle samples starting in mid-November of 2000.

⁶ Regulation (EC) No 999/2001 of the European Parliament and the Council of 22 May 2001 (Official Journal of the European Communities of 31 May 2001, L147, p. 1) laying down rules on prevention, control and eradication of certain transmissible spongiform encephalopathies.

These examinations revealed the first indigenous German BSE case in Schleswig-Holstein confirmed by the National Reference Laboratory on 26 November 2000. This was followed by the introduction of rapid test examinations throughout Germany within a short period of time. After the extensive introduction of BSE rapid tests in December 2000 for all slaughtered cattle as well as for fallen stock (first over 30, then over 24 months old; since June 2006 again over 30 months old), 390 BSE cases were identified in following years (reference date: 16 January 2006) (Table 1). The number of cases reported annually is steadily declining, despite a slight increase from 2003 to 2004.

Altogether, these data indicate that the BSE “epidemic” in Germany may have already exceeded its peak before the first case was even diagnosed. Simultaneous to the introduction of the BSE rapid test, a total ban on feeding protein-containing products and fats derived from warm-blooded land animals to ruminants throughout Europe was imposed in the year 2000. In Germany, this ban was extended to the feeding of all productive livestock as defined in the Futtermittelgesetz (Act on Feeding-Substances).

While during the first two years of BSE monitoring in Germany the disease was predominantly diagnosed in animals born in 1995 and 1996, BSE has been increasingly identified in animals born in later years (particularly in 1998/99) since 2004. This suggests that after a significant entry of BSE infectivity into the feeding-stuff chain in 1995/96, a reduction must have occurred, followed by a second increase in the pathogen content around 1998/99. It is still unknown what caused these two BSE waves. Until the end of 2004, BSE was diagnosed in ten bovine animals born in 2000. Then, in April 2005, BSE was diagnosed for the first time in a bovine born in May 2001, i.e. after the implementation of the total feed ban of MBM from warm-blooded land animals to productive livestock in Germany. A second case followed in June 2005 when a BSE infection was diagnosed in an animal born in March 2001. It must be assumed that these two cases were caused by a contamination with the pathogen beyond the feed ban. In this context, it must be mentioned that in the UK, 95 cases born after the reinforced feed ban of August 1996 (so-called BARB-BSE cases) were diagnosed up to April 2005 (source: DEFRA-statistics). Two explanations must be considered as the cause for the occurrence of such cases:

1. The routes of infection have not yet been fully identified, and a transmission cannot be excluded 100% despite a strict adherence to the feed ban.
2. In isolated cases, MBM was fed to animals even after the feed ban came into force. This is very difficult to prove after so many years, and would imply that the control mechanisms might have to be made even more restrictive.

4. BSE in small ruminants

The theoretical risk of transmission of the BSE pathogen to small ruminants has been scientifically discussed for some

time, resulting in the introduction of an active TSE surveillance of these species by rapid BSE test pursuant to Regulation (EC) 999/2001. After the introduction of this intensive monitoring, the number of reported TSE cases in small ruminants markedly increased in nearly all member states.

In Germany, 0–3 cases of scrapie had been diagnosed for many years; the figure has risen to 31–119 individual animals with altogether 68 outbreaks of classical and atypical scrapie per year since 2002. In some cases, the disease could be detected in up to 56 animals of the same herd. In Germany, no TSE infection has been diagnosed thus far in any of the 12,000 goats tested since the beginning of the intensified monitoring. Regulation (EC) 999/2001 also laid down that each TSE case in small ruminants was to be tested by means of biochemical methods or animal experiments (“strain typing”). This measure serves to guarantee that a possible BSE infection in these small ruminant species would not remain undetected. Since the animal experimental methods used up to now mainly for scientific interest [11,12] are very time-consuming and costly, the samples are usually first tested by means of biochemical methods (analysis of the molecular weight, the glycosylation profile, and the antibody binding affinity of the accumulated pathological prion protein) [13–17]. So far, evidence of BSE infection in sheep has not been found in any of the 37 classical scrapie outbreaks in Germany [17], nor during the relevant tests performed in other member states. The cases of atypical scrapie were excluded from the strain typing, since this TSE type is clearly distinct from BSE [18]. Active surveillance in France, however, and subsequent strain typing tests gave clear evidence of a BSE infection in a goat that had been diagnosed with a TSE infection in 2002.

