Variant Creutzfeldt-Jakob disease

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変異型クロイツフェルト・ヤコブ病について

英国　エジンバラ大学
国立CJDリサーチ＆サーベイランスユニット
ロバート・ウィル教授

Prion Diseases

Transmissible spongiform encephalopathies

HUMAN	ANIMAL
Sporadic CJD	Scrapie
Iatrogenic CJD	TME
Genetic - CJD	Chronic wasting disease
- GSS	
- FFI	BSE
Variant CJD	FSE
Kuru	SE of captive ungulates
	Atypical scrapie/BSE

プリオン病

伝達性海綿状脳症（TSE）

人間	動物
孤発性クロイツフェルト・ヤコブ病（CJD）	スクレイピー
医原性CJD	伝達性ミンク脳症(TME)
遺伝性 - CJD	慢性消耗性疾患
- GSS	牛海綿状脳症（BSE）
- FFI	猫海綿状脳症（FSE）
変異型CJD	捕獲された有蹄類の海綿状脳症
クールー	非定型スクレイピー/BSE

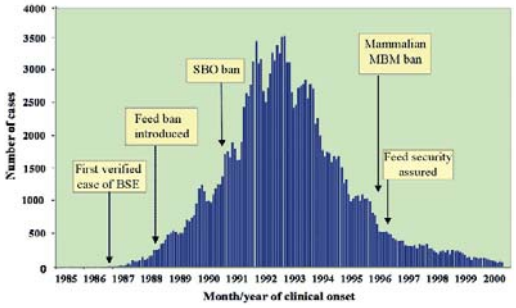
CHARACTERISTICS OF PRION DISEASES

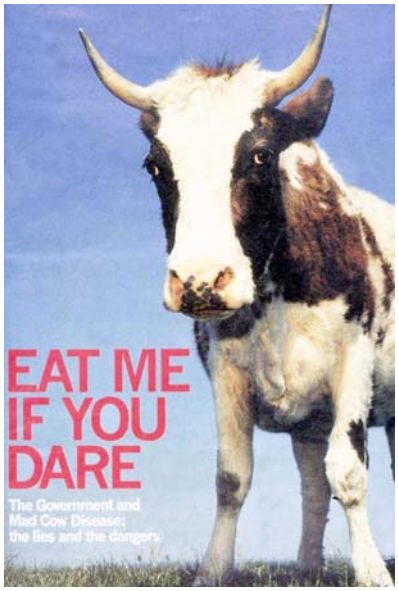
- Prolonged incubation periods.
- Uniformly fatal neurological diseases.
- Causal agents (prions) relatively resistant to sterilisation.
- No validated serological test for infection.
- Infection may be present in peripheral tissues during the incubation period eg LRS.

プリオン病の特徴

- 長期にわたる潜伏期間
- 一様に致命的な神経学的疾患
- 原因物質（プリオン）は滅菌に比較的抵抗性が高い
- 感染に対する検証された血清学的検査はない
- 潜伏期間において末梢組織が感染性を有する可能性がある　例：リンパ網内系

The UK BSE epidemic

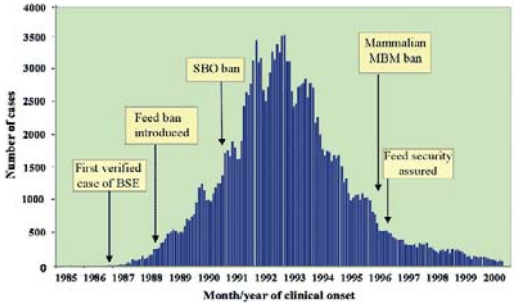


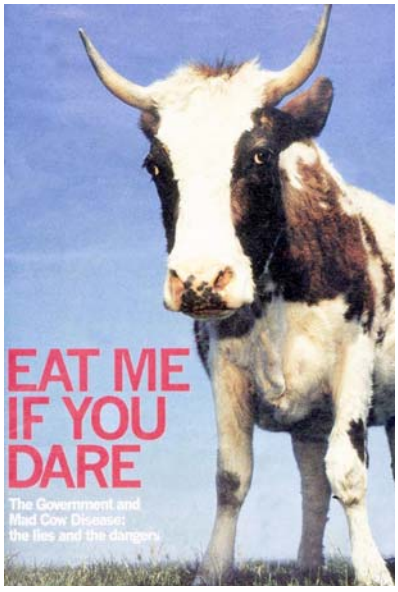


1989: Tyrrell Committee recommends reinstitution of national CJD surveillance

1st May 1990: National CJD Surveillance Unit established in Edinburgh

英国におけるBSEの発生





1989年: ティレル委員会が、国家的なCJDのサーベイランスの再制定を提言

1990年5月1日: エジンバラに英国CJDサーベイランスユニットを設立

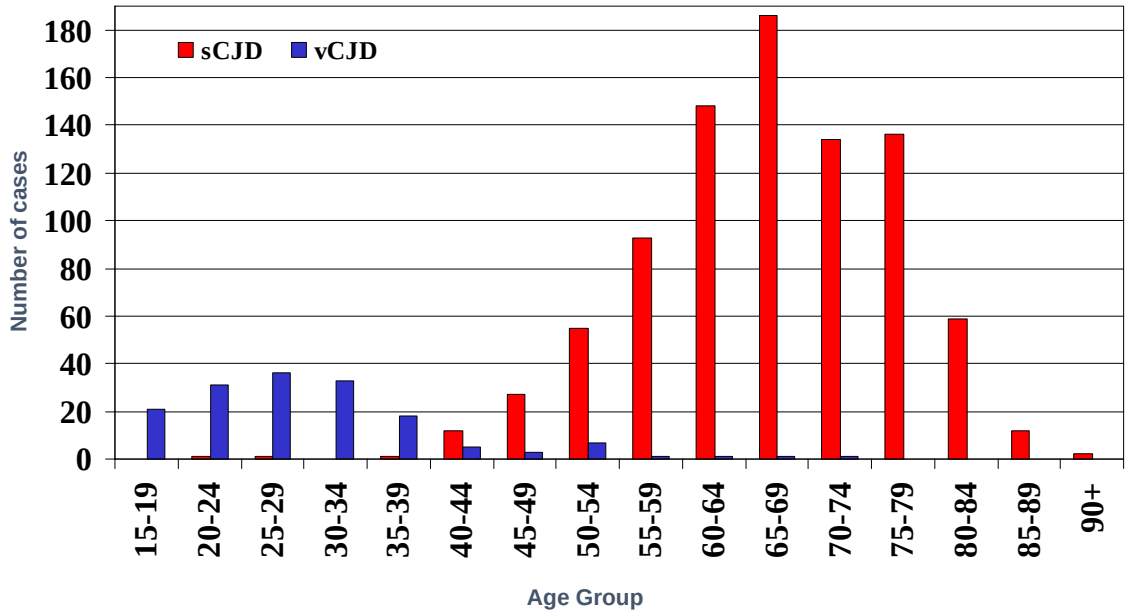
Surveillance of CJD in the UK

- Methodology based on previous project in 1980s in Oxford
- Notification of suspected cases from healthcare professionals - neurologists, pathologists, psychiatrists
- Review of death certificate data
- Case control study to identify risk factors

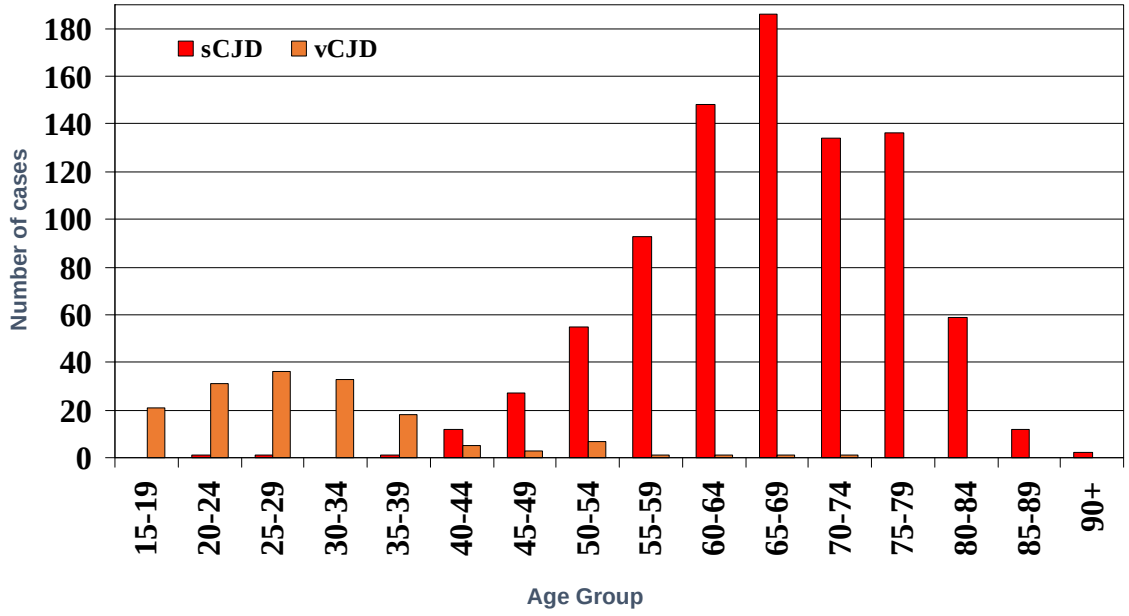
英国におけるCJDのサーベイランス

- オックスフォードで1980年代に行われた従来のプロジェクトに基づく方法
- 医療従事者（神経学者、病理学者、精神科医）からの疑い事例の報告
- 死亡証明書データの見直し
- リスク要因を特定するための症例対照研究

AGE AT DEATH FOR SPORADIC CJD CASES
AND vCJD CASES
BY 5-YEAR AGE GROUP



孤発性CJD（sCJD）及び変異型CJD（vCJD）事例の死亡時の年齢
（5歳ごとの年齢グループ別）



Articles

A new variant of Creutzfeldt-Jakob disease in the UK

R G Will, J W Ironside, M Zeidler, S N Cousens, K Estibeiro, A Alperovitch, S Poser, M Pocchiari, A Hofman, P G Smith

Summary

Background Epidemiological surveillance of Creutzfeldt-Jakob disease (CJD) was reinstituted in the UK in 1990 to identify any changes in the occurrence of this disease after the epidemic of bovine spongiform encephalopathy (BSE) in cattle.

Methods Case ascertainment of CJD was mostly by direct referral from neurologists and neuropathologists. Death certificates on which CJD was mentioned were also obtained. Clinical details were obtained for all referred cases, and information on potential risk factors for CJD was obtained by a standard questionnaire administered to patients' relatives. Neuropathological examination was carried out on approximately 70% of suspect cases. Epidemiological studies of CJD using similar methodology to the UK study have been carried out in France, Germany, Italy, and the Netherlands between 1993 and 1995.

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Because of the epidemic of bovine spongiform encephalopathy (BSE) in cattle, surveillance of Creutzfeldt-Jakob disease (CJD) in the UK was reinstituted in May, 1990. The purpose of the surveillance is to identify changes in the pattern of CJD which might indicate an association with BSE. We report ten cases of CJD in the UK with clinical onset of disease in 1994 and 1995. These cases all have neuropathological changes which, to our knowledge, have not been previously reported. They are also unusual in that they occurred in relatively young people, and the clinical course was not typical of cases of sporadic CJD in the UK.

