

Origins of BSE, past and present, in Great Britain

Dr James Hope
Animal and Plant Health Agency, UK

Science of BSE and Food Safety Conference
Food Safety Commission Japan, Tokyo
May 11th, 2016



英国における BSEの起源、過去及び現在

ジェームス・ホープ
英国動植物衛生庁

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Prion diseases

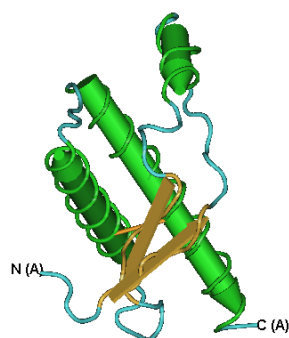
- Bovine spongiform encephalopathy, Creutzfeldt-Jakob disease, scrapie
 - Loss of neurons, gliosis and vacuolation. Amyloidosis.
 - Long, asymptomatic incubation periods
 - Inherited, acquired, sporadic
 - Prions and the prion protein

プリオン病

- 牛海綿状脳症、クロイツフェルト・ヤコブ病、スクレイピー
- 神経の消失、グリオースिस及び空胞形成。アミロイド沈着。
 - 長期間にわたる、無症状性の潜伏期間
 - 遺伝性、後天性、孤発性
 - プリオン及びプリオンたん白

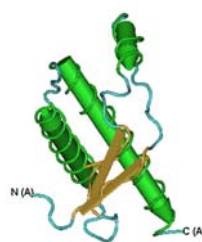
Prions and Prion Diseases

- What is a prion?
- What is a prion disease?



プリオン及びプリオン病

- プリオンとは？
- プリオン病とは？





An appeal to Europe's leaders - Get a grip on the refugee crisis P5&11

Alzheimer's may be infectious disease

» 'Seeds' of illness could be passed via infected blood and tissue
 » Shock finding raises fears about the safety of some surgery
 » Caring for someone with dementia does not pose any risk

SPECIAL REPORT P6

The essential daily briefing
 FROM THE INDEPENDENT

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Apocalypse Slough
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COVER STORY

Alzheimer's 'may be transmitted by surgery and blood transfusions'

By Anne Corcoran
WASHINGTON

The "seeds" of Alzheimer's disease may be transmitted from one person to another during certain medical procedures, scientists have found. A study into people who have died of a sporadic kind of brain disease after receiving injections of human growth hormone suggests that Alzheimer's may also be a transmissible disease.

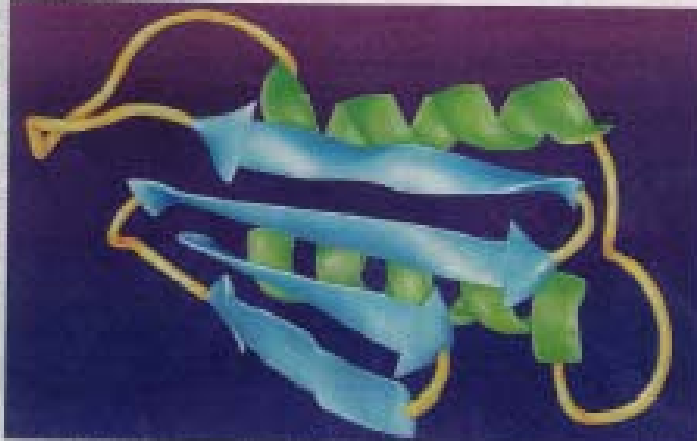
The findings, published in the journal *Nature*, have raised questions about the safety of some medical procedures, possibly including blood transfusions and invasive dental treatments, that may involve the transfer of contaminated tissues or medical equipment.

The findings of a study last night made people who were given growth hormone injections when they were children have raised the disturbing possibility that Alzheimer's can be transmitted under certain circumstances when infected tissues or surgical instruments are passed between individuals.

Until now, it was thought that Alzheimer's was caused by a result of inheriting certain genetic mutations, causing the buildup of amyloid plaques, or "beta plaques," in the brains of elderly people, said Professor John Collinge, head of neurodegenerative diseases at University College London.

The study subjects, aged between 35 and 65, all died of Creutzfeldt-Jakob disease (CJD) after receiving contaminated hormone injections as children. The subjects in their family also revealed that some of them harbored the mutated gene

Disseminating Prions



Alzheimer's disease is now considered a "prion disease." Prion-like proteins, which are infectious particles, are believed to carry the ability to trigger further proteins to misfold.

Collinge added: "Certainly there are potential risks to dietary intake of a misfolded protein form."

But in a statement issued last night, Collinge stressed that more research was needed before any conclusions

leading to debilitating brain disorders, such as CJD in humans, BSE in cattle and scrapie in sheep.

Prions are unique in being able to copy themselves without any genes, while viruses or bacteria. They

are extremely infectious, and can be spread by contact with infected tissues, or by surgical instruments and chemical agents that kill off infectious viruses and bacteria.

Q & A Should I be worried?

Q: What has the study shown?
After the first misfolded prion has been introduced into the brain,

Q: Does this mean we can 'catch' Alzheimer's?

REACTION

Findings need further investigation, say experts

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Dame Sally Davies, the Government's Chief Medical Officer, yesterday played down the significance of the research, saying that it was a small study with only eight samples.

"There is no evidence that Alzheimer's disease can be transmitted in humans, nor is there any evidence that Alzheimer's disease can be transmitted through any medical procedures," said Dame Sally yesterday.

"I am concerned people that the NHS has extremely stringent procedures in place to minimise infection risk from surgical equipment, and patients are very well protected," she added.

John Hardy, professor at Newcastle in 1991, said: "I think we can be reasonably sure that it is possible to transmit any kind of pathology by the action of human tissue which is the origin of Alzheimer's disease. There is some speculation that blood transfusion is probably not, but this definitely deserves systematic epidemiological investigation."

Doug Brown, director of research at the Alzheimer's Society, said: "While these findings are interesting and warrant further investigation,



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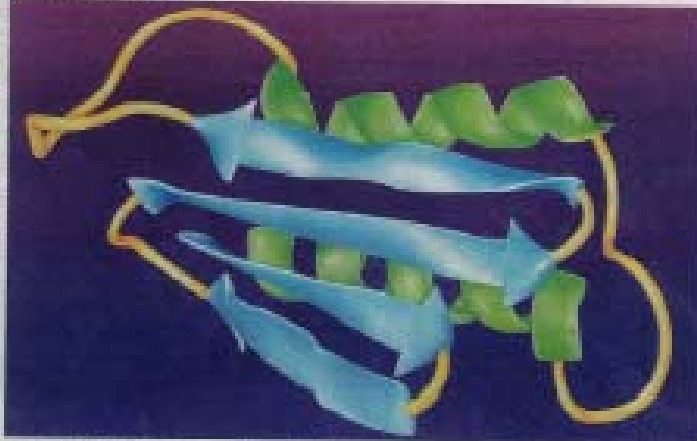
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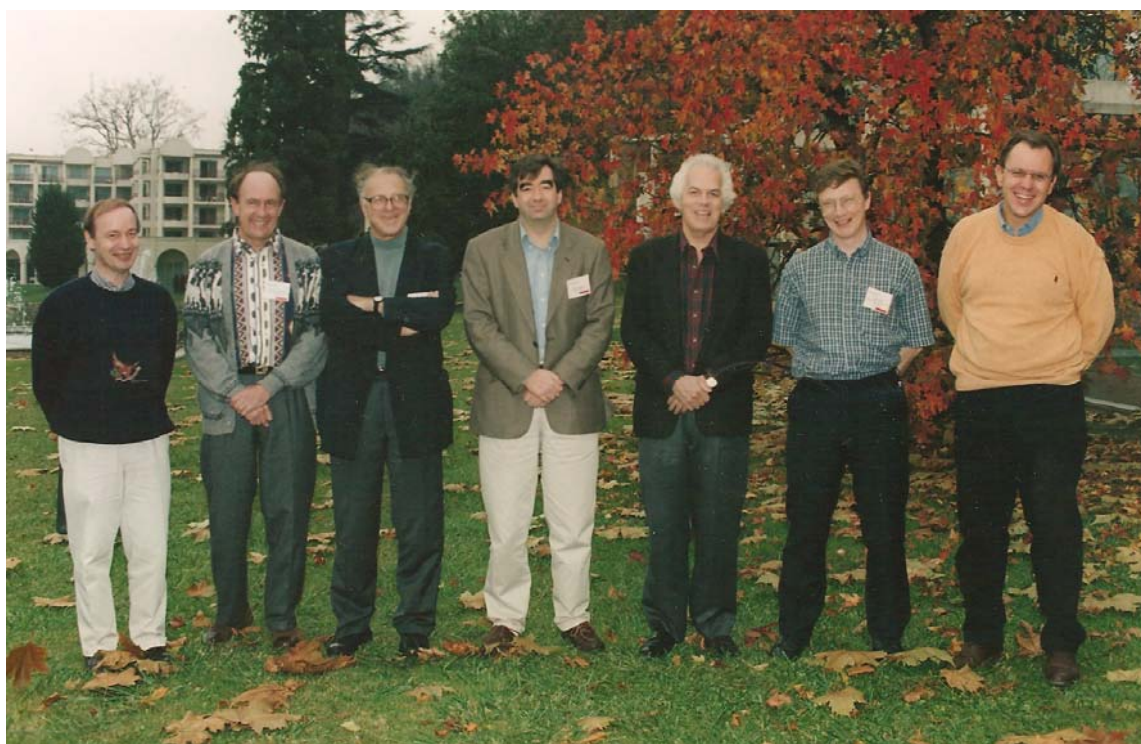
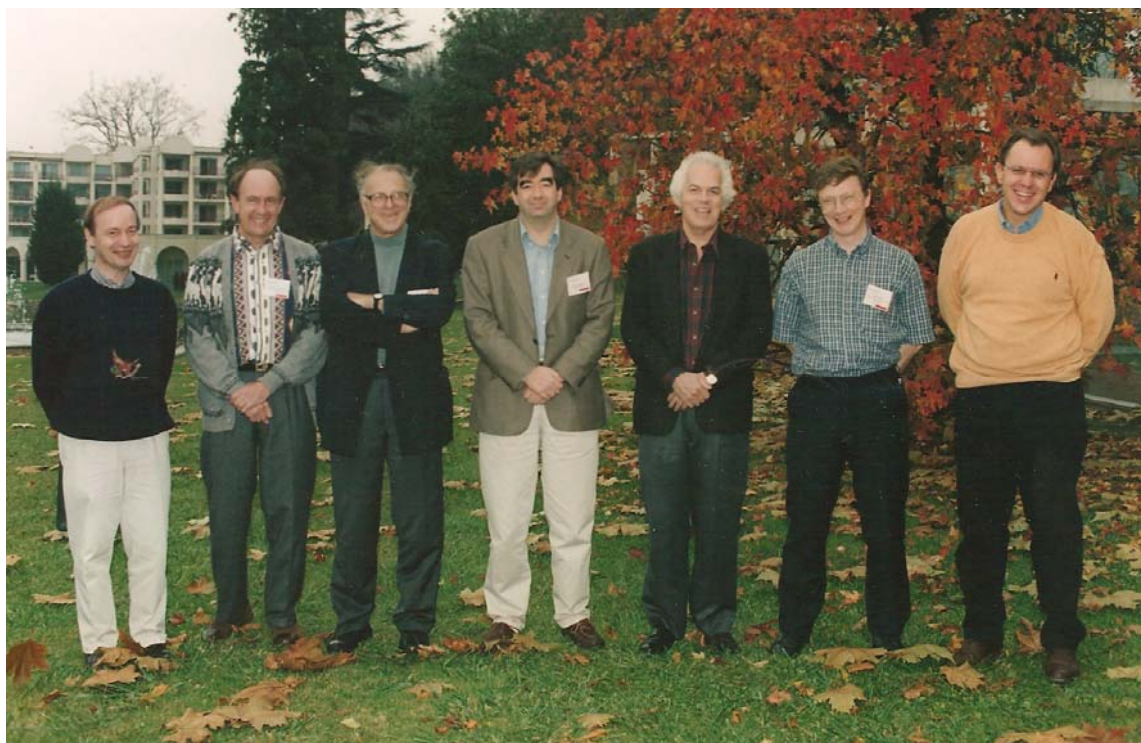
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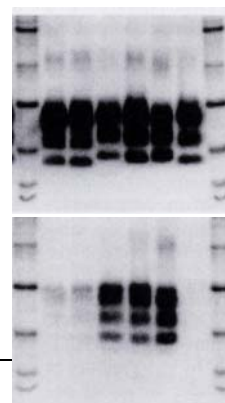
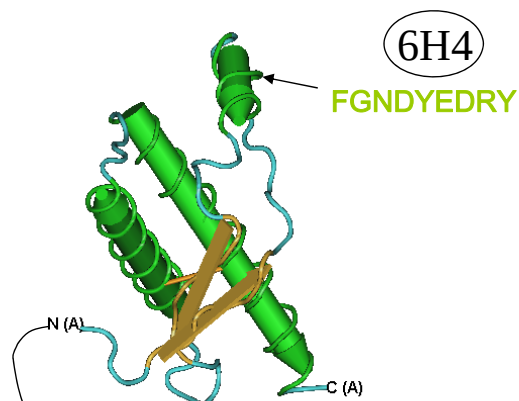
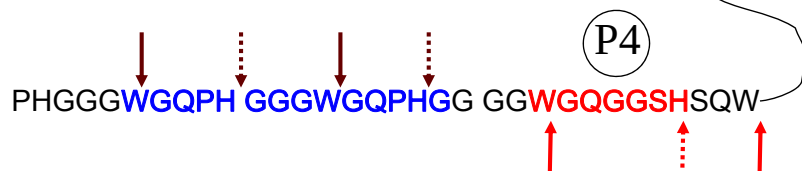
Prions are :