This first evidence that the BSE pathogen can cross the species barrier between cattle and small ruminants gave rise to special concern in expert circles; in small ruminants, the TSE pathogenesis clearly differs from that in cattle. In cattle, pathological prion protein and BSE infectivity remain strictly limited to the central nervous system and only become detectable immediately before the occurrence of clinical symptoms [19]. The combination of rapid testing of all beef cattle above a certain age (30 months in the EU, first 24 months which was raised to 30 months in June 2006 in Germany), in combination with the safe removal of SRM, thus presents an effective consumer protection measure. The situation is different in sheep, where the pathogen can be detected in various organ systems very soon after the infection, above all in the nervous and lymphatic systems [20–22]. It is therefore well possible that an animal testing negative in the rapid test of the brain stem has already accumulated disease-related prion protein and infectivity in other organs. Since, however, TSE pathogenesis in sheep depends on various factors, e.g. the PrP^{Sc} genotype of the affected animal and the TSE strain, no uniform testing concept for this animal species would guarantee TSE detection at the earliest possible point in time after infection. Any BSE infection in small ruminants thus presents a potentially enhanced risk for the consumer as compared to the occurrence of the same disease in cattle.

Table 3
Patients with vCJD worldwide and duration of stay in the UK

Country	Total number of cases (number alive)	Cases with cumulative residence in UK > 6 months during the period 1980–1996
UK	162 (6) ^a	162
France	20 (3)	1 ^b
Republic of Ireland	4 (1)	2
The Netherlands	2 (1)	0
USA	2 (0)	2
Canada	1 (0)	1
Italy	1 (0)	0
Japan	1 ^c (0)	0
Portugal	1 (1)	0
Saudi Arabia	1 (1)	0
Spain	1 (0)	0

^a As of 7 August 2006 (<http://www.cjd.ed.ac.uk>).

^b The person from France had traveled regularly to UK over more than 10 years since 1987.

^c The person from Japan had resided in the UK for 24 days in the period 1980–1996.

5. The occurrence of vCJD

First described in the UK in 1996, vCJD can be distinguished from the classical forms of CJD both by its clinical and neuropathological characteristics [23–25]. The numbers of cases observed world-wide are shown in Table 3.

Out of the 162 confirmed or probable cases diagnosed in the UK, 156 patients have died, and in 112 cases the diagnosis was neuropathologically confirmed. One Chinese patient who died in Hong Kong had stayed in the UK for several years and is included in the UK cases. The number of vCJD deaths in the UK reached its peak in 2000 with 28 cases; then, the number of deaths due to vCJD dropped sharply through 2005. This development currently supports the hope that the epidemic has surpassed its peak in the UK. This assumption, however, is still unsafe due to the lack of knowledge about the disease, duration of the incubation period, and frequency of manifestation dependent on the genotype at codon 129 of the prion protein gene.

As of 28 July 2006, 20 cases have been diagnosed in France. The number of probable and confirmed vCJD cases in France has not shown any decline; 3 cases were diagnosed in 2004 and 6 cases in 2005.⁷ Seventeen individuals in France have died of vCJD. The number of persons who died of probable or confirmed vCJD in the UK and in France up to 2005 is shown in Fig. 1 (status of the data UK: 3 March 2006, France: 28 February 2006).

It is assumed that vCJD is caused by the same pathogen as BSE in cattle. This is based on the geographic occurrence of BSE and vCJD, the biochemical similarity between BSE and vCJD associated prion proteins [26,27], the non-distinguishability of the pathogen strain typing (incubation periods in different mouse strains, lesion patterns in the brain) [28,29], induction of neuropathological changes in macaques after

⁷ <http://www.invs.sante.fr/surveillance>

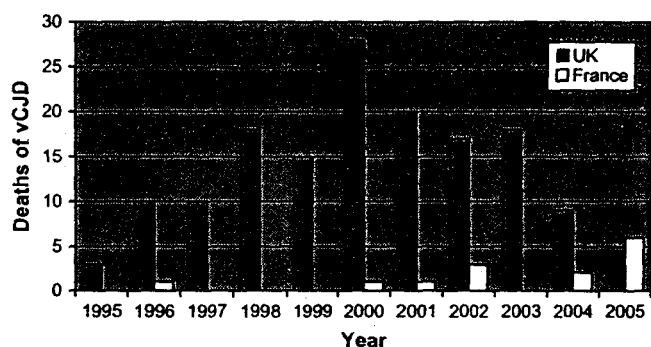


Fig. 1. Deaths caused by probable and confirmed vCJD in the UK and France from 1995 to 2005.

infection with BSE material very similar to those in vCJD patients [30], identical biological characteristics during transmission of BSE and vCJD material to transgenic mice [31], and comparable pathogen characteristics (e.g. lesion patterns, PrP^{Sc} protein patterns) [32].