Methods

Since May, 1990, cases of CJD have been identified to the CJD Surveillance Unit, usually by direct referral from professional groups, which include neurologists and neuropathologists. All

論文：英国におけるクロイツフェルト・ヤコブ病の新たな変異型

THE LANCET

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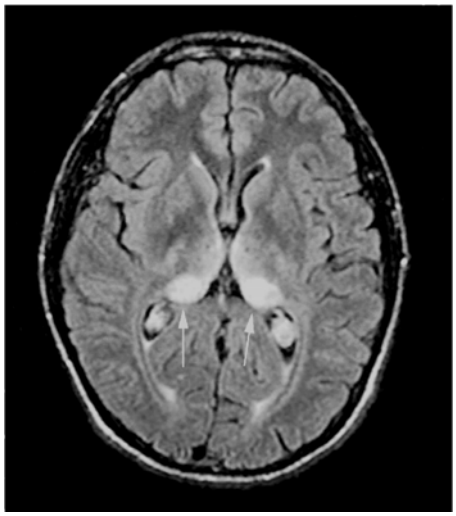
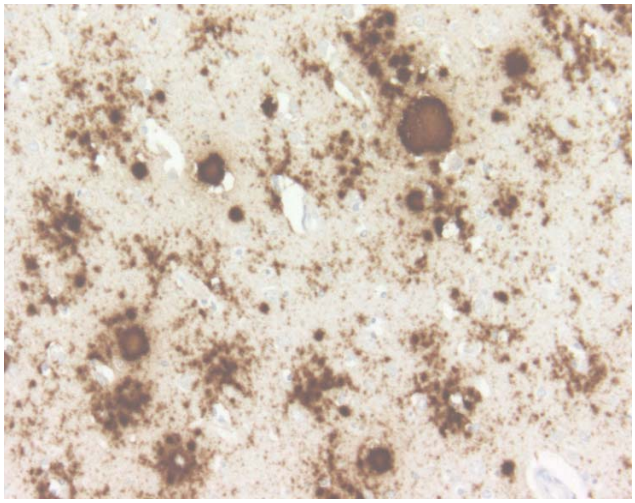
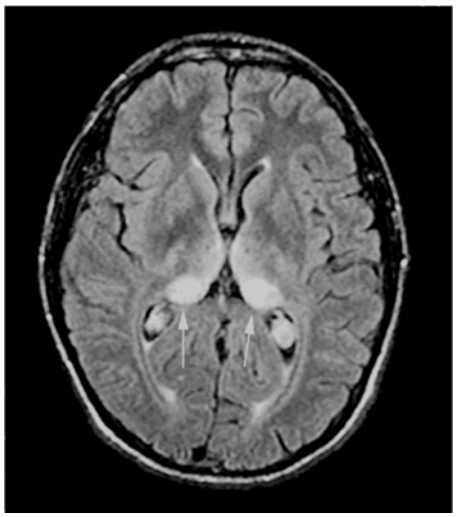
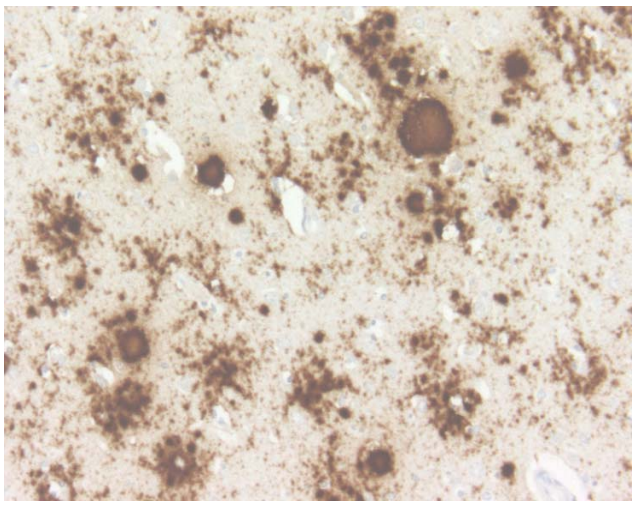
MRI scan and brain immunocytochemistry in variant CJD





変異型CJDにおけるMRI画像及び脳の免疫細胞化学





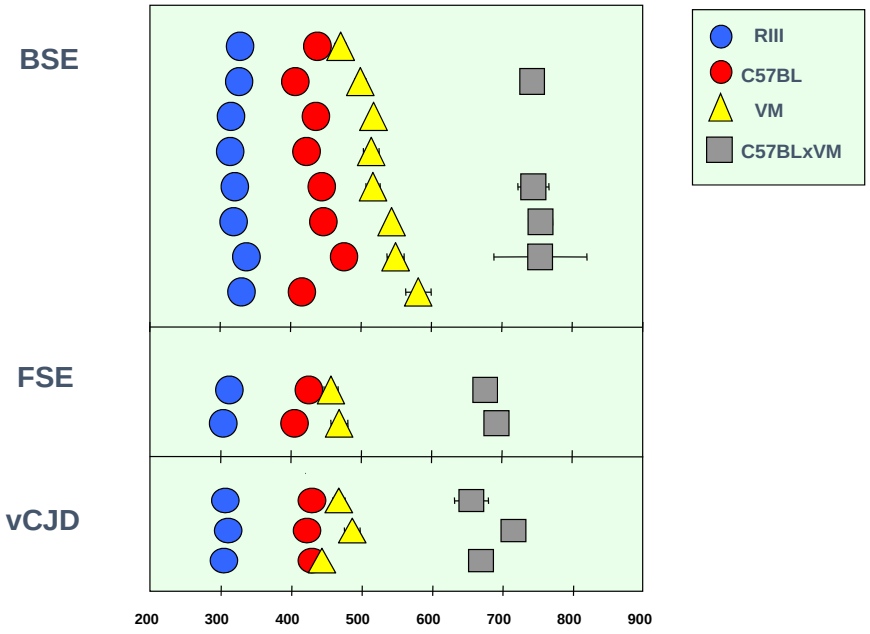
DIFFERENCES BETWEEN SPORADIC AND VARIANT CJD

	SPORADIC	VARIANT
Mean age at death	66 years	29 years
Median duration of illness	4 months	13 months
Thalamic MRI high signal	Caudate/Putamen 80%	Pulvinar 90%
EEG	“Typical” 70%	“Typical” 1%
Neuropathology	Plaques 10%	Florid plaques 100%

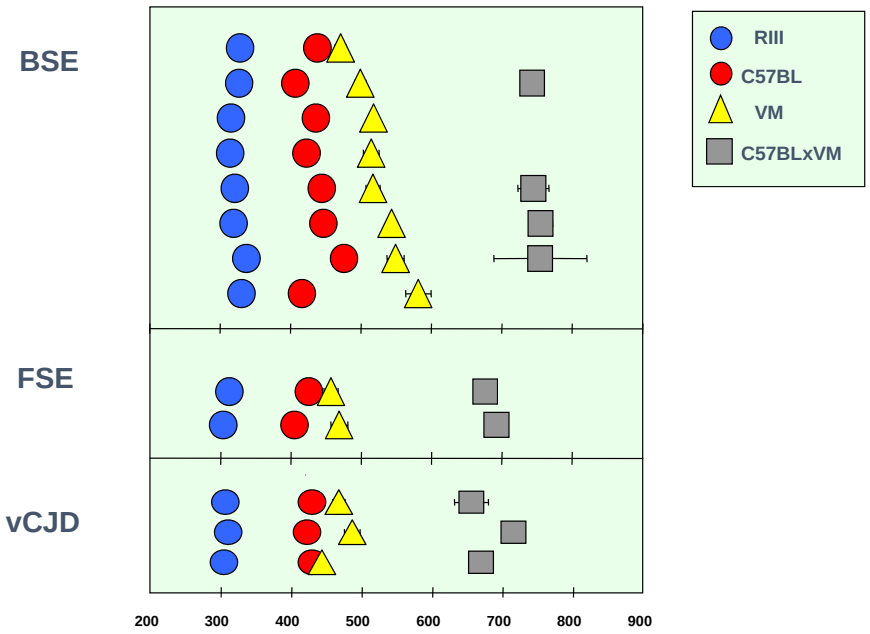
孤発性CJD及び変異型CJDの違い

	孤発性	変異型
平均死亡年齢	66歳	29歳
平均罹患期間	4か月	13か月
視床部MRI高信号	尾状核／被殻 80%	視床枕 90%
脳波	“典型的” 70%	“典型的” 1%
神経病理	プラーク（斑） 10%	フローリッド・プラーク 100%

Transmission of TSEs to mice

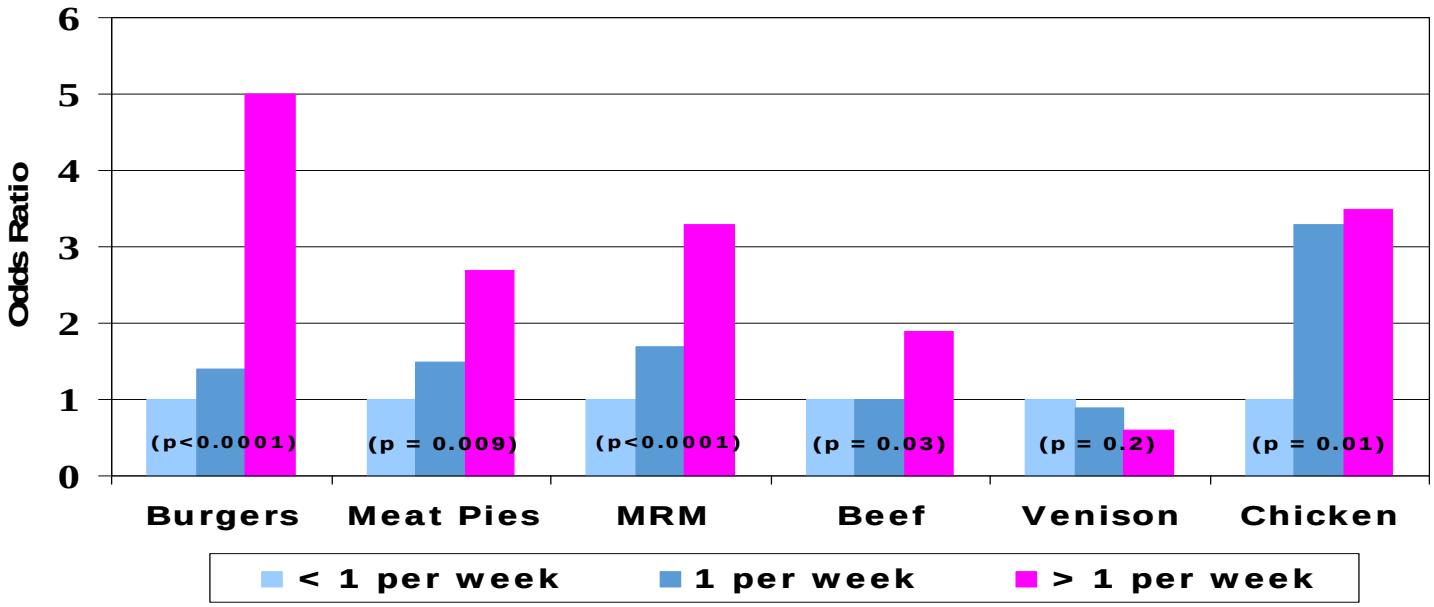


TSEのマウスへの伝播



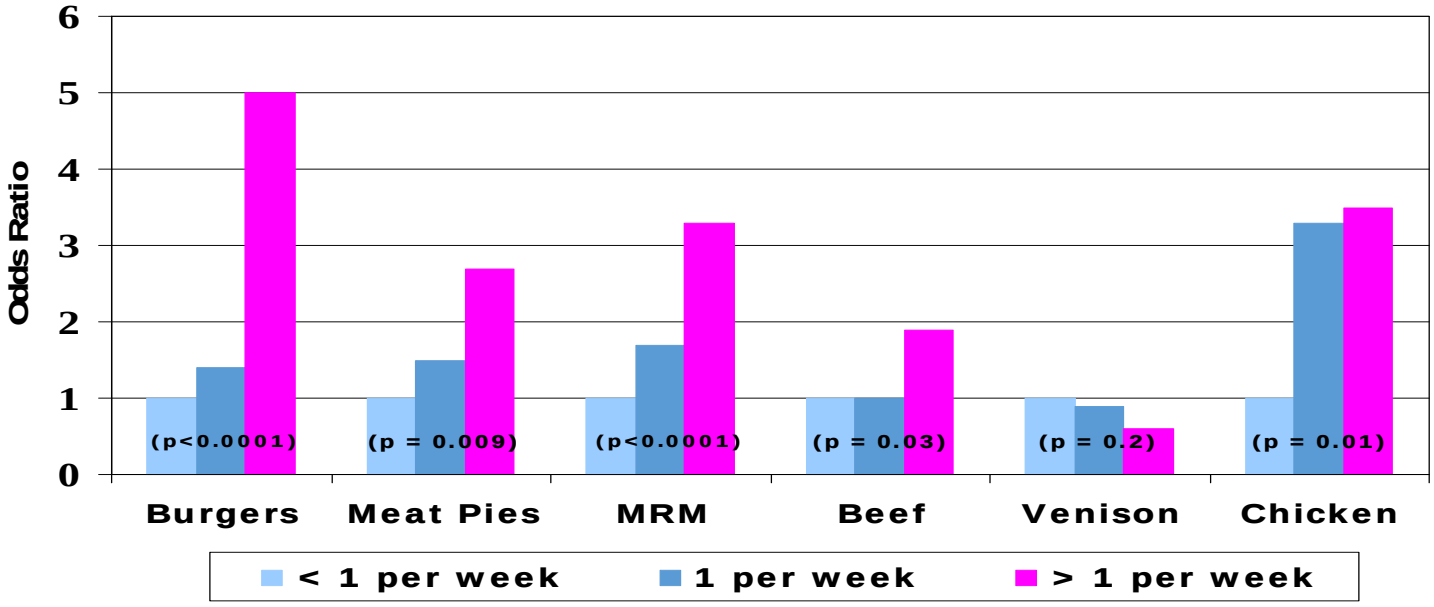
DIETARY RISK FACTORS
REPORTED AVERAGE FREQUENCY OF CONSUMPTION
SINCE 1980 OF SELECTED FOOD ITEMS