- Chromosomally-encoded proteins
- Two forms : “Normal” and “Prion”
- The Prion form can induced the Normal form into a new copy of the prion form
- Over-producing the protein increases the frequency of prion generation
- Biochemical proof of a prion by infectivity of recombinant protein in altered form

プリオンとは :

- 染色体上にエンコードされているたん白
- 二つの形態 : “正常” と “プリオン”
- プリオンは、正常形態のものを新たなプリオンのコピーへと誘導することがある
- たん白の過剰生産は、プリオン生成の頻度を高める
- 変化した形態のリコンビナントたん白の感染性が、プリオンの生化学的な裏付けとなる

PK cleavage sites in ovine PrP^D
linked to scrapie (↓) or
BSE (↓) in sheep

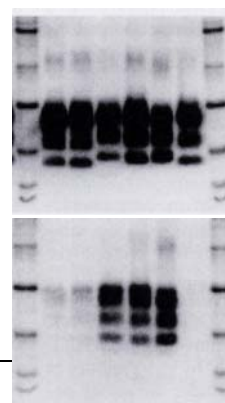
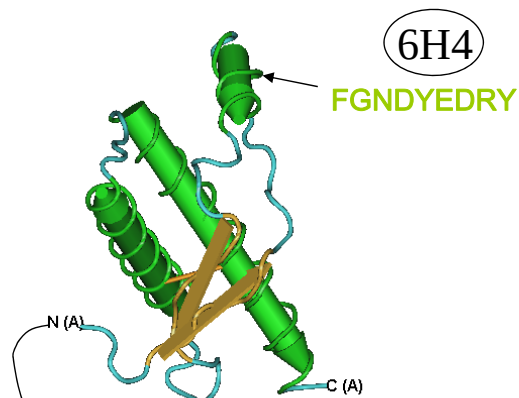
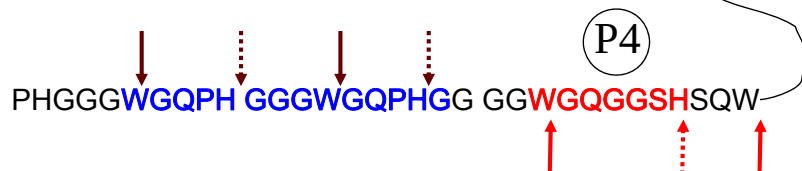


6H4

P4

Stack et al., 2002; Thuring et al., 2004;
Baron et al., 2004;

羊のPrP^DのPK切断部位は、羊
におけるスクレイピー(↓)もしくは
BSE(↓)に関連していた



6H4

P4

Stack et al., 2002; Thuring et al., 2004;
Baron et al., 2004;

Bovine spongiform encephalopathy

- prion protein disease
- single strain phenomenon
- extended common source of infection

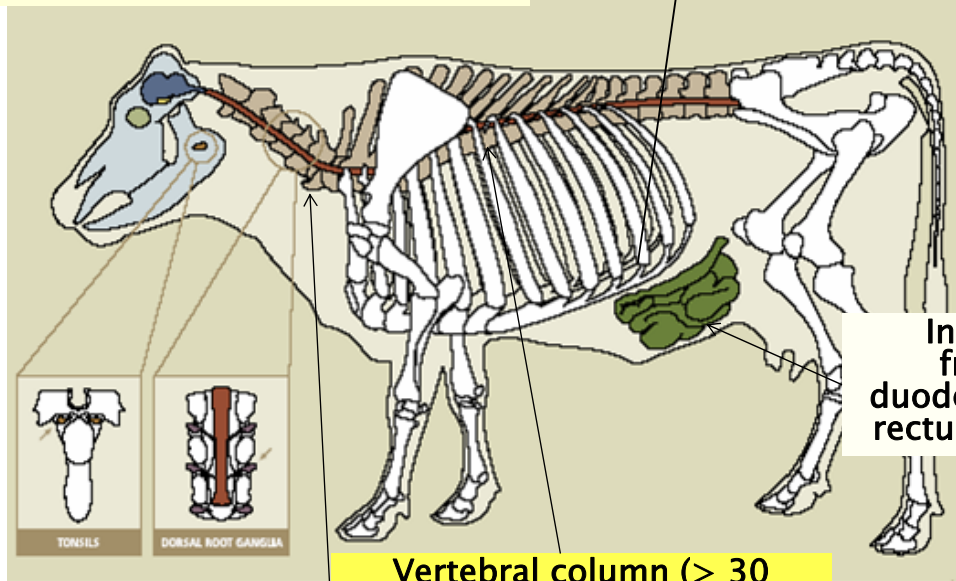
牛海綿状脳症

- プリオンたん白病
- 単一の系統の現象
- 拡大した共通の感染源

Where are the BSE prions?

Skull, excluding mandible (>12 months)
Brain (>12 months)
Eye (>12 months)

Spinal cord (>12 months)



Intestines,
from the
duodenum to the
rectum (All ages)

Tonsils (all ages)

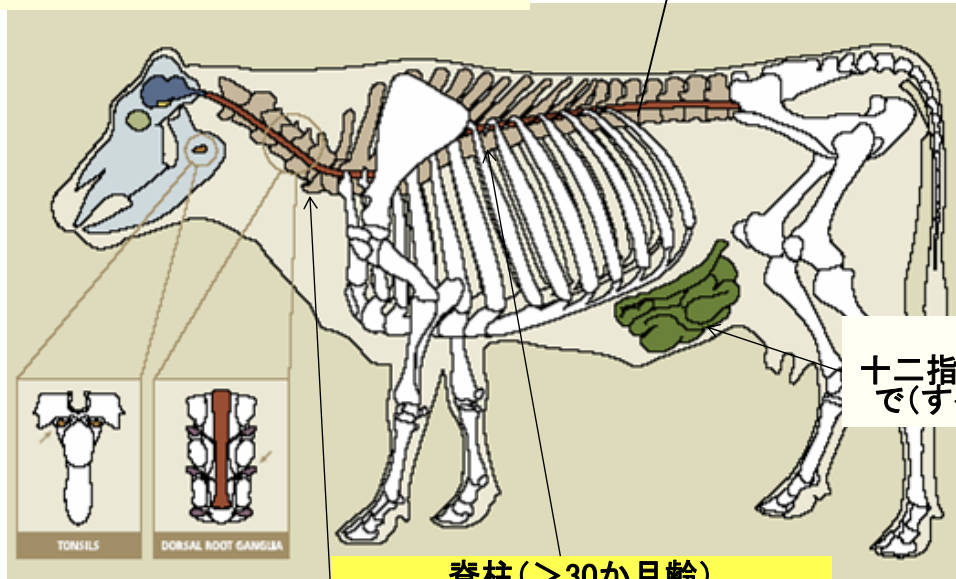
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Vertebral column (>30 months)
Dorsal root ganglia

どこにBSEプリオンがあるのか?