It is assumed that infection of humans occurs via the food chain by contaminated beef. It is highly likely that for food production, tissue of infected animals with high pathogen content, especially brain and/or spinal cord tissue, was used consciously or unconsciously. The route of infection from uptake of the pathogen in the gastro-intestinal duct via the N. vagus and the N. splanchnicus into the central nervous system could be shown experimentally [33]. A possible transmission of pathological prion by medicinal products, medical devices, and cosmetics containing bovine material seems to play at best a subordinate role, since the analysis of the vCJD cases up to now for possible risk factors did not reveal any suspicion.⁸

Concerning human to human transmission, there is currently no evidence for transmission of vCJD by transplants or other medicinal products derived from human material, e.g. plasma derivatives, albeit transmission by this route cannot be excluded in principle. However, three vCJD cases are seriously suspected to have been caused by blood transfusions (cf. Section 7).

Apart from this, there are no reports on iatrogenic vCJD infections worldwide, contrary to classical CJD, which was transmitted in more than 100 cases by pituitary (growth hormone, follicle stimulating hormone) and dura mater products. In isolated cases, infection by corneal transplantation and by reused surgical instruments (intracerebral electrodes) was reported [34]. The transmission risk was minimized by suitable measures (e.g. replacement of the pituitary extracts by recombinant products, critical selection of dura mater and cornea donors, treatment of the dura mater with sodium hydroxide solution, use of disposable instruments).

In contrast to the classical forms of CJD, however, vCJD patients have measurable pathogen content not only in the

central nervous system but also in peripheral tissues [35], especially in lymphatic tissues (tonsil, appendix, spleen). It is therefore conceivable that infection is possible in principle by reuse of instruments in general surgery, including flexible endoscopes. Recommendations for minimizing iatrogenic vCJD transmissions were put forth in April 2002 [36], with notes on the validation of decontamination [37], and the testing of new, instrument-compatible methods [38].

6. Estimation of the extent of the spread of vCJD

Mathematical models have been developed to assess the extent of the vCJD epidemic. Estimates would require sufficiently reliable information on relevant parameters, e.g. minimum infectious dose in the event of oral route of transmission, extent of consumption of contaminated beef, distribution of the incubation periods, and information on the susceptibility of the exposed population. These basic parameters are still not sufficiently known, and every model calculation is therefore inevitably fraught with uncertainties. As a rule, the models take into account the uptake of the pathogen via contaminated beef only. Since human to human transmission might add to the epidemic, infectivity of parenteral administration of the pathogen needs to be known. No estimates have so far been published on the portion of possible vCJD cases that follows this infection route.

Models developed to assess the vCJD epidemic in the UK initially assumed that only a portion of the population can contract the disease, based on the observation that clinical vCJD has developed only in individuals who are homozygous for methionine (M/M) at codon 129 of the prion protein gene. This applies to approx. 40% of the Caucasian population (Table 4) [39–43].

In each model, different incubation periods for vCJD (up to 60 years) and differing age-related susceptibilities were taken into account. The models improved with the increase of data on the actual progression of the epidemic. The estimated number of future vCJD cases in the UK caused by food of up to several million [44] could be revised first to 136,000 [45] and later to 7,000 [46].

Currently, the incubation period and degree of susceptibility of the exposed population are still uncertain. Above all, the polymorphism at codon 129 seems to play a role in individual susceptibility. While up to now all vCJD patients were homozygous M/M, in the year 2004 a transfusion recipient who was heterozygous at codon 129 (methionine/valine, M/V) was

Table 4
Polymorphism of the prion protein gene in the general population, in CJD and vCJD patients

Individuals tested	M/M	M/V	V/V
General population	39–48%	42–50%	10–13%
Sporadic CJD	69–78%	12–15%	10–16%
vCJD ^a	100%	0%	0%

M: methionine, V: valine.

^a Clinical vCJD cases.

⁸ The National Creutzfeldt–Jakob Disease Surveillance Unit (UK): www.cjd.ed.ac.uk