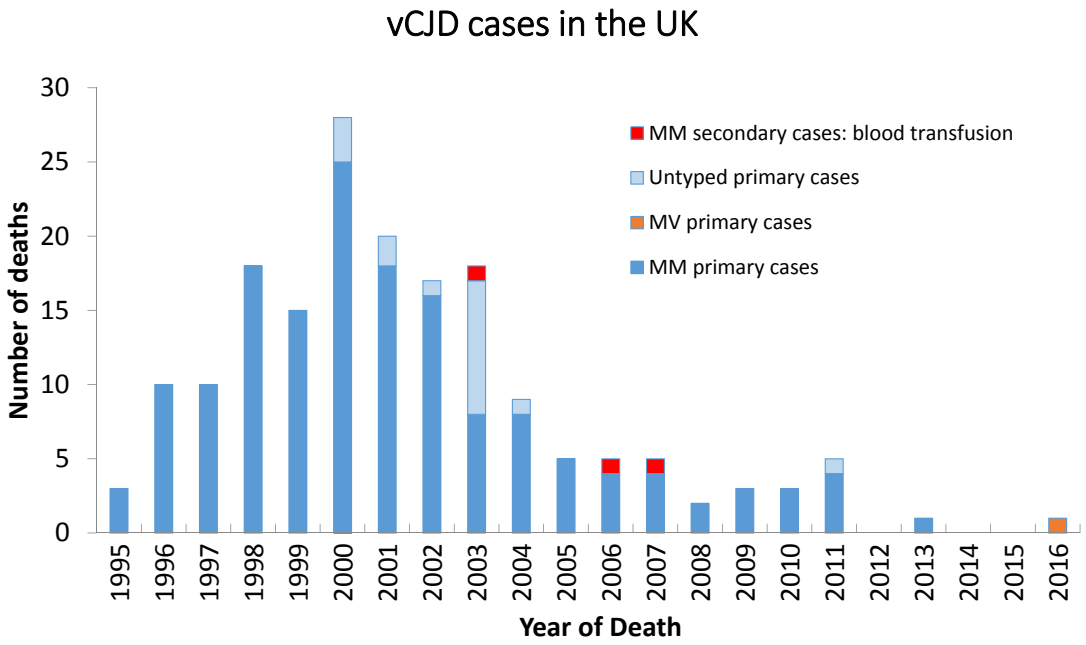
Ward et al Ann Neurol 59; 111-120: 2006

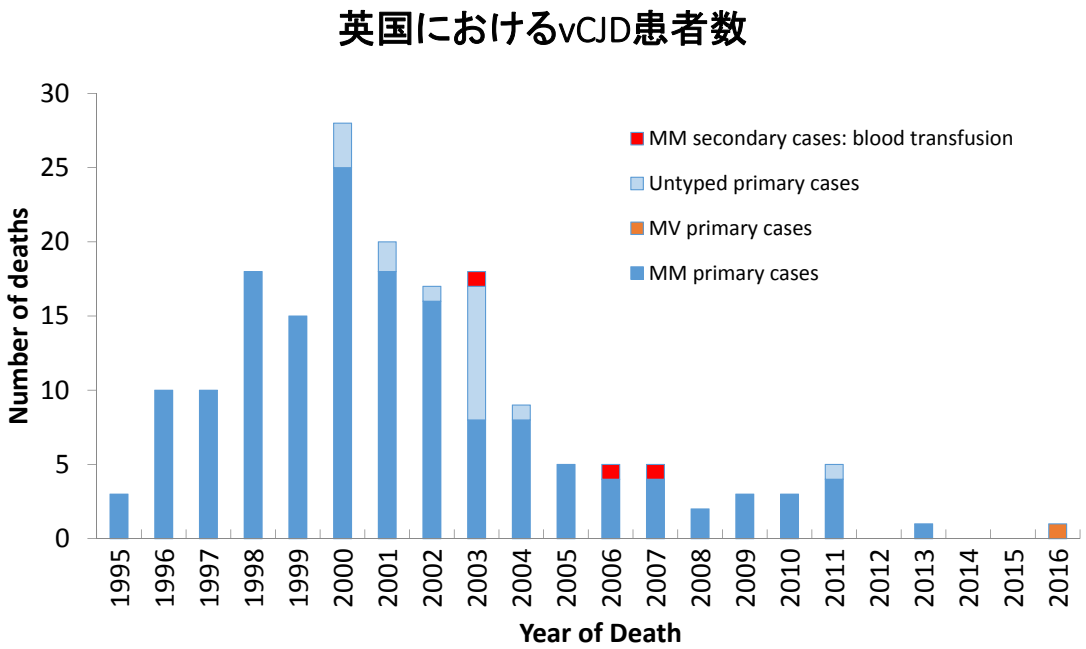


食事性の危害要因
特定の食品についての1980年以降の平均摂取頻度の報告値

Ward et al Ann Neurol 59; 111-120: 2006




vCJD cases in the UK
Number of deaths
30
25
20
15
10
5
0
MM secondary cases: blood transfusion
Untyped primary cases
MV primary cases
MM primary cases
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year of Death


英国におけるvCJD患者数
Number of deaths
30
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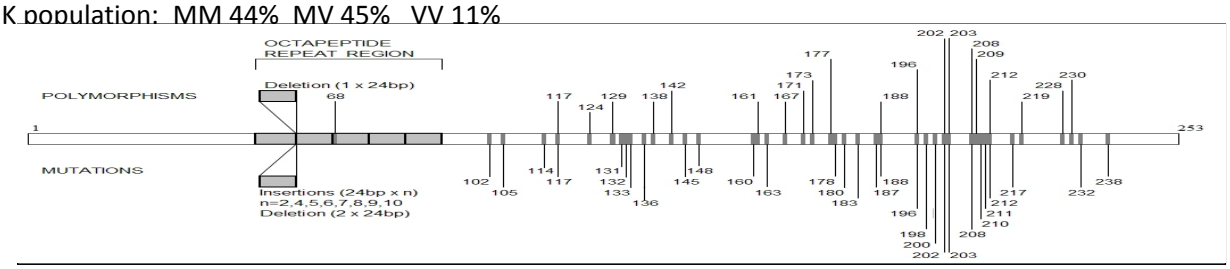
MM secondary cases: blood transfusion
Untyped primary cases
MV primary cases
MM primary cases
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year of Death

Codon 129 genotype in vCJD

- 160/161 tested cases in UK : MM
- 1/161 tested cases in UK : MV
- 52/52 cases outside UK: MM

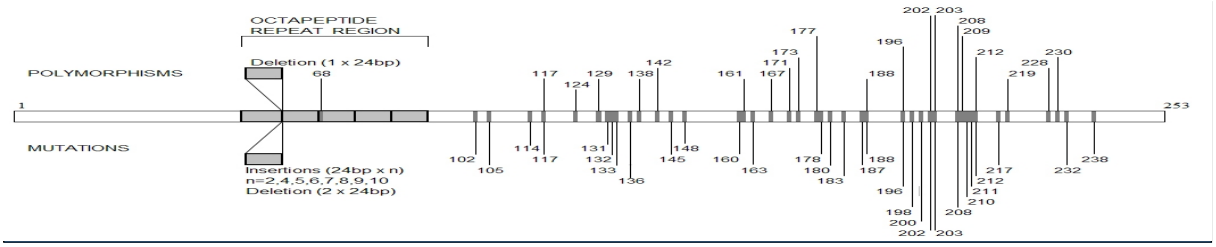
- Normal UK population: MM 44% MV 45% VV 11%



vCJDにおけるコドン129遺伝子型

- 160/161英国における検査事例 : MM
- 1/161英国における検査事例 : MV
- 52/52英国外の事例: MM

- 英国の一般集団: MM 44% MV 45% VV 11%



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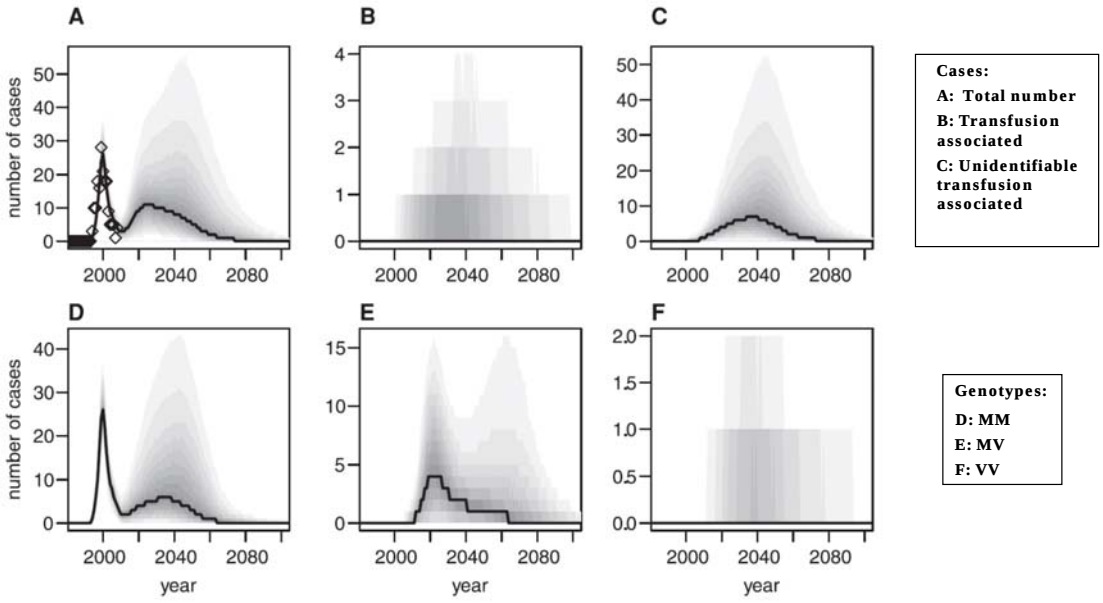
Median and posterior distributions of projected time series



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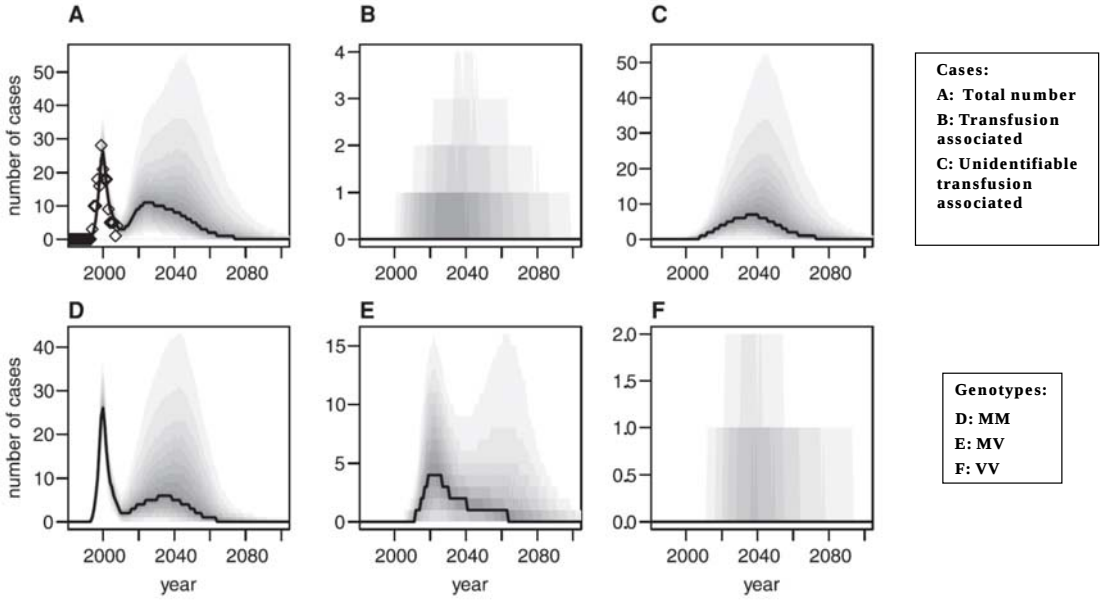
PLoS one

算定年代での中央値と事後分布



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What is the incubation period of vCJD?
Mathematical models (means)

11 years	(SD 1.5)	Post 1969 birth cohort	Cooper 2003
26 years	(SD 16.5)	1940-1969 birth cohort	Cooper 2003
16.5 years	(SD 2.8)		Boelle 2003
13 years	(median)		Belay 2006
13.5 years	(CI 10-19)	France	Chadeau-Hyam 2010
11.6 years	(CI 10.9-12.2)		Garske 2010
34 years	(CI 19-73)	MV	Garske 2010
52 years	(CI 26-77)	VV	Garske 2010

vCJDの潜伏期間とは?
数学的モデル（平均）

11 years	(SD 1.5)	Post 1969 birth cohort	Cooper 2003
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SD：標準偏差
Median：中央値
CI：信頼区間