下顎を除く頭蓋(>12か月齢)
脳(>12か月齢)
眼(>12か月齢)

脊髄(>12か月齢)



腸管、
十二指腸から回腸ま
で(すべての月齢)

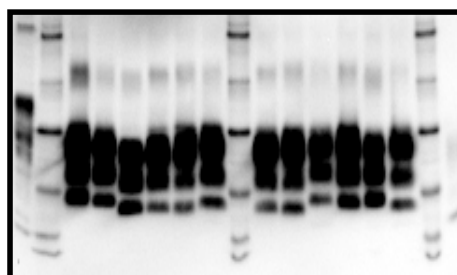
扁桃(すべての月齢)

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脊柱(>30か月齢)
背根神経節

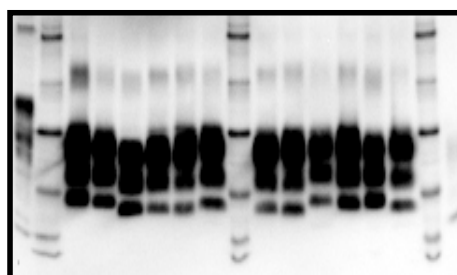
Molecular signals for BSE

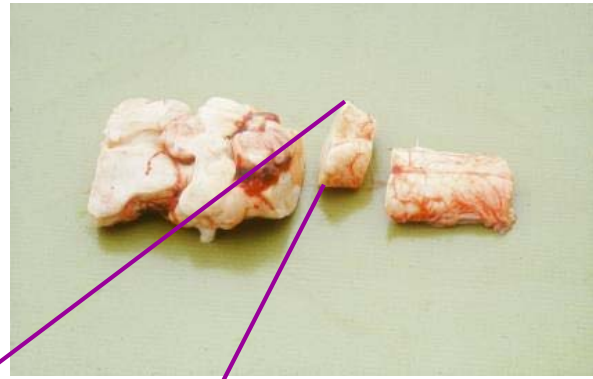
- PrP detection in **ELISA** formats – ‘rapid testing’ - usual primary screening tool
- Banding patterns of PrP^d on **Western blotting** - screening and/or confirmation



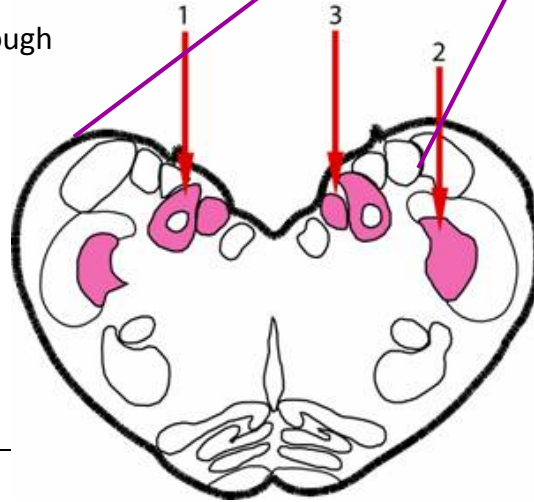
BSEの分子シグナル

- **ELISA** 法によるPrPの検出 – ‘迅速試験’ - 通常的一次スクリーニング・ツール
- **ウェスタン・ブロット法**におけるPrP^d バンド・パターン - スクリーニング及び／又は確認

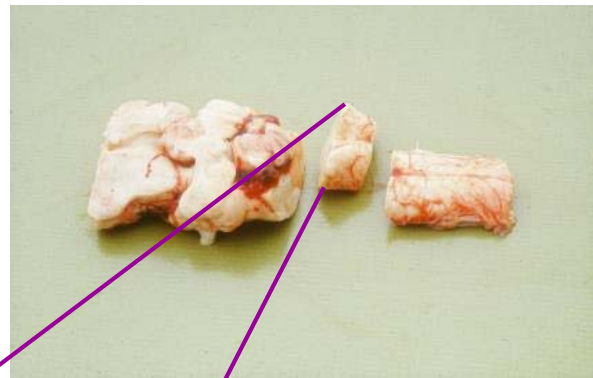




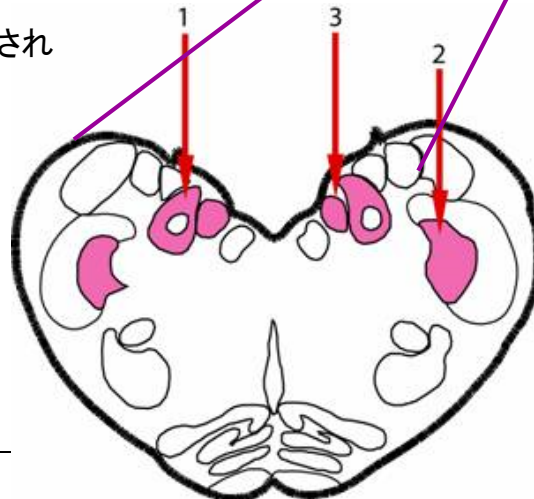
Brainstem sampled through the *foramen magnum*



Key diagnostic target areas



大後頭孔を通じて採取された脳幹標本



鍵となる診断上の標的領域

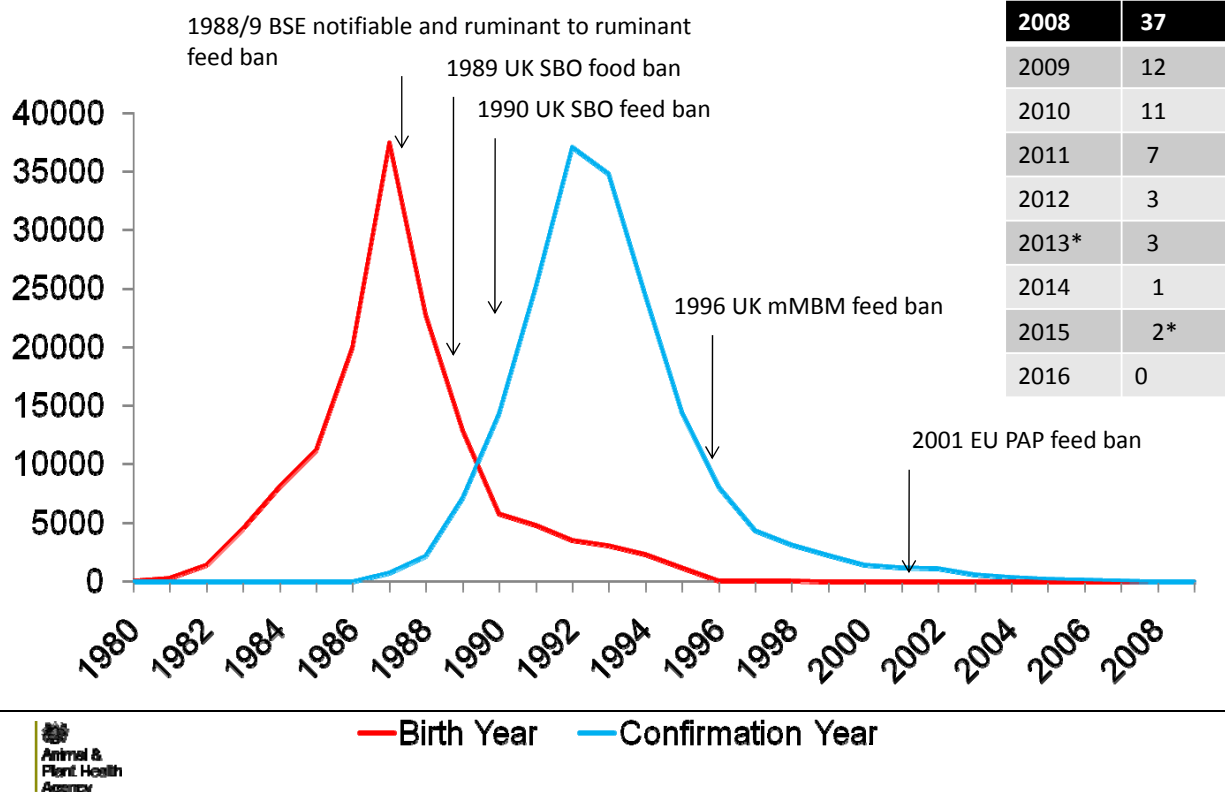
Controls on BSE in the EU

- **Public health** protected through the removal of the **Specified Risk Materials**
- **Animal health** protected through the **ban** on the use of proteins of animal origin in **feed**
- **Monitoring of BSE is an epidemiological tool** to monitor declining trend of BSE