Variant CJD in an individual heterozygous for *PRNP* codon 129

Diego Kaski, Simon Mead, Harpreet Hyare, Sarah Cooper, Ravi Jampana, James Overell, Richard Knight, John Collinge, Peter Rudge

www.thelancet.com Vol 374 December 19/26, 2009

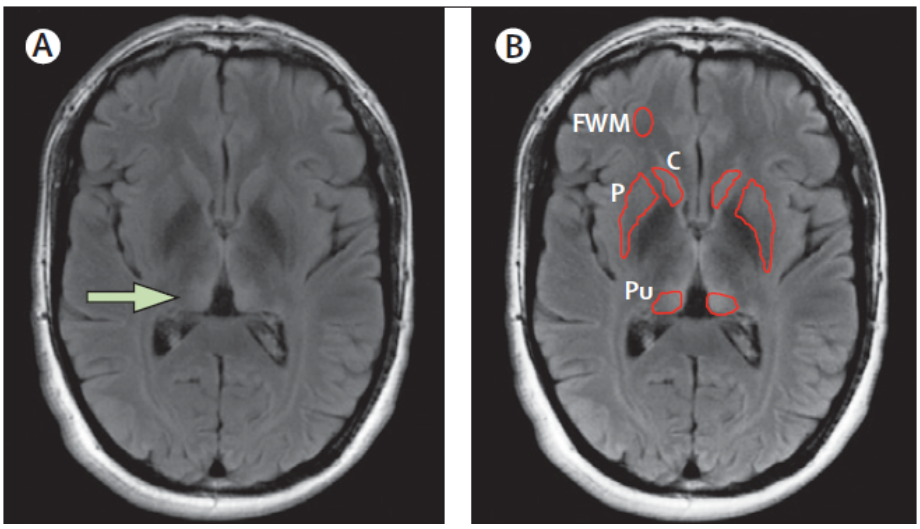

Figure: MRI
(A) Increased signal intensity in the pulvinar nucleus bilaterally (arrow).
(B) MR signal intensity in the pulvinar (Pu) is higher than in the head of the caudate nuclei (C), putamen (P), and right frontal white matter (FWM).

PRNPコドン129ヘテロ接合者における変異型クロイツフェルト・ヤコブ病

Diego Kaski, Simon Mead, Harpreet Hyare, Sarah Cooper, Ravi Jampana, James Overell, Richard Knight, John Collinge, Peter Rudge

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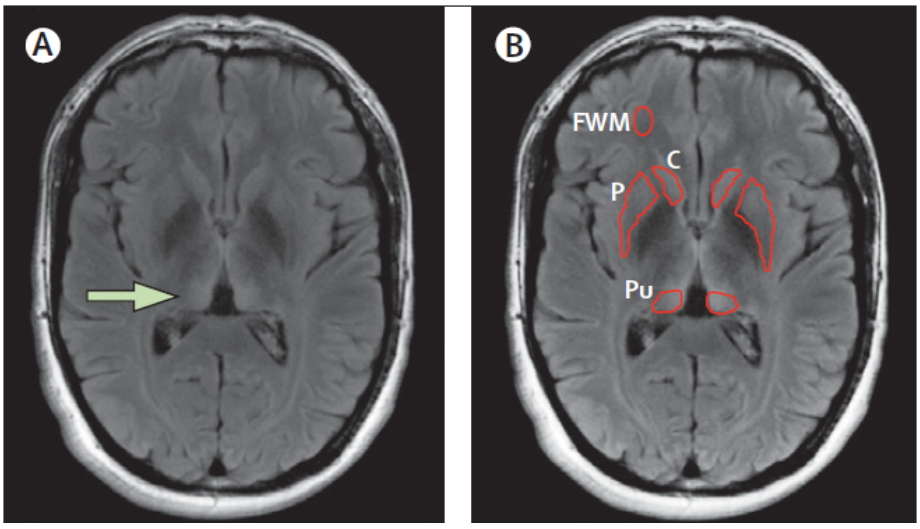

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(A) Increased signal intensity in the pulvinar nucleus bilaterally (arrow).
(B) MR signal intensity in the pulvinar (Pu) is higher than in the head of the caudate nuclei (C), putamen (P), and right frontal white matter (FWM).

Why has the vCJD outbreak been limited?

- UK population exposed to > **50,000,000** bovine ID 50s
  - 1 cattle ID 50 = **0.21G** (0.04-1.02G)

- **Significant species barrier with rare exposure to sufficient dose to result in infection**
- Non-PRNP genetic determinants with restricted susceptible population
- Co-factors enhancing chance of infection eg inflammatory bowel disease or dental procedures at the time of exposure

なぜ変異型CJDの発生は限られていたのか？

- UK population exposed to > **50,000,000** bovine ID 50s
  - 1 cattle ID 50 = **0.21G** (0.04-1.02G)

- **感染を引き起こすのに十分な量にばく露されることが稀であり、大きな動物種間バリアがある**
- 非PRNP遺伝的因子と一部の感受性集団
- 感染の機会を増幅する共因子：ばく露時の炎症性腸疾患または歯科処置

Estimation of the Exposure of the UK Population to the Bovine Spongiform Encephalopathy Agent through Dietary Intake During the Period 1980 to 1996

Chu-Chih Chen*, Yin-Han Wang

Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan

PLOS One April 2014 Volume 9 Issue 4 e94020

1980年から1996年までの英国民における、食事の摂取を通じた牛海綿状脳症プリオンへのばく露量の推計

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Furthermore, the threshold dose estimate of approximately 12 bID_{50} with an equivalent weight of 1.2g of a BSE infected bovine brain also appears reasonable, which may alternatively be interpreted as the species barrier between bovine and human.

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人での推定閾値が、BSE感染牛脳組織1.2gに相当する牛ID50（牛の50%感染量）の約12倍量であることも妥当と思われる。
このことは、牛と人の種間バリアと解釈することも可能である。

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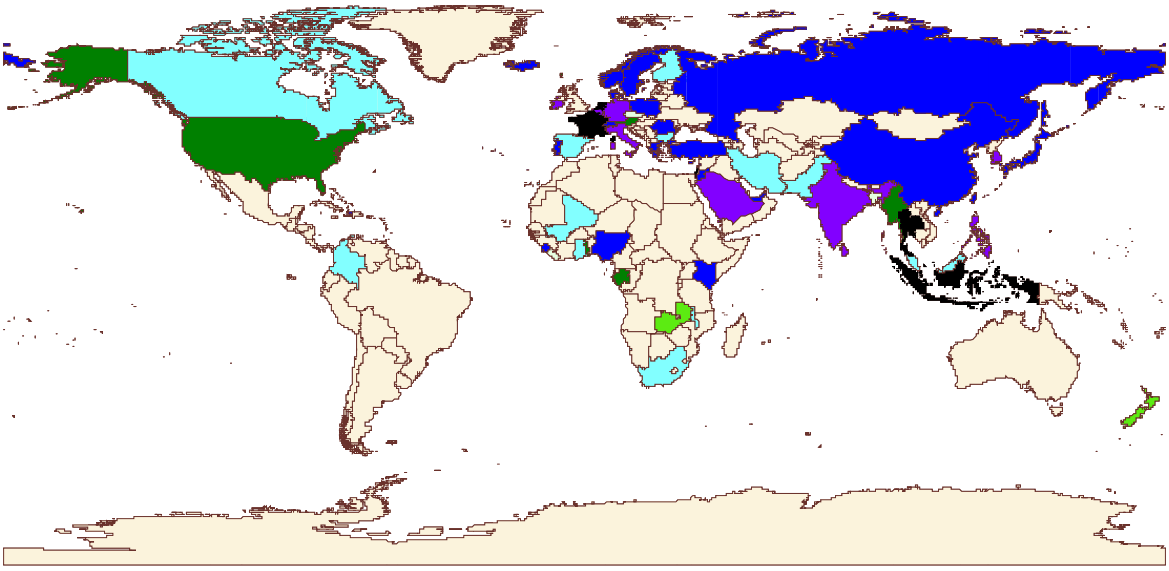
Total UK exports of MBM 1986 -1995

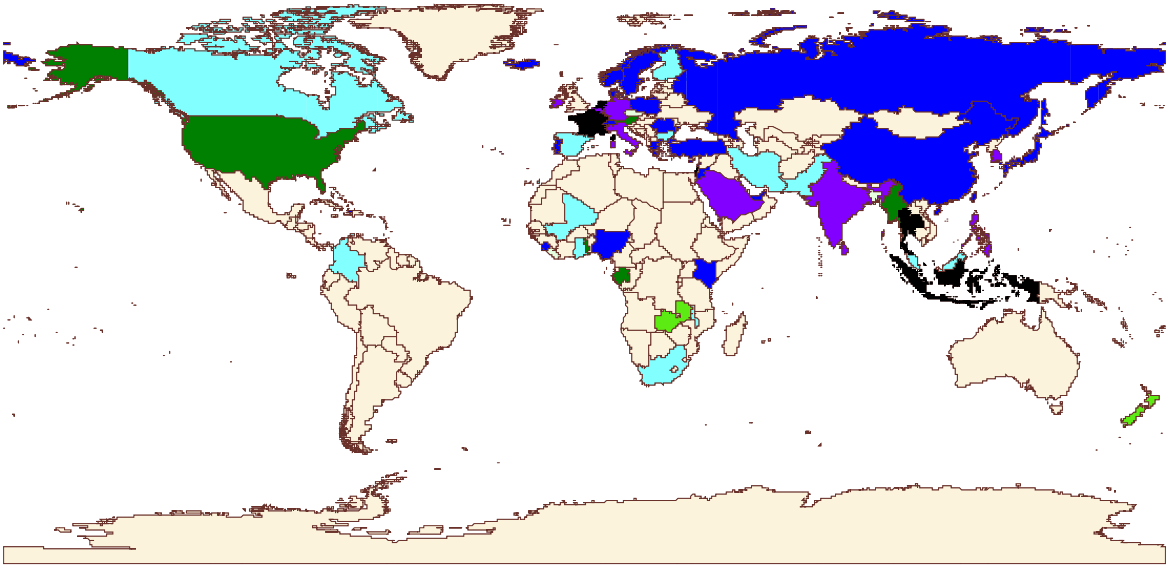


Legend:

(in tonnes)

No data		20 - < 100	
0 - < 5		100 - < 1.000	
5 - < 10		1.000 - < 10.000	
10 - < 20		> 10.000	

英国からの肉骨粉の輸出総量（1986 -1995）



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(in tonnes)

No data		20 - < 100	
0 - < 5		100 - < 1.000	
5 - < 10		1.000 - < 10.000	
10 - < 20		> 10.000	

VARIANT CJD CASES WORLDWIDE

COUNTRY	TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)	TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)	RESIDENCE IN UK > 6 MONTHS DURING PERIOD 1980-1996
UK	175 (0)	3 (0)	178[3]
France	27 (0)	-	1
Republic of Ireland	4 (0)	-	2
Italy	2 (0)	-	0
USA	4[1] (0)	-	2
Canada	2 (0)	-	1
Saudi Arabia	1 (0)	-	0
Japan	1[2] (0)	-	0
Netherlands	3 (0)	-	0
Portugal	2 (0)	-	0
Spain	5 (0)	-	0
Taiwan	1 (0)	-	1

1. 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 completed investigation of the fourth US patient did not support the patient's having had extended travel to European countries, including the United Kingdom or travel to Saudi Arabia. It confirmed that the case was in a US citizen born outside the Americas and indicated that his infection occurred before he moved to the United States; the patient had resided in Kuwait, Russia and Lebanon (see http://wwwnc.cdc.gov/eid/article/21/5/pdfs/14-2017.pdf
2. The case from Japan had resided in the UK for 24 days in the period 1980-1996.
3. Case 178 from the UK was methionine heterozygous at codon129 of the *PRNP* gene

April 2016

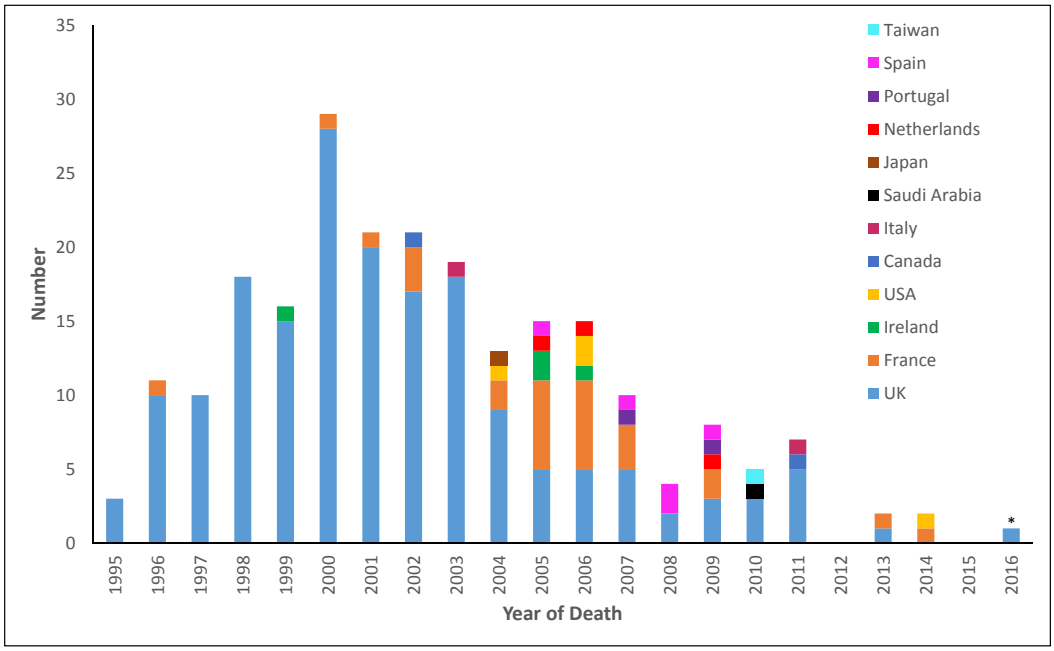
世界における変異型クロイツフェルト・ヤコブ病患者

国	PRIMARY CASES の総数 (生存者数)	SECONDARY CASES の総数: 輸血 (生存者数)	1980年から1996年の間、6か月より長期にわたり、英国に居住していた者
UK	175 (0)	3 (0)	178[3]
France	27 (0)	-	1
Republic of Ireland	4 (0)	-	2
Italy	2 (0)	-	0
USA	4[1] (0)	-	2
Canada	2 (0)	-	1
Saudi Arabia	1 (0)	-	0
Japan	1[2] (0)	-	0
Netherlands	3 (0)	-	0
Portugal	2 (0)	-	0
Spain	5 (0)	-	0
Taiwan	1 (0)	-	1

1. 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 completed investigation of the fourth US patient did not support the patient's having had extended travel to European countries, including the United Kingdom or travel to Saudi Arabia. It confirmed that the case was in a US citizen born outside the Americas and indicated that his infection occurred before he moved to the United States; the patient had resided in Kuwait, Russia and Lebanon (see http://wwwnc.cdc.gov/eid/article/21/5/pdfs/14-2017.pdf
2. The case from Japan had resided in the UK for 24 days in the period 1980-1996.
3. Case 178 from the UK was methionine heterozygous at codon129 of the *PRNP* gene

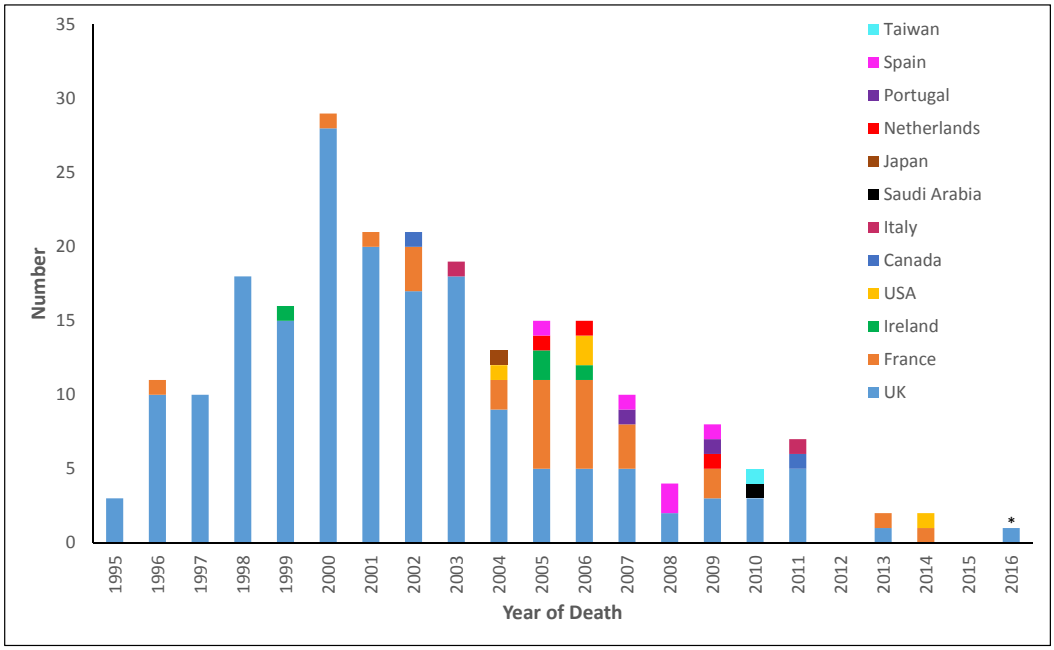
April 2016

vCJD CASES BY YEAR AND COUNTRY
1994-2016 (n=230)



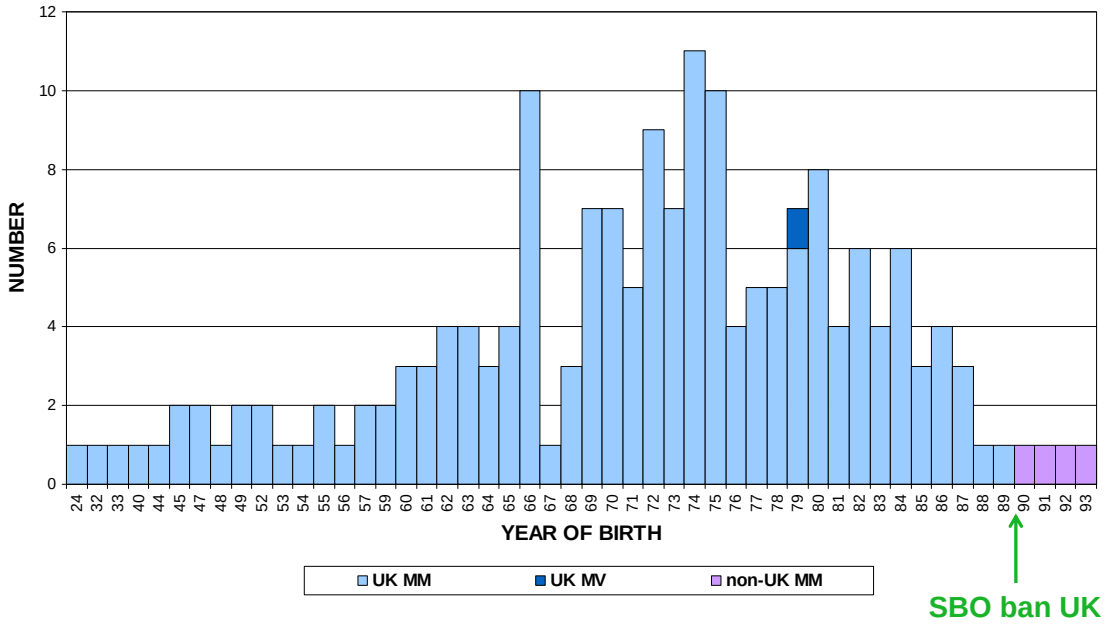
*MV at codon129 of the *PRNP* gene

年及び国別のvCJD患者数
1994-2016 (n=230)

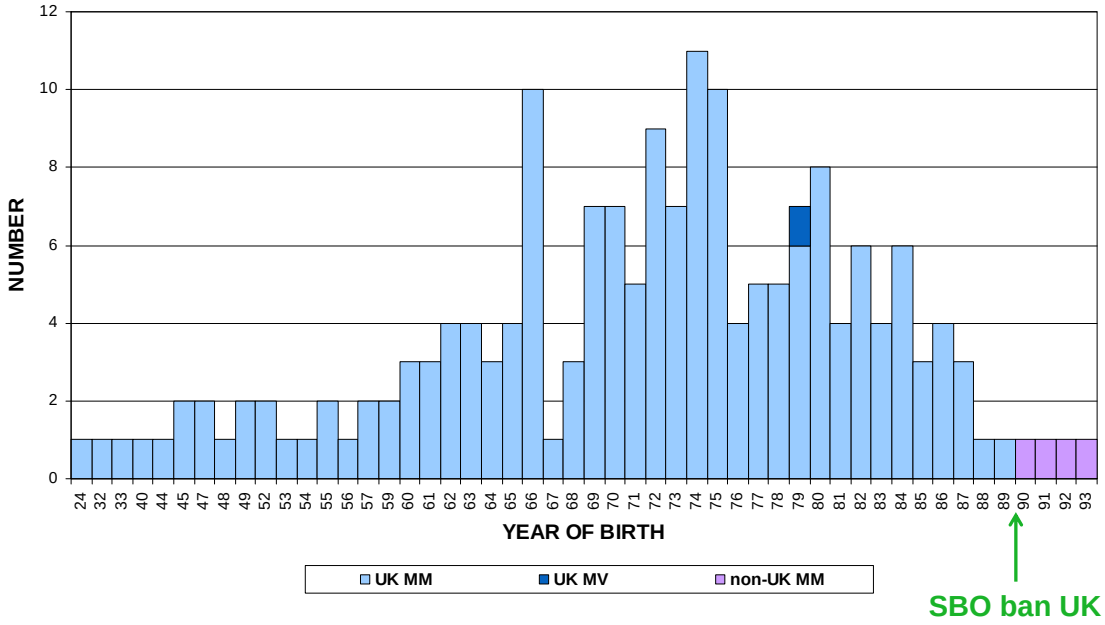


*MV at codon129 of the *PRNP* gene

UK CASES OF vCJD BY YEAR OF BIRTH AND NON-UK CASES BORN AFTER 1989



出生年別の英国における症例数及び1989 年以降出生のその他の国の症例数



Furthermore, the almost exact match between the predicted and observed vCJD cases and the threshold infectious dose estimate has greatly reduced the uncertainty regarding future incidents via the primary transmission route, food intake. However, the results obtained cannot infer the likelihood of secondary transmission from the asymptomatic carriers of prion disease.

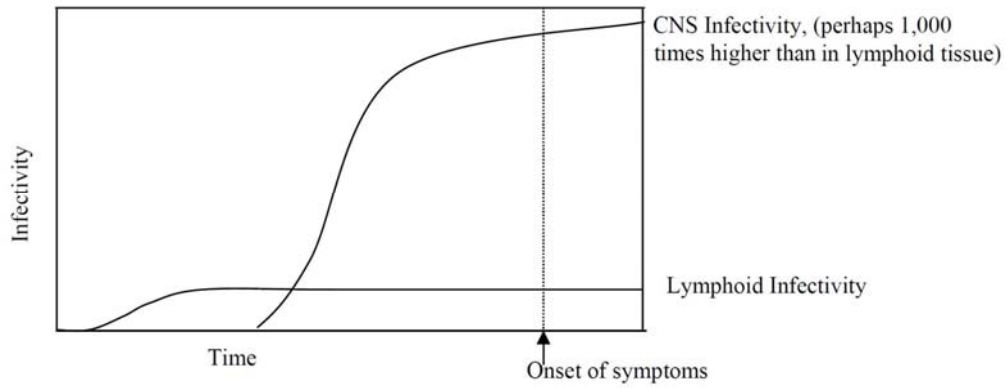
PLOS One April 2014 Volume 9 Issue 4 e94020

vCJDの予測数と確認数がほぼ完全に一致していたことに加え、人における推定感染閾値は、食品を介した伝達による今後の発生に関する不確実性を大幅に減少させた。
しかしながら、この結果からは、プリオン病の無症状キャリアーからの二次的な伝達の可能性を推察することはできない。