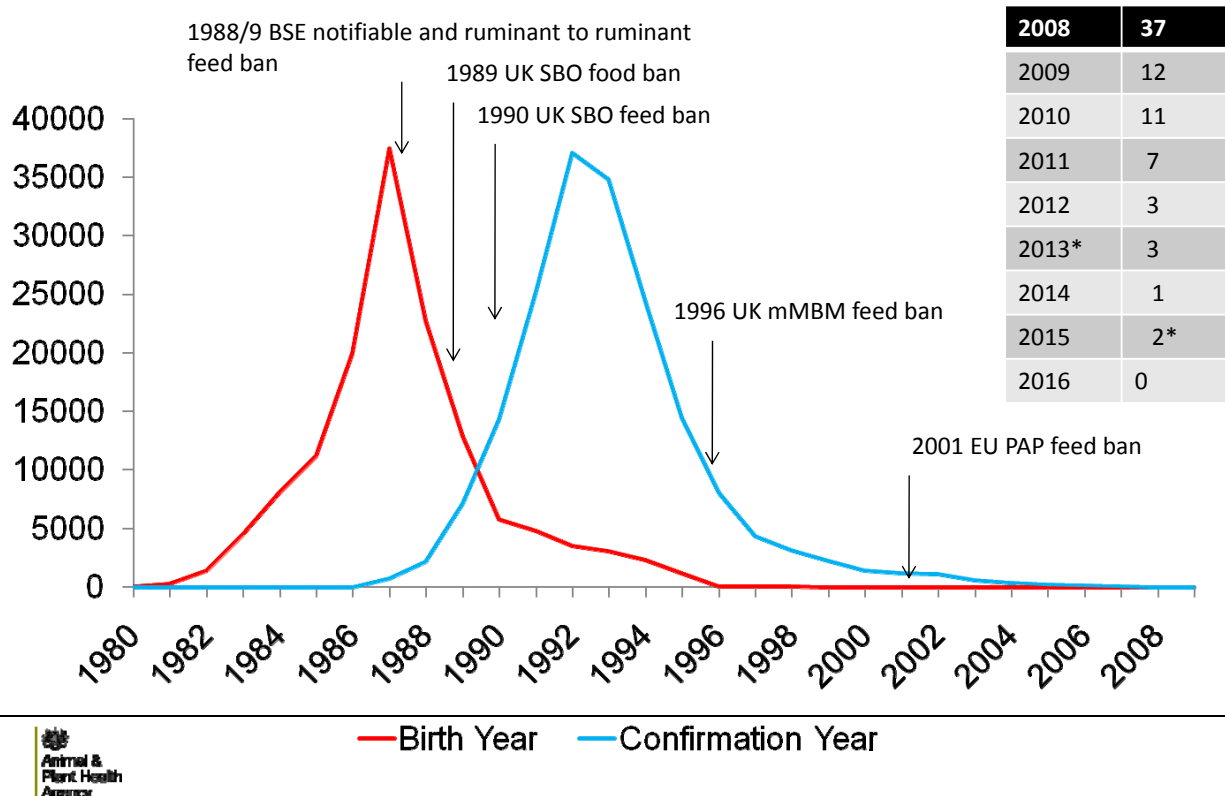
EUにおけるBSEのコントロール

- 特定危険部位の除去を通じて公衆衛生を確保。
- 家畜衛生は、飼料に動物由来たん白の使用を禁止することで確保。
- BSEモニタリングは、BSEの減少傾向を監視するための疫学的ツール

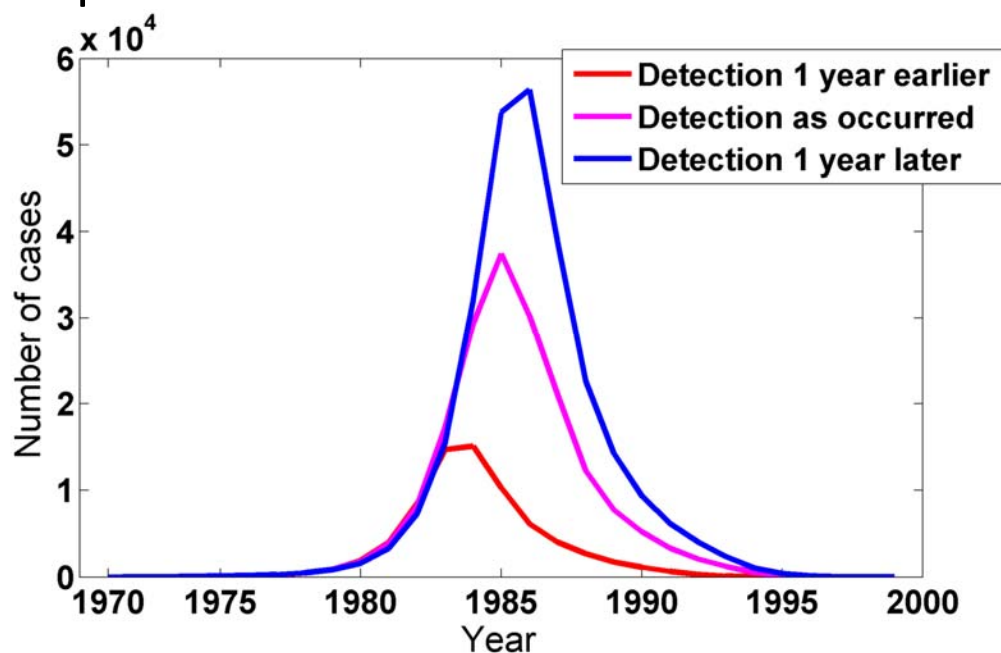
The rise and fall of the UK BSE epidemic