PLOS One April 2014 Volume 9 Issue 4 e94020

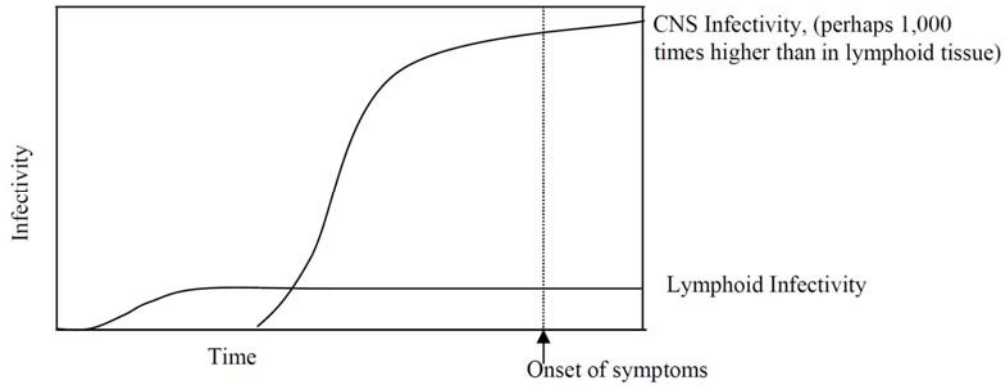
CJD INCIDENTS PANEL

Probable pattern of tissue infectivity in variant CJD, based on scrapie models



CJD INCIDENTS PANEL

スクレイピーのモデルに基づき推定された、vCJD感染者の組織の感染性の推移

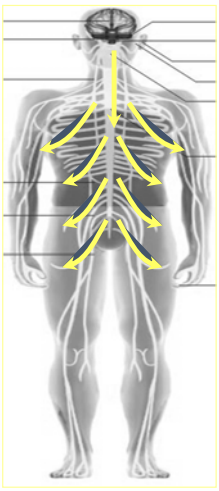


Tissue Infectivity in CJD

sCJD *centrifugal spread*

HIGH
Brain
Spinal cord
Cranial nerves & ganglia
Posterior eye
Pituitary gland

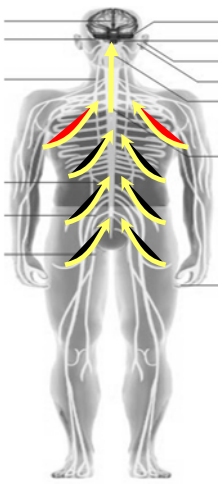
MEDIUM
Spinal ganglia
Olfactory epithelium



vCJD *peripheral pathogenesis*

HIGH
Brain
Spinal cord
Cranial nerves & ganglia
Posterior eye
Pituitary gland

MEDIUM
Spinal ganglia
Olfactory epithelium
Tonsil
Appendix
Spleen
Thymus
Adrenal gland
Lymph nodes and gut associated lymphoid tissue

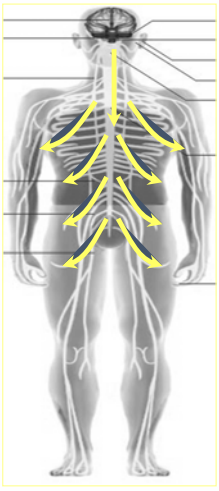


CJDにおける組織の感染性

sCJD **遠心性の分布**

高度
脳
脊髄
頭蓋神経及び神経節
後眼部
下垂体

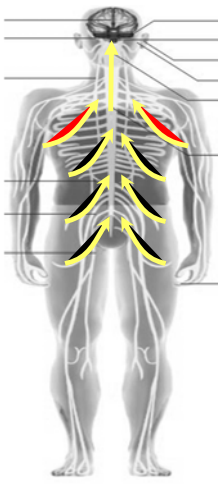
中程度
脊髄神経節
嗅上皮



vCJD **末梢組織の病原性**

高度
脳
脊髄
頭蓋神経及び神経節
後眼部
下垂体

中程度
脊髄神経節
嗅上皮
扁桃
虫垂
脾臓
胸腺
副腎
リンパ節及び腸管付属リンパ組織



THE TMER STUDY

(TRANSFUSION MEDICINE EPIDEMIOLOGY REVIEW)

- National Blood Service
- Scottish National Blood Transfusion Service
- Welsh Blood Service
- Northern Ireland Blood Transfusion Service
- National CJD Surveillance Unit
- Office of National Statistics

TMER研究

(輸血医学疫学レビュー)

- National Blood Service
- Scottish National Blood Transfusion Service
- Welsh Blood Service
- Northern Ireland Blood Transfusion Service
- National CJD Surveillance Unit
- Office of National Statistics

Articles

Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion

C A Llewelyn, P E Hewitt, R S G Knight, K Amar, S Cousens, J Mackenzie, R G Will

Summary

Background Variant Creutzfeldt-Jakob disease (vCJD) is a novel human prion disease caused by infection with the agent of bovine spongiform encephalopathy (BSE). Epidemiological evidence does not suggest that sporadic CJD is transmitted from person to person via blood transfusion, but this evidence may not apply to vCJD. We aimed to identify whether vCJD is transmissible through blood transfusion.

Introduction

Human prion diseases include sporadic Creutzfeldt-Jakob disease (CJD), which is of unknown cause; hereditary forms associated with mutations of the prion protein gene; variant CJD (vCJD), which has been causally linked to the bovine spongiform encephalopathy (BSE) agent; and iatrogenic cases transmitted via human pituitary hormones, human dura mater grafts, corneal grafts, and neurosurgical devices. All instances of iatrogenic transmission of CJD to date have been due to cross-

論文：輸血による変異型クロイツフェルト・ヤコブ病伝達の可能性

ARTICLES

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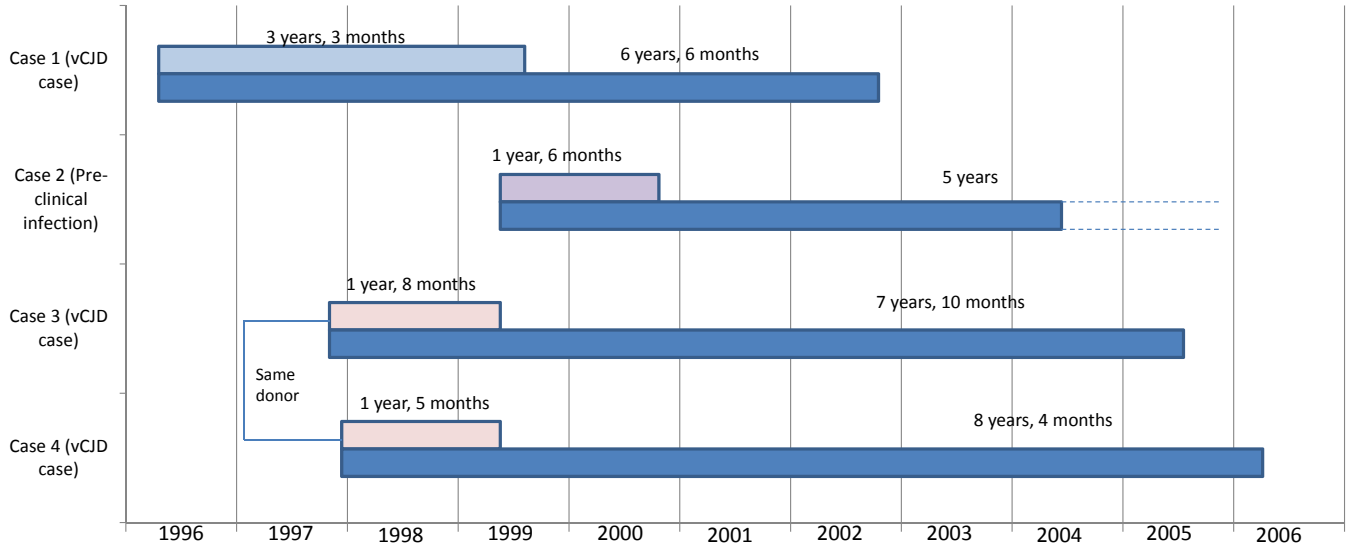
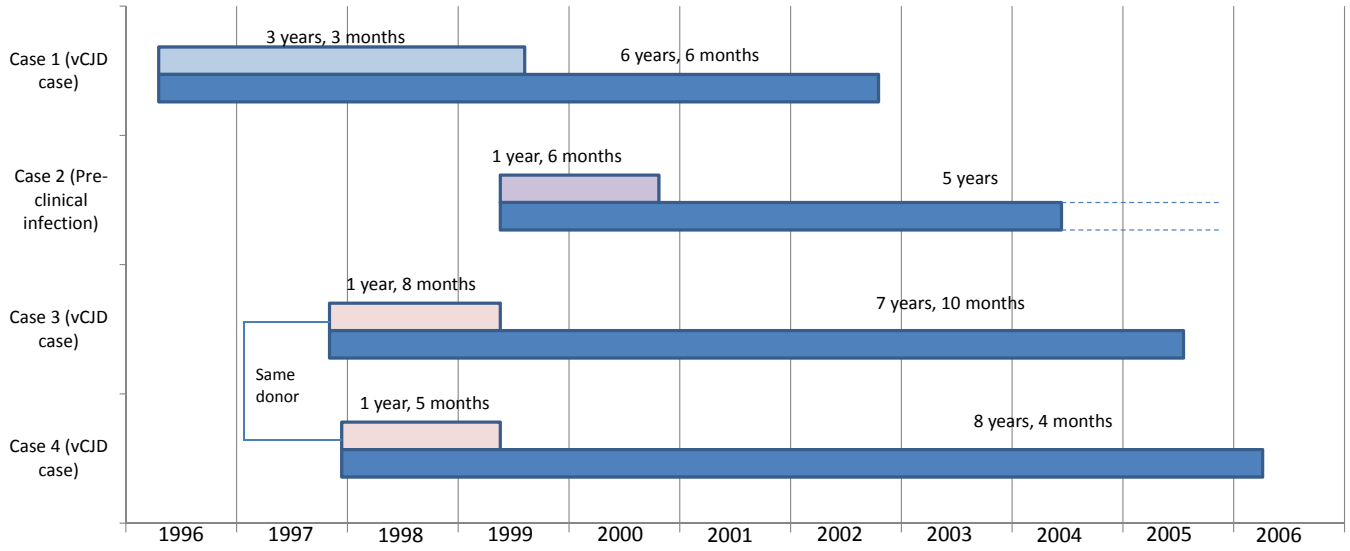
TRANSFUSION TRANSMISSION OF vCJD



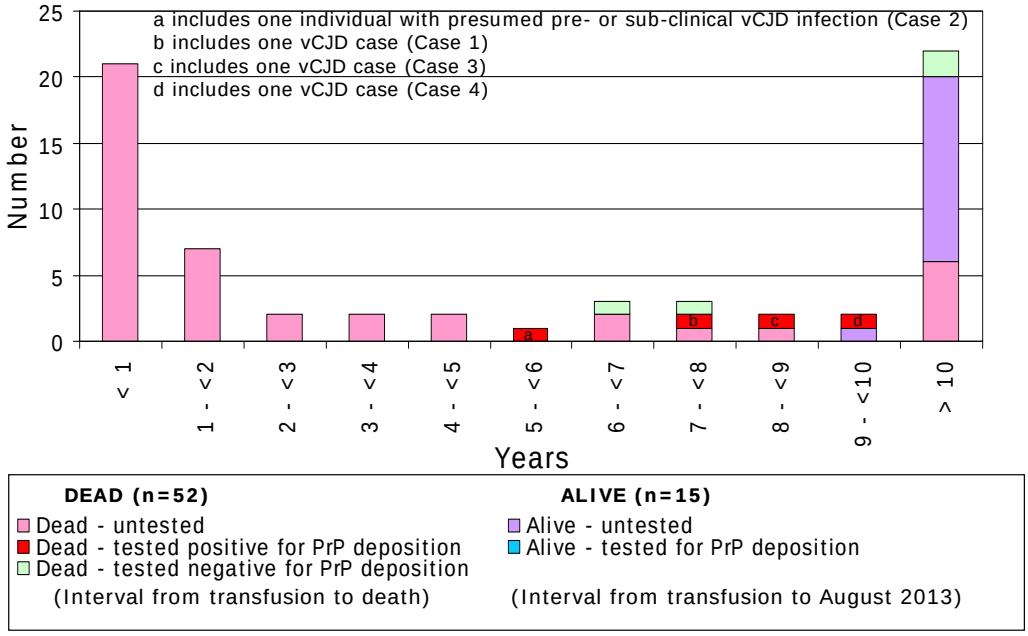
Interval from recipient transfusion to disease onset in donor (top bar) and interval from transfusion to disease onset in recipient (bottom bar)