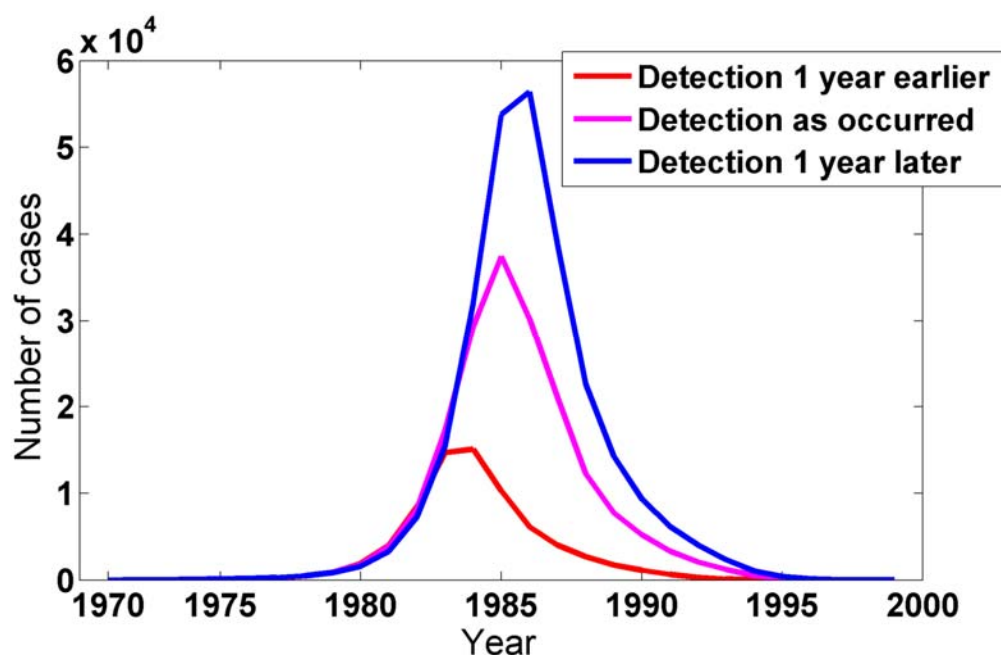
英国におけるBSE発生の増加と減少



Predicted impact of earlier/later implementation of BSE control measures



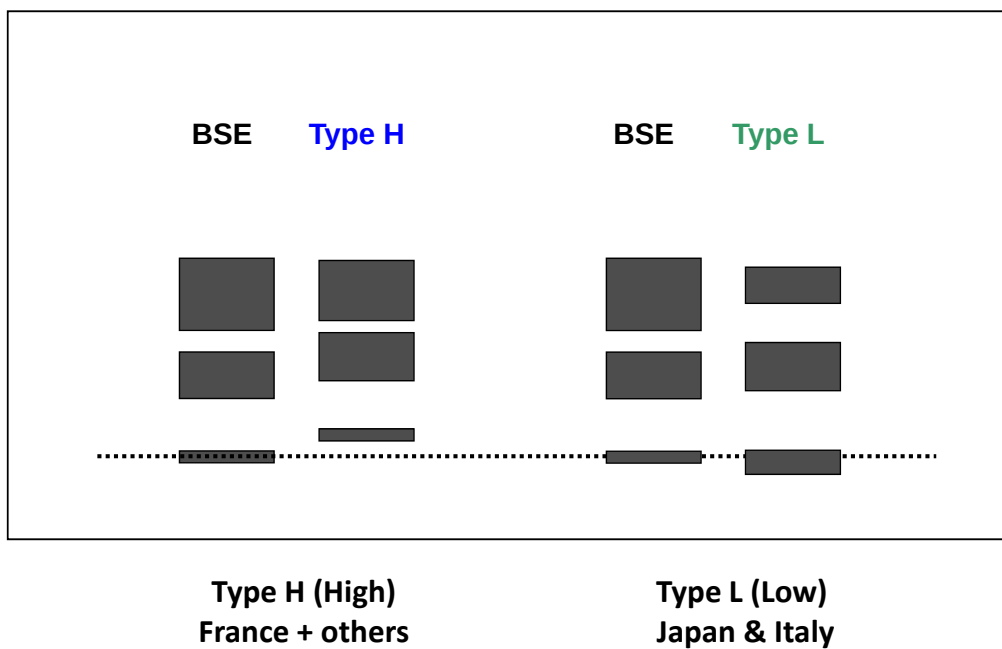
BSE管理措置を早期／後期に実行したことにより 予想される効果



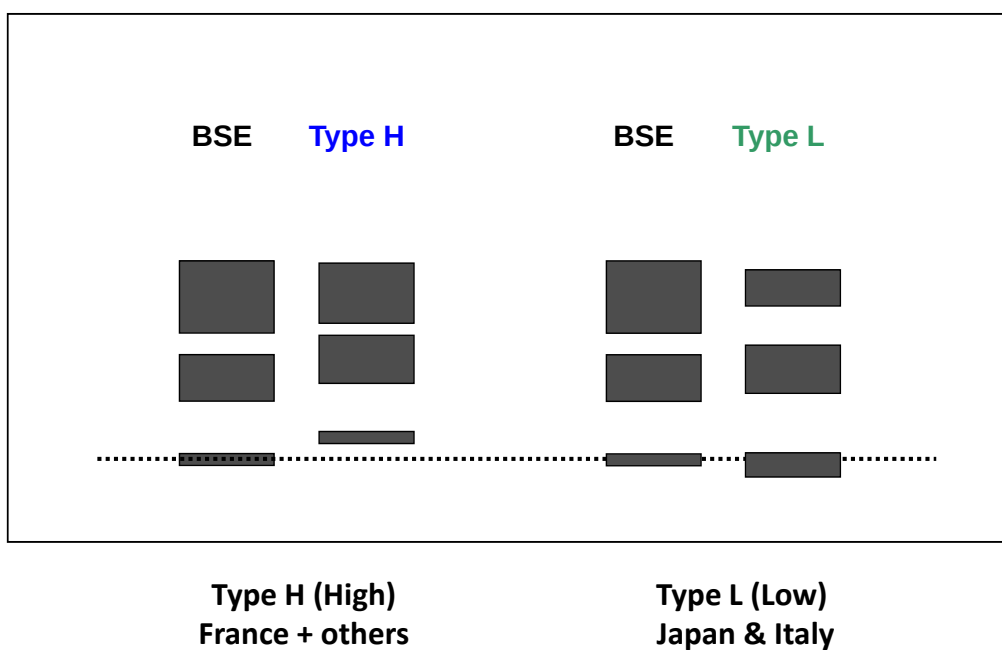
Classical and Atypical types of BSE

BSEの定型と非定型

Molecular patterns of PrPres in classical and atypical BSEs

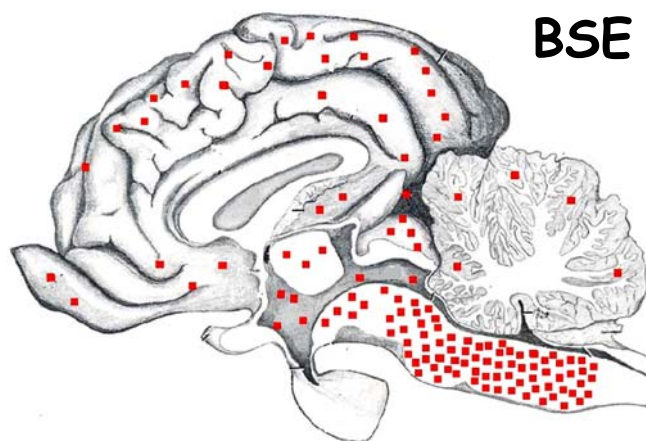


定型及び非定型BSEのPrPreの分子パターン

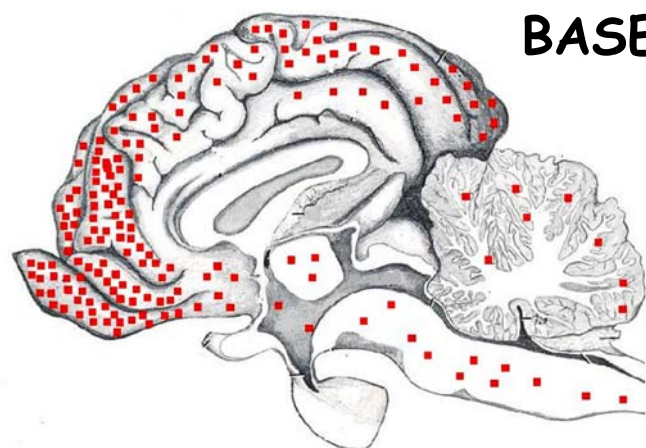


Brain regional distribution of PrP^D in BSE and BASE

Casalone et al., 2004



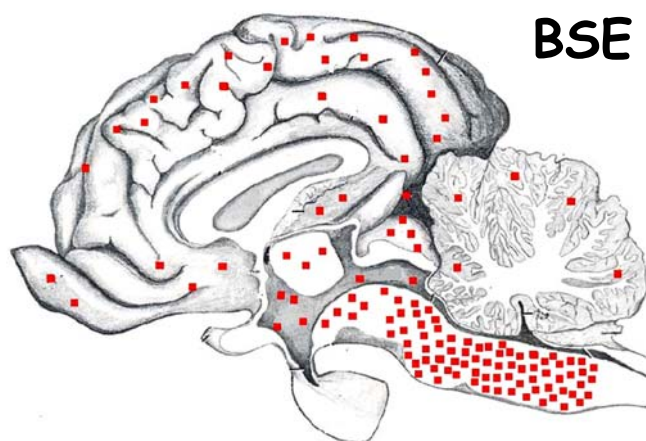
BSE



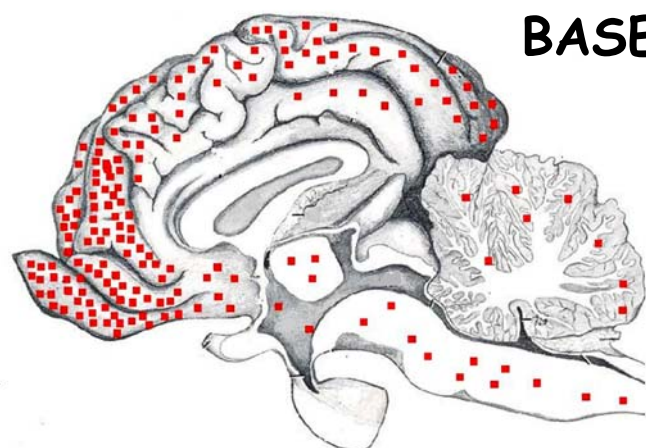
BASE

BSE及びBASEにおけるPrP^Dの脳内分布

Casalone et al., 2004



BSE

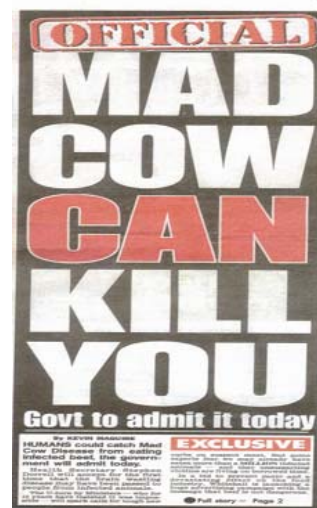


BASE

Mad Cow Disease or Bovine Spongiform Encephalopathy



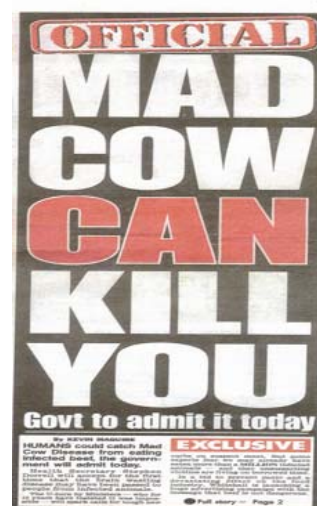
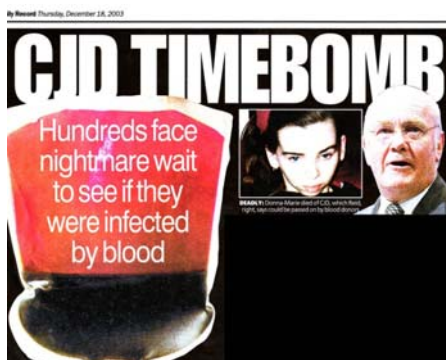
New variant Creutzfeldt-Jakob disease



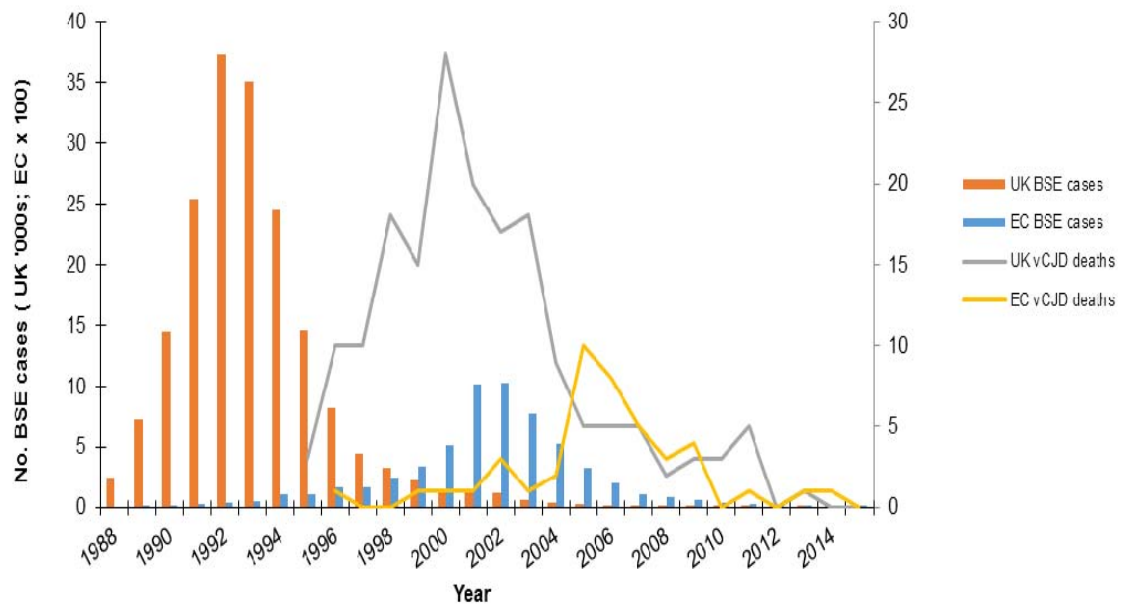
狂牛病もしくは牛海綿状脳症



新たな変異型 クロイツフェルト・ヤコブ病

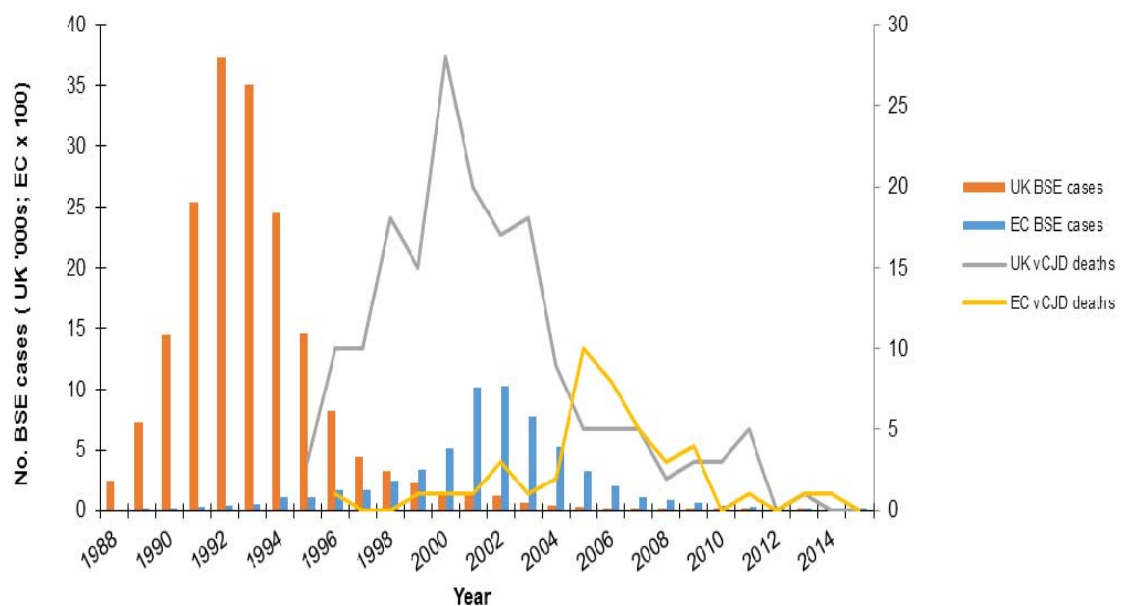


Cases of BSE (1988-2015) and vCJD (1994-2015) in UK and Europe



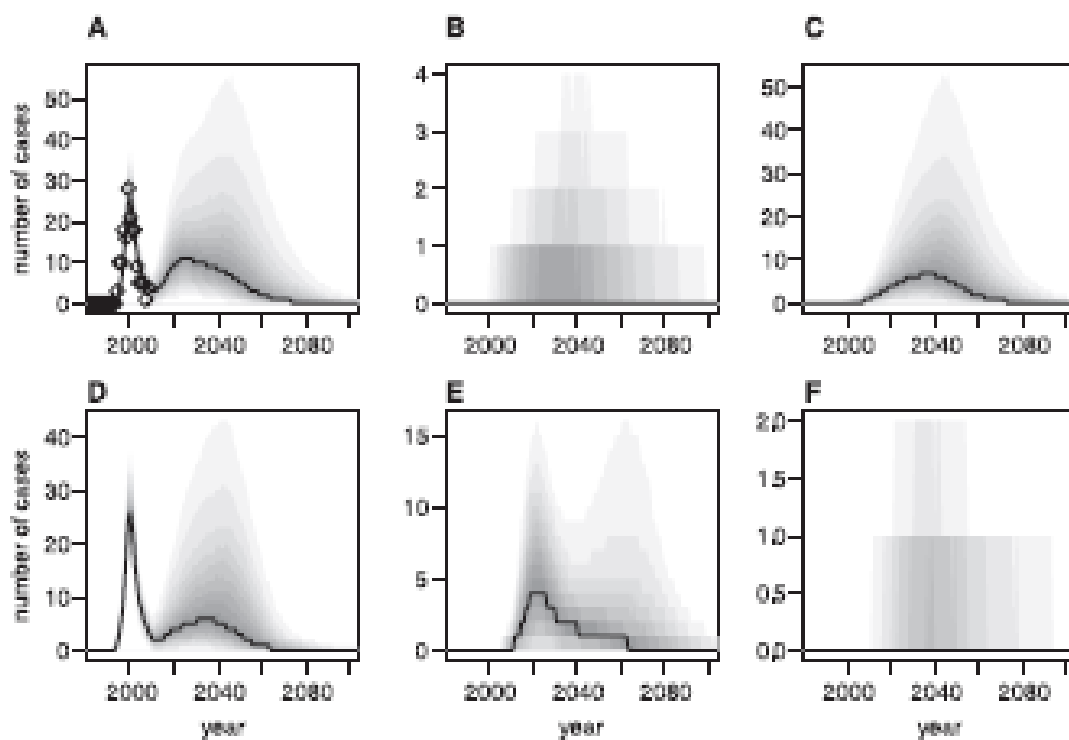
Animal & Plant Health Agency

英国及びヨーロッパにおける BSE(1988-2015) 及びvCJD (1994-2015)の発生数

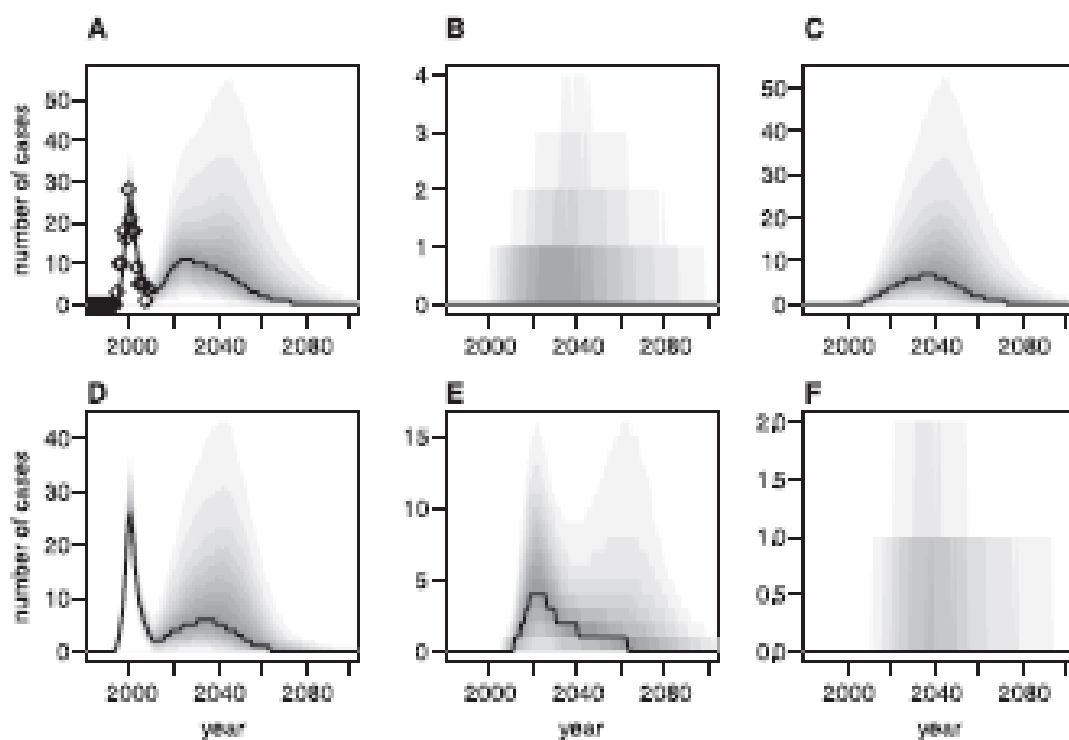


Animal & Plant Health Agency

Uncertainty in the tail of the vCJD epidemic Garske & Ghani, PLoS One, 2010



vCJD 発生のテールにおける不確実性 Garske & Ghani, PLoS One, 2010



Origins of BSE, past and present, in Great Britain