輸血によるvCJDの伝達

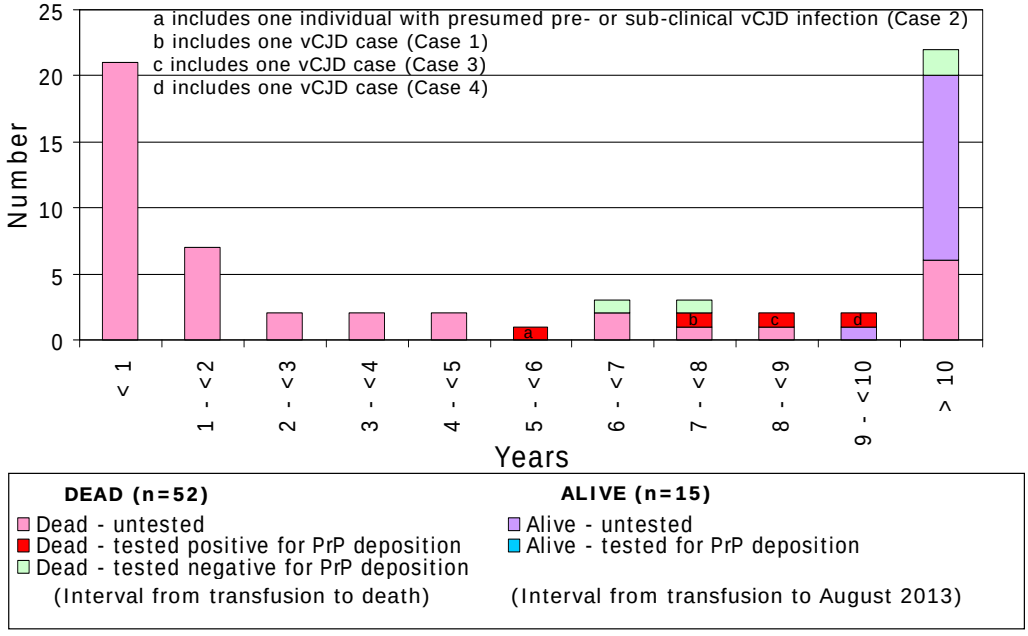


輸血から供血者の発症までの期間（上のバー）
輸血から受血者の発症までの期間（下のバー）

RECIPIENTS OF LABILE BLOOD COMPONENTS DONATED BY vCJD CASES (n=67)

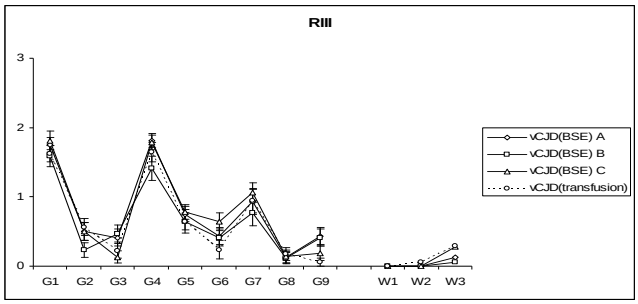


vCJD患者から提供された血液成分(Labile Blood Components)の受血者 (n=67)



No Major Change in vCJD Agent Strain after Secondary Transmission via Blood Transfusion

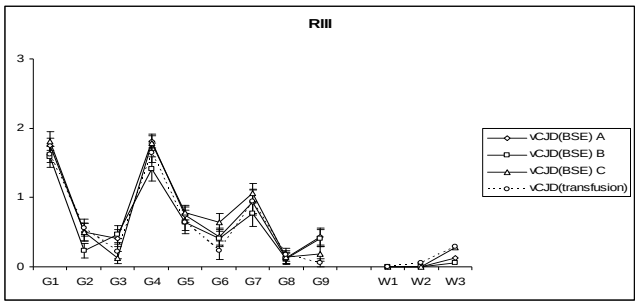
Matthew T. Bishop, Diane L. Ritchie, Robert G. Will, James W. Ironside, Mark W. Head, Val Thomson, Moira Bruce, Jean C. Manson



Citation: 2008 PLoS ONE 3(8): e2878. doi:10.1371/journal.pone.0002878

輸血による二次的伝達後に、vCJDプリオンに大きな変化は見られない

Matthew T. Bishop, Diane L. Ritchie, Robert G. Will, James W. Ironside, Mark W. Head, Val Thomson, Moira Bruce, Jean C. Manson



Citation: 2008 PLoS ONE 3(8): e2878. doi:10.1371/journal.pone.0002878

Brain Advance Access published February 28, 2013
doi:10.1093/brain/awt032 Brain 2013: Page 1 of 7 | 1
BRAIN
A JOURNAL OF NEUROLOGY

Prion infectivity in the spleen of a *PRNP* heterozygous individual with subclinical variant Creutzfeldt–Jakob disease

Matthew T. Bishop, Abigail B. Diack, Diane L. Ritchie, James W. Ironside, Robert G. Will and Jean C. Manson

This study provides definitive evidence that spleen tissue from an asymptomatic individual contains variant Creutzfeldt-Jakob disease infectivity and that the variant Creutzfeldt-Jakob disease agent retains infectivity following passage through an MV genotype host.

論文：無症状の変異型クロイツフェルト・ヤコブ病を罹患しているPRNPヘテロ接合者の脾臓のプリオン感染性

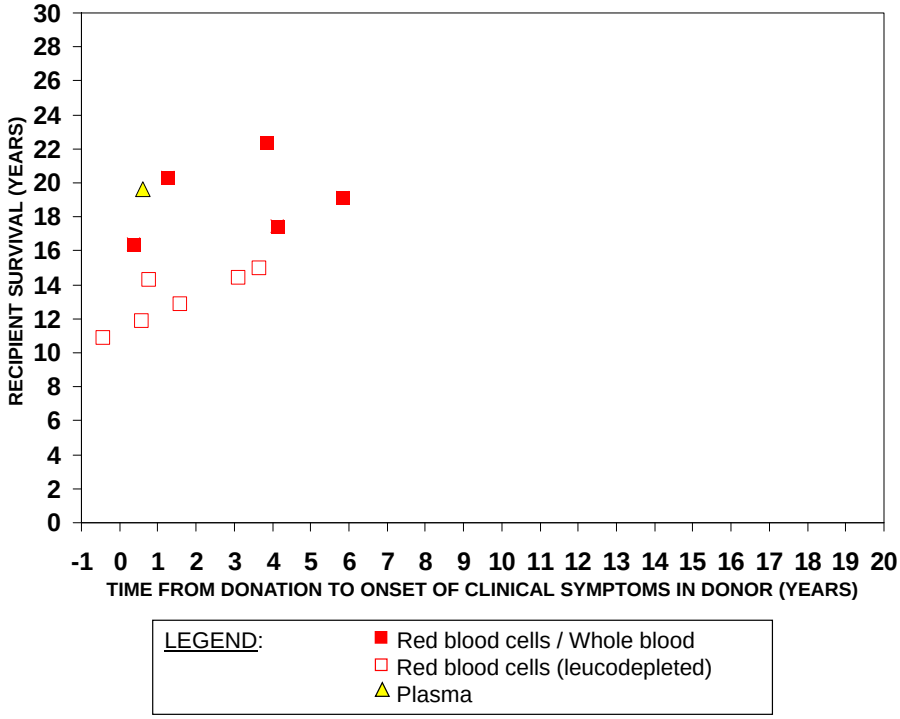
Brain Advance Access published February 28, 2013
doi:10.1093/brain/awt032 Brain 2013: Page 1 of 7 | 1
BRAIN
A JOURNAL OF NEUROLOGY

Prion infectivity in the spleen of a *PRNP* heterozygous individual with subclinical variant Creutzfeldt–Jakob disease

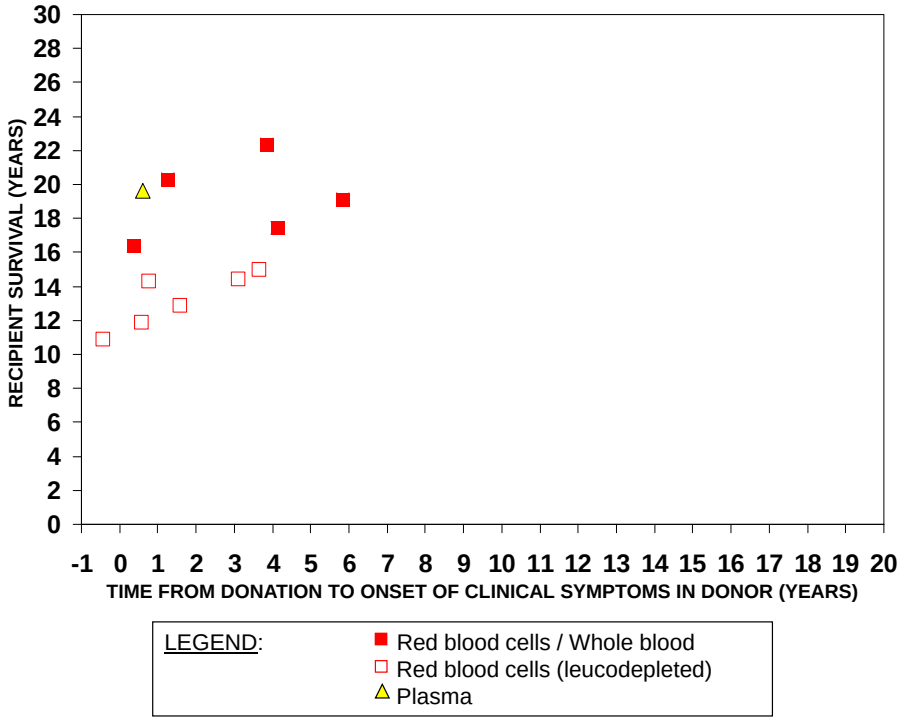
Matthew T. Bishop, Abigail B. Diack, Diane L. Ritchie, James W. Ironside, Robert G. Will and Jean C. Manson

本研究は、症状を示していない人から採取された脾臓の組織が、変異型クロイツフェルト・ヤコブ病の感染性を有していること、ならびに、MV遺伝子型宿主での継代後も、変異型クロイツフェルト・ヤコブ病因子が感染性を保持していることを明確に証明している。

Survival of live recipients (n=14) of components from vCJD donors according to interval between donation and onset of clinical symptoms in donor (as at May 2015)



vCJD患者の血液成分を受血した者の生存期間（投与時点から発症時点までの期間との関係）（2015年5月現在）



RECIPIENTS ALIVE
WITH CODON 129 STATUS AVAILABLE

AGE	CODON 129	TIME SINCE TRANSFUSION TO 11 MAY 2015	DONATION TO ONSET IN DONOR
77	MV	22 yrs	3.85 yrs
58	MV	20 yrs	1.25 yrs
51	MV	16 yrs	5 months*
67	MM	13 yrs[a]	1.6 yrs
48	MM	12 yrs[a]	7 months

*same donor as 2 of the transfusion transmitted cases
(tonsil biopsy negative – June 2008)
[a] leucodepleted

コドン129の情報が入手可能である生存受血者

年齢	コドン129	輸血から2015年5月11日までの期間	供血者における供血から発症までの期間
77	MV	22 yrs	3.85 yrs
58	MV	20 yrs	1.25 yrs
51	MV	16 yrs	5 months*
67	MM	13 yrs[a]	1.6 yrs
48	MM	12 yrs[a]	7 months

*same donor as 2 of the transfusion transmitted cases
(tonsil biopsy negative – June 2008)
[a] leucodepleted

Public Health England

Enhanced surveillance of people at increased risk of Creutzfeldt-Jakob Disease
Biannual Report, February 2015

Summary of groups identified as at increased risk of CJD on which data are collected (Data correct as at 31st December 2014)

'At risk' Group	Identified as 'at risk'	Number notified as being 'at risk'		Cases	Asymptomatic infections [a]
		All	Alive		
Recipients of blood from donors who later developed vCJD	67	27	14	3	1
Blood donors to individuals who later developed vCJD	112	108	104	0	0
Other recipients of blood components from these donors (reverse risk recipients)	34	32[b]	18	0	0
Plasma product recipients (non-bleeding disorders) who received UK sourced plasma products 1980-2001 [c]	2	2	2	0	0
Certain surgical contacts of patients diagnosed with CJD	196	163 [d]	139[e]	0	0
Highly transfused recipients [f]	3	3	3	0	0