The BSE Inquiry, 2000
The Horn Review, 2001

EU SSC “Hypotheses on the origin
and transmission of BSE” , 2001



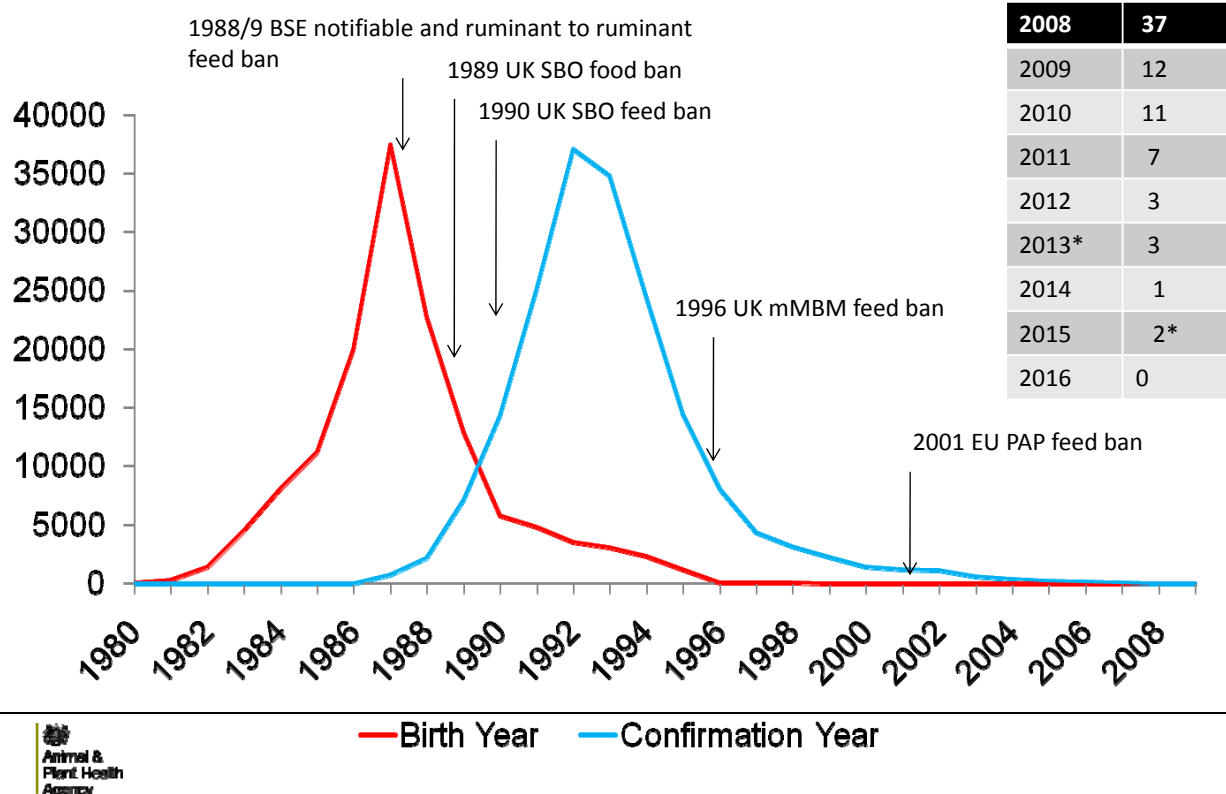
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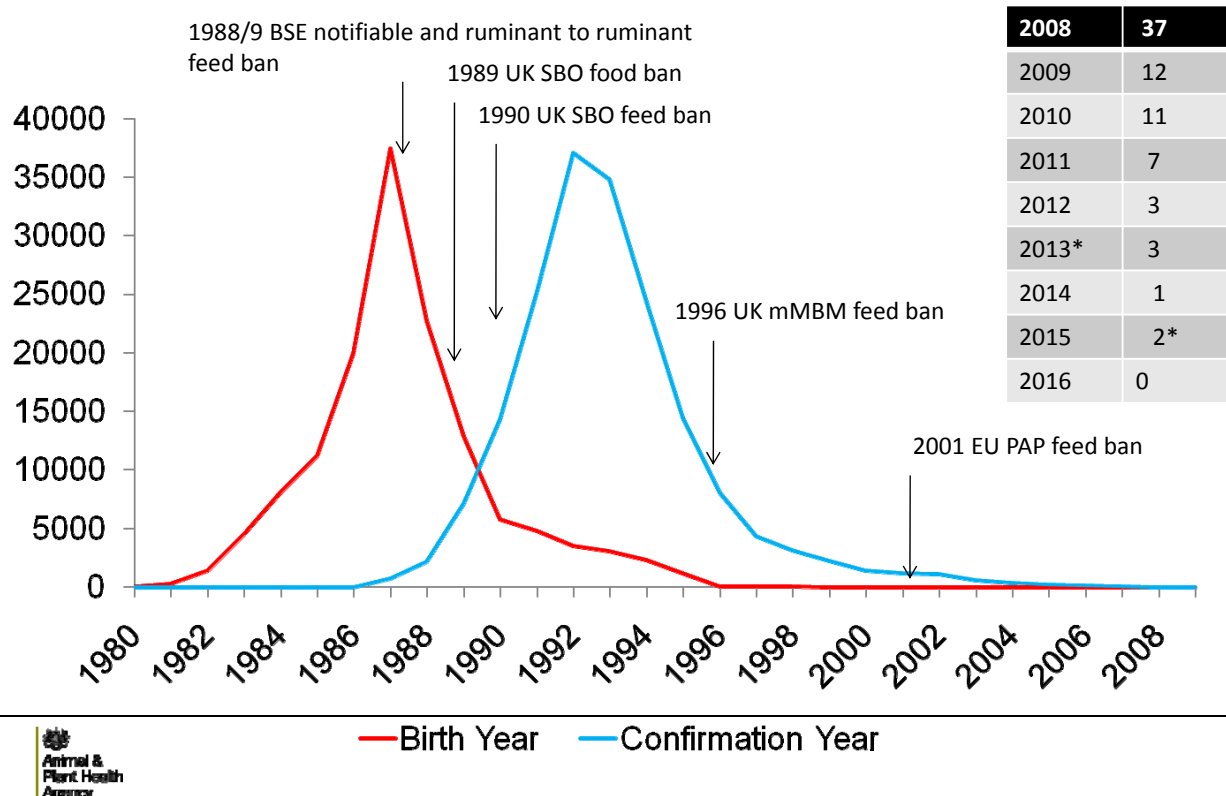
欧州委員会科学運営委員会（EU SSC）
「BSEの起源及び伝播に関する仮説」、2001年



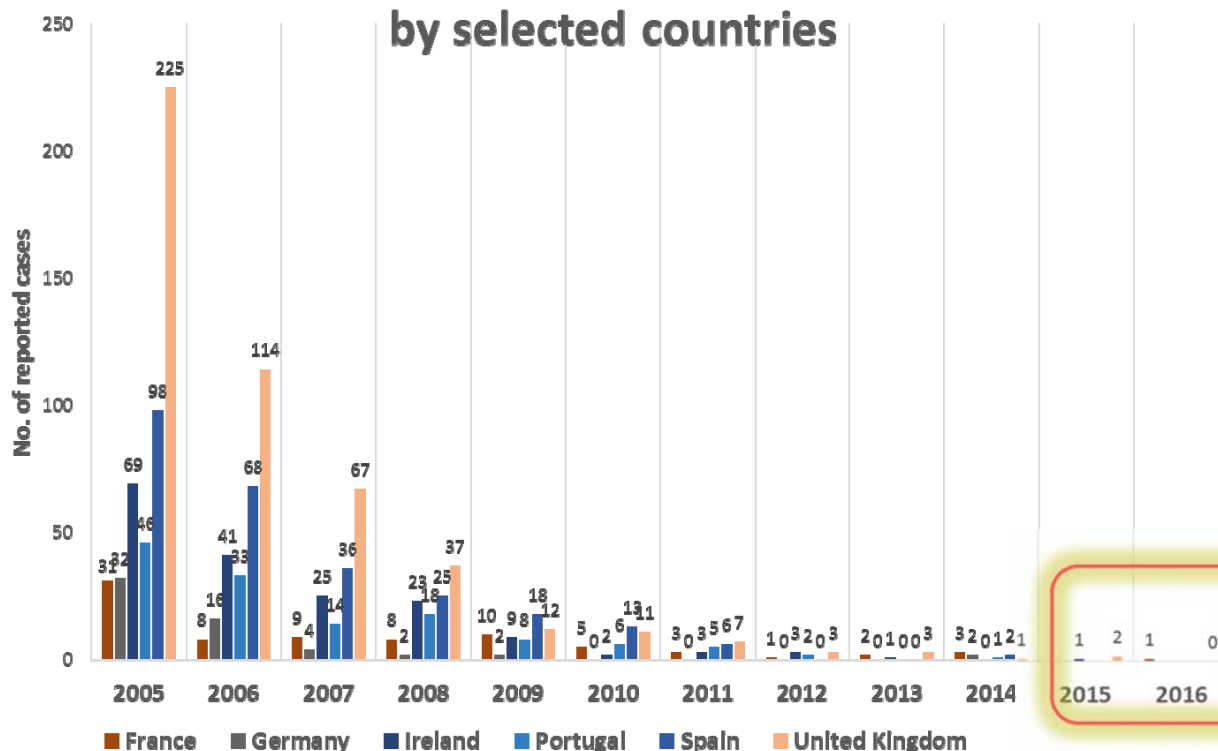
The rise and fall of the UK BSE epidemic



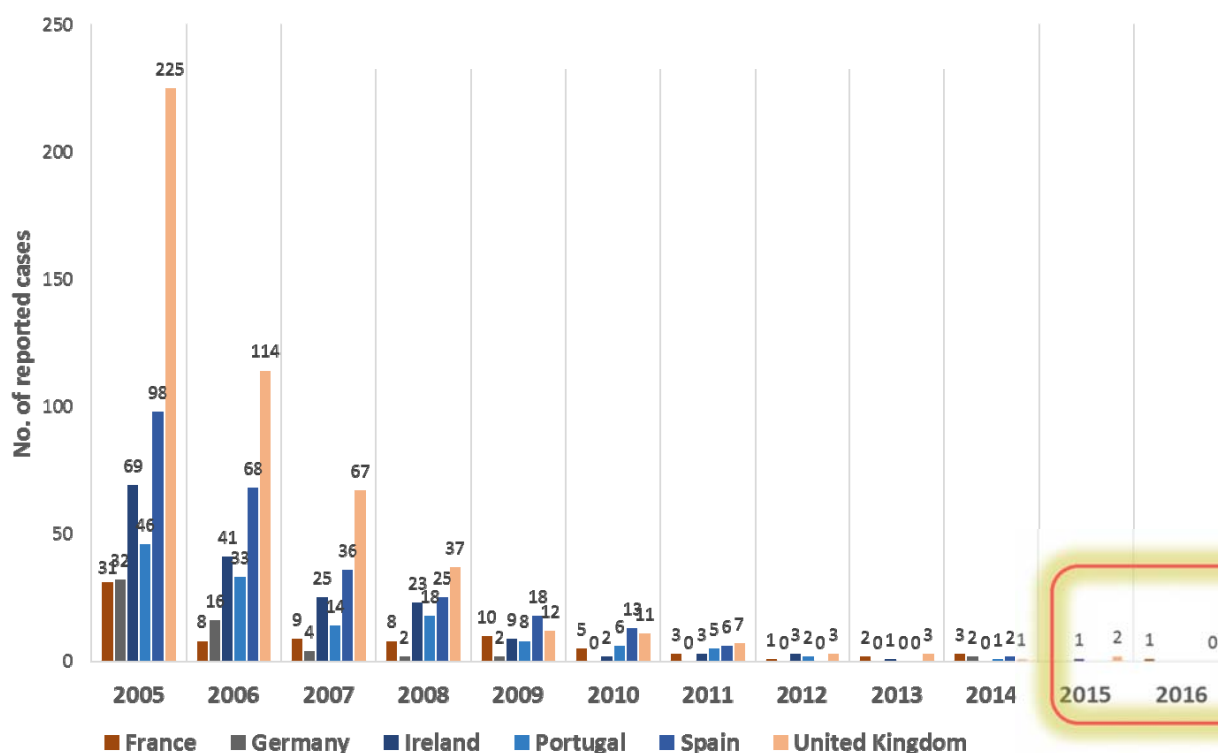
英国におけるBSE発生の増加と減少



Number of BSE cases reported to OIE each year by selected countries



主要国がOIEに通報したBSE発生例の数(年別)