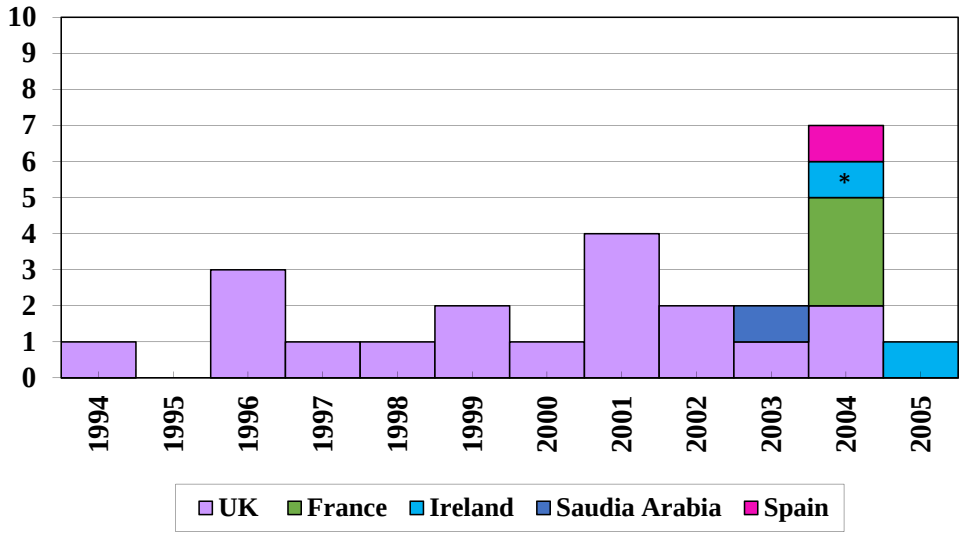
Public Health England

クロイツフェルト・ヤコブ病のリスクが高い人々に関する拡大サーベイランス
Biannual Report, February 2015

データ収集によりCJDのリスクが高いと特定されたグループの概要
（収集データは2014年12月31日現在のもの）

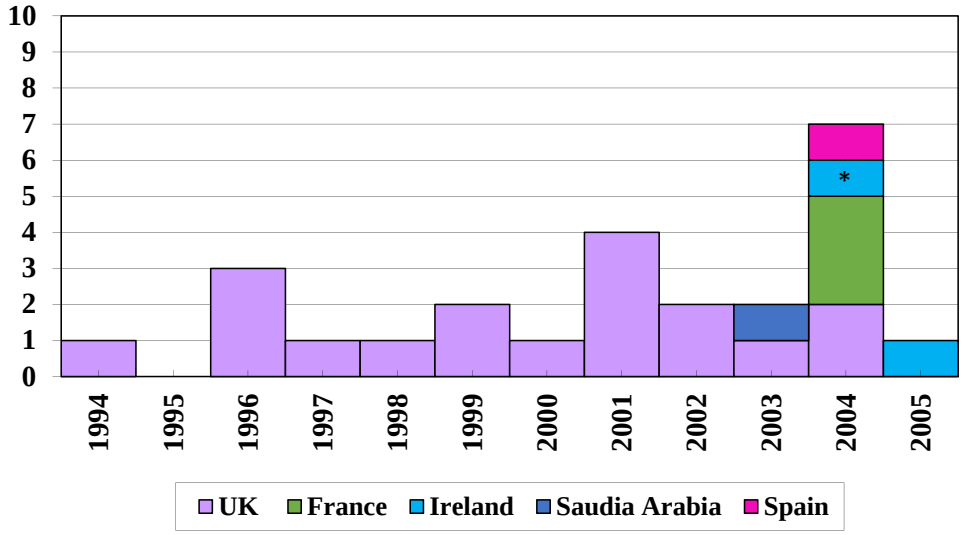
'At risk' Group	Identified as 'at risk'	Number notified as being 'at risk'		Cases	Asymptomatic infections [a]
		All	Alive		
後にvCJDを発症した供血者からの受血者	67	27	14	3	1
後にvCJDを発症した受血者への供血者	112	108	104	0	0
これら供血者からの他の受血者	34	32[b]	18	0	0
UK（1980-2001）製の血漿製剤を受けた者	2	2	2	0	0
CJDと診断された患者との外科的接触	196	163 [d]	139[e]	0	0
高度に輸血された者	3	3	3	0	0

VARIANT CJD BLOOD DONORS BY YEAR OF ONSET



*one case from Ireland with onset in 2004 was a blood donor while resident in the UK – recipients not identified

発症年別　変異型CJD供血者



*one case from Ireland with onset in 2004 was a blood donor while resident in the UK – recipients not identified

PLASMA FROM vCJD DONORS SENT FOR FRACTIONATION WITHIN UK

YEAR SENT	NUMBER OF UNITS
1986	1
1987	4
1989	1
1990	2
1991	1
1992	3
1993	2
1994	2
1995	2
1996	4
1997	2
1998	1
TOTAL	25

英国内で分画のために送られたvCJD供血者の血漿

YEAR SENT	NUMBER OF UNITS
1986	1
1987	4
1989	1
1990	2
1991	1
1992	3
1993	2
1994	2
1995	2
1996	4
1997	2
1998	1
TOTAL	25

VoxSanguinis
The International Journal of Transfusion Medicine

Variant Creutzfeldt–Jakob disease and exposure to fractionated plasma products

H. J. T. Ward,[1] J. M. MacKenzie,[1] C. A. Llewelyn,[2] R. S. G. Knight,[1] P. E. Hewitt,[3] N. Connor,[4] A. Molesworth[4] & R. G. Will[1]

Results Nine out of 168 UK vCJD cases had a history of receipt of fractionated plasma products on 12 different occasions (1 pre-vCJD risk in 1970, the remaining between 1989-1998). According to the UK CJD Incident Panel risk assessment criteria, 11 were low-risk products and one was low or medium risk.

Conclusions It is unlikely that any of the UK vCJD clinical cases to date were infected through exposure to fractionated plasma products. However, the possibility that such transmission may result in vCJD cases in the future cannot be excluded.

Vox Sanguinis (2009) **97**, 207–210

VoxSanguinis
The International Journal of Transfusion Medicine

論文：変異型クロイツフェルト・ヤコブ病と血漿分画製品へのばく露

Variant Creutzfeldt–Jakob disease and exposure to fractionated plasma products

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結果
英国におけるvCJD症例168例中9例は、12の異なる血漿分画製品(1 pre-vCJD risk in 1970, the remaining between 1989-1998)を受血したという経緯がある。
英国CJD発生パネルのリスク評価基準によれば、11件は低リスク製品で、もう1件は低もしくは中リスク製品である。

結論
今日までに確認されている英国におけるvCJD症例のいずれについても、血漿分画製品へのばく露を通じて感染した可能性は低い。しかしながら、将来的に、そのような伝達経路でvCJDが発生する可能性は否定できない。

Vox Sanguinis (2009) **97**, 207–210

Haemophilia

Haemophilia (2010), 16, 296–304 DOI: 10.1111/j.1365-2516.2009.02181.x

ORIGINAL ARTICLE *Transfusion transmitted disease*

Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia

A. PEDEN,* L. MCCARDLE,* M. W. HEAD,* S. LOVE,† H. J. T. WARD,* S. N. COUSENS,‡ D. M. KEELING,§ C. M. MILLAR,¶ F. G. H. HILL** and J. W. IRONSIDE*

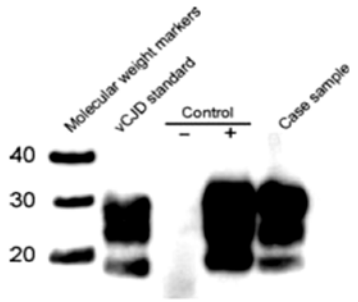

Fig. 1. Sodium phosphotungstic acid (NaPTA) precipitation/Western blotting analysis of spleen tissue samples for the presence of protease-resistant prion protein (PrP^{res}).

Haemophilia

Haemophilia (2010), 16, 296–304 DOI: 10.1111/j.1365-2516.2009.02181.x

論文：血友病を罹患している、神経学的に無症状な英国の成人患者の脾臓のvCJD感染性

ORIGINAL ARTICLE *Transfusion transmitted disease*

Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia

A. PEDEN,* L. MCCARDLE,* M. W. HEAD,* S. LOVE,† H. J. T. WARD,* S. N. COUSENS,‡ D. M. KEELING,§ C. M. MILLAR,¶ F. G. H. HILL** and J. W. IRONSIDE*

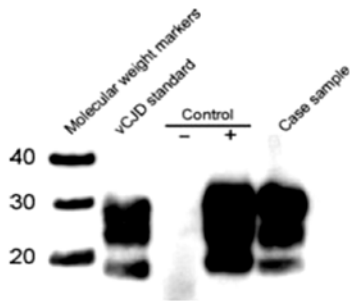

Fig. 1. Sodium phosphotungstic acid (NaPTA) precipitation/Western blotting analysis of spleen tissue samples for the presence of protease-resistant prion protein (PrP^{res}).

VoxSanguinis
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Removal of TSE agent from plasma products manufactured in the United Kingdom

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Results Many of the manufacturing process steps produced significant reduction in the scrapie agent. Particularly effective were steps such as ethanol fractionation, depth filtration, ion-exchange and copper chelate affinity chromatography. Virus retentive filters, of nominal pore size 15 or 20 nm, removed >3 log. The total cumulative reduction capacity for individual products was estimated to range from 7 to 14 log. In the case of factor VIII (8Y), the total removal was limited to 3 log.

Conclusions All the processes showed a substantial capacity to remove the TSE agent. However, this was more limited for the intermediate purity factor VIII 8Y which included fewer manufacturing steps.

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論文：英国において製造された血漿製品からのTSE因子の除去

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結果
製造プロセスの多くがスクレイピー因子を大幅に減少させる。特に、エタノール分画、深層濾過、イオン交換及び銅キレートアフィニティークロマトグラフィーなどのステップが効果的。
孔径15もしくは20nmのウイルス保持性フィルターは、3 logを超える低減効果を示した。個々の製品に対する総累積低減効果は、7から14logの間と推測される。VIII (8Y)因子の場合、総低減効果は3logにとどまった。

結論
全てのプロセスが、相当なTSE因子除去能を示した。
しかし、製造ステップの数が少ない、中程度精製VIII (8Y)因子に対しては、この除去能は比較的低かった。

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BMJ

BMJ 2013;347:f5675 doi: 10.1136/bmj.f5675

RESEARCH

Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey

O Noel Gill *head of department*[1], Yvonne Spencer *head of pathology*[2], Angela Richard-Loendt *senior research histologist*[3], Carole Kelly *senior CJD scientist*[1], Reza Dabaghian *senior scientific and technical manager*[4], Lynnette Boyes *histologist*[3], Jacqueline Linehan *senior research histologist*[5], Marion Simmons *veterinary research pathologist, head of EU Reference Laboratory for TSE*[2], Paul Webb *pathology research scientist*[2], Peter Bellerby *pathology research scientist*[2], Nick Andrews *senior statistician*[1], David A Hilton *consultant neuropathologist*[6], James W Ironside *professor of clinical neuropathology*[7], Jon Beck *research scientist*[5], Mark Poulter *research scientist*[5], Simon Mead *reader in neurology, consultant neurologist*[5], Sebastian Brandner *professor of neuropathology, honorary consultant neuropathologist*[3]

- 16/32,441 samples positive
- 493 per million (95%CI: 282-801)
- 1 in 2,000
- Codon 129: MM 8, MV 4, VV 4

論文：BSE流行後の人の虫垂における異常プリオンたん白の分布：大規模調査

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BLOOD-BORNE TRANSMISSION OF vCJD
RE-EXAMINATION OF SCENARIOS

Summary of issues by UK Blood Services 1999-2009 (SHOT, 2010)

Year	Red Blood Cells	Platelets	FFP	Cryoprecipitate	Totals
1999–2000	2,737,572	249,622	365,547	94,114	**3,446,855**
2000–2001	2,706,307	250,259	374,760	95,456	**3,426,782**
2001–2002	2,679,925	251,451	385,236	88,253	**3,404,865**
2002–2003	2,678,098	251,741	377,381	92,768	**3,399,988**
2003–2004	2,607,410	264,539	372,855	95,417	**3,340,221**
2004–2005	2,428,934	258,528	313,019	102,719	**3,103,200**
2005–2006	2,316,152	259,654	320,852	106,139	**3,002,797**
2006–2007	2,235,638	255,474	306,444	116,672	**2,914,228**
2007–2008	2,174,256	258,419	295,085	117,699	**2,845,459**
2008–2009	2,209,153	266,312	306,740	121,555	**2,903,760**

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RE-EXAMINATION OF SCENARIOS
血液由来のvCJD伝達　シナリオの再検討

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Current studies

Further Survey of Archived Appendix Specimens
Public Health England & partners

3 year study

- Samples prior to the BSE outbreak (pre-1980)
- Samples after further measures put in place to protect the human food chain (post-1996)

最新の研究

保管されていた虫垂標本に関するさらなる調査
Public Health England & partners

3年間の研究

- BSE発生の前に採取された標本（1980年以前）
- 人のフードチェーンを守るためのさらなる措置が講じられた後に採取された標本（1996年以降）

Continuing public health concerns

- Prevalence of human BSE infection
- vCJD in non-MM genotypes
- Transmission by blood and plasma products
- ?Surgical transmission of vCJD
- ?Vertical transmission of vCJD
- Atypical BSE/scrapie
- Chronic wasting disease of deer (North America/South Korea/Norway)
- Countries exposed to BSE with inadequate animal or human surveillance

公衆衛生上の懸念

- 人におけるBSE感染の実態
- 非MM遺伝子型におけるvCJD
- 血液及び血漿製品による伝達
- vCJDの手術による感染？
- vCJDの垂直感染？
- 非定型BSE/scrapie
- 鹿の慢性消耗性疾患（北米、韓国、ノルウェー）
- 動物または人のサーベイランスが不十分な国におけるBSEへのばく露

Staff at the NCJDRSU

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- Richard Knight
- Alison Green
- Mark Head
- Matthew Bishop
- Patrick Urwin
- Michelle Gillies
- Gurjit Chohan
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Clinicians throughout the UK

Patients and their families

The Roslin Institute

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