Recent cases of classical BSE in Europe and Canada (b, born; d, died)

Great Britain : b. May 31st, 2009; d. Sept 15th, 2015 **(75.5 mo)**

Ireland: b. June 2010; d. June 2015 **(60 mo)**

France: b. April, 2011; d. March 2016 **(59 mo)**

Canada: b. March, 2009; d. Feb, 2015 **(71 mo)**

欧州及びカナダにおける定型BSEの 最近の事例 (b, born; d, died)

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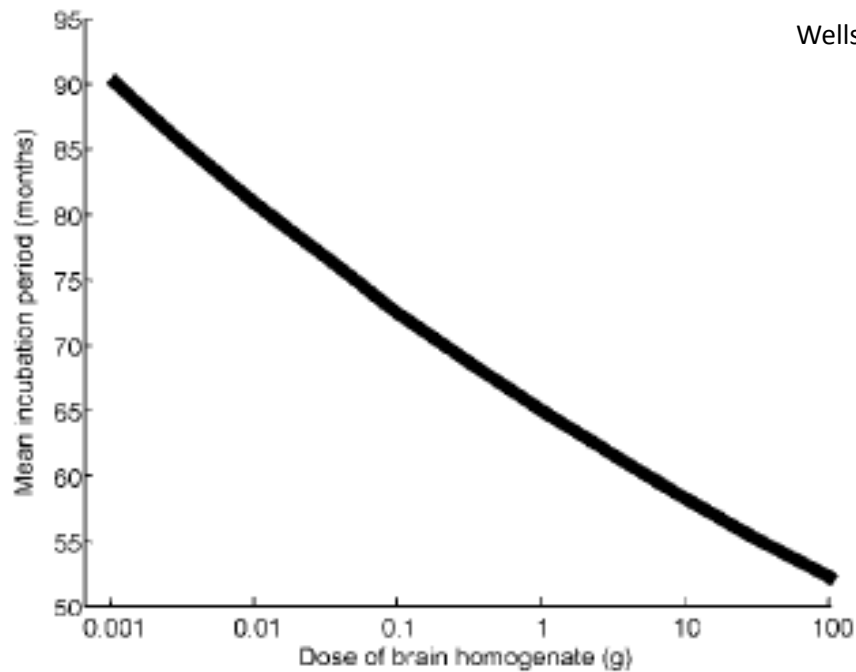
Canada: b. March, 2009; d. Feb, 2015 **(71 mo)**

How much infectivity....?

感染性はどの程度か....?

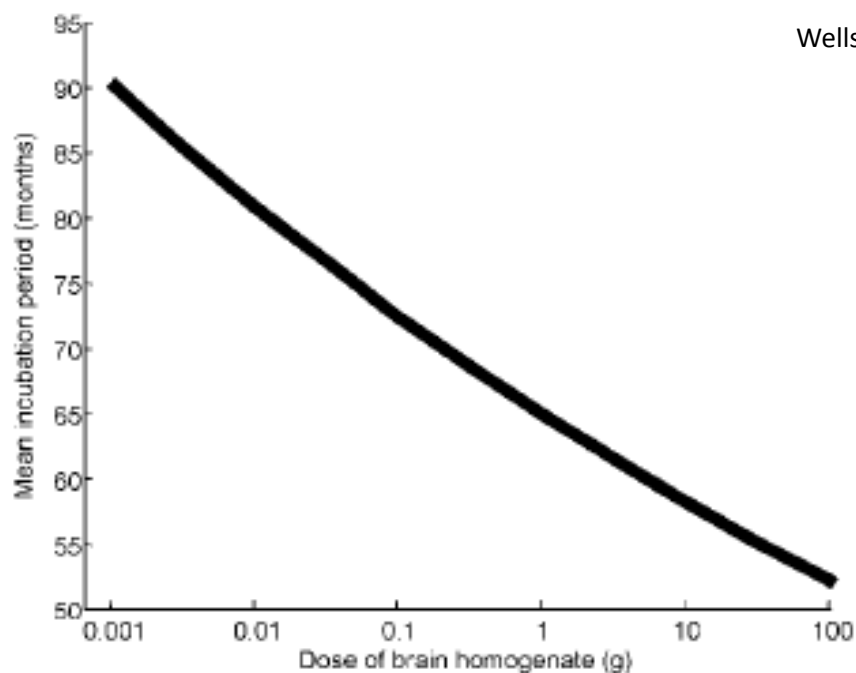
Dose-survival time curve for oral infection of cattle with classical BSE prions

Wells et al, 2007

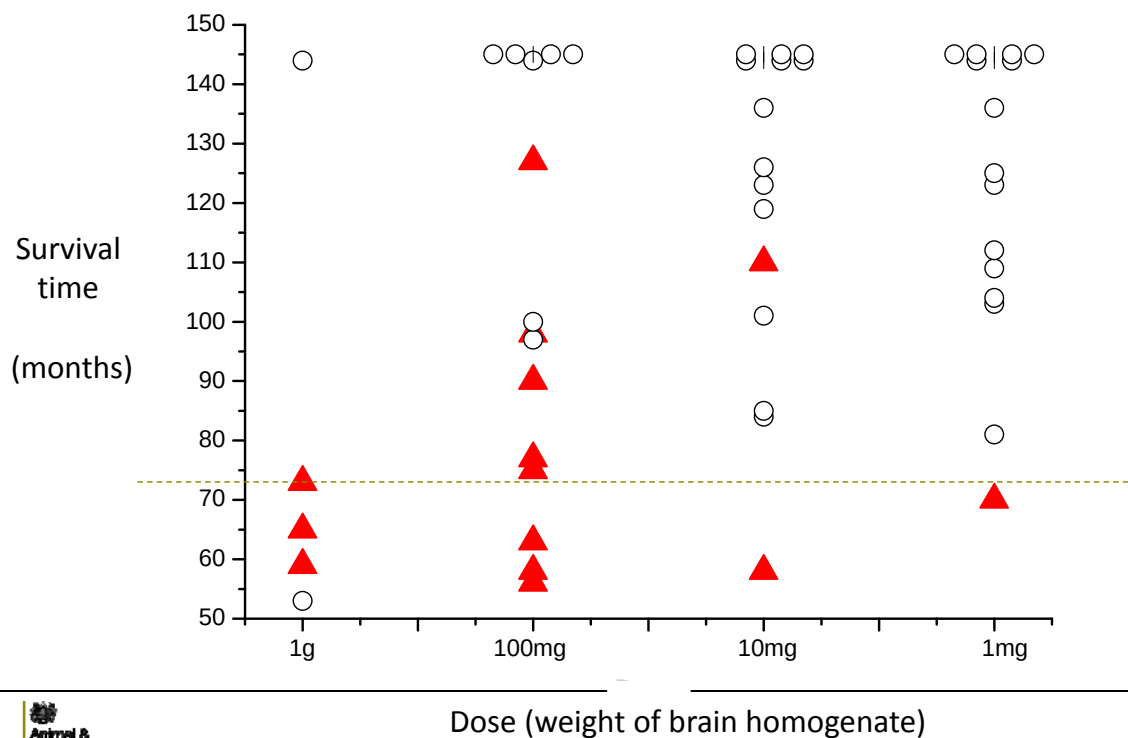


定型BSEプリオンによる牛の経口感染の投与量-生存時間曲線

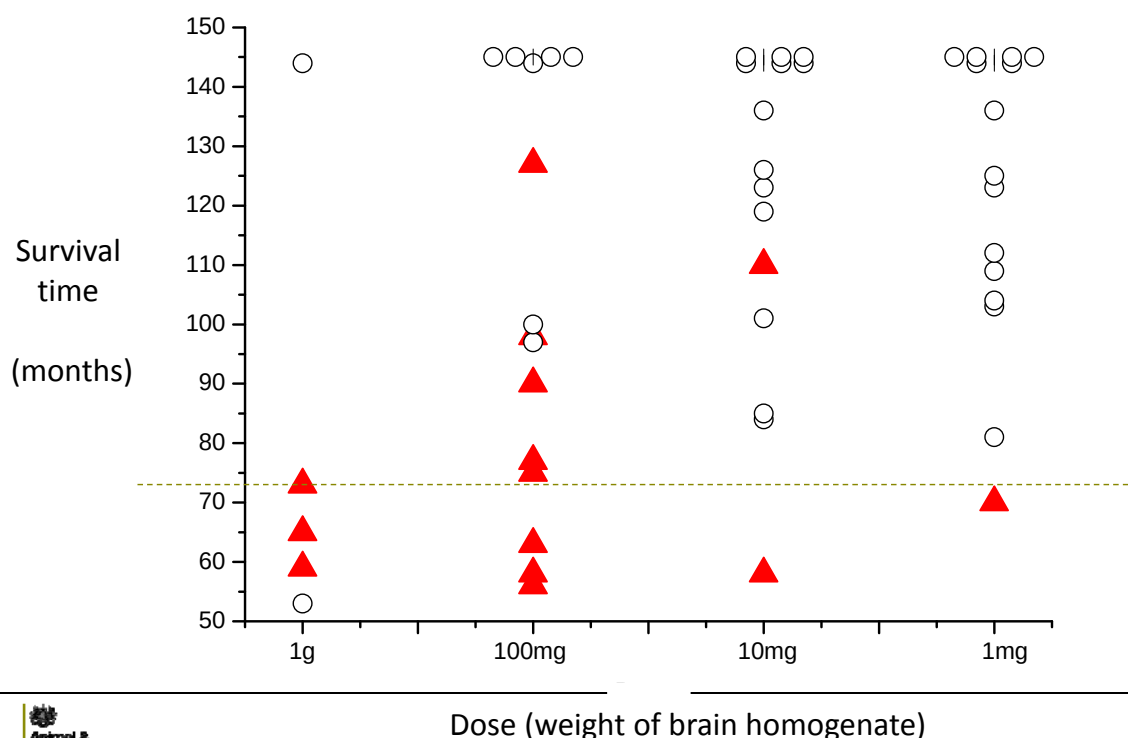
Wells et al, 2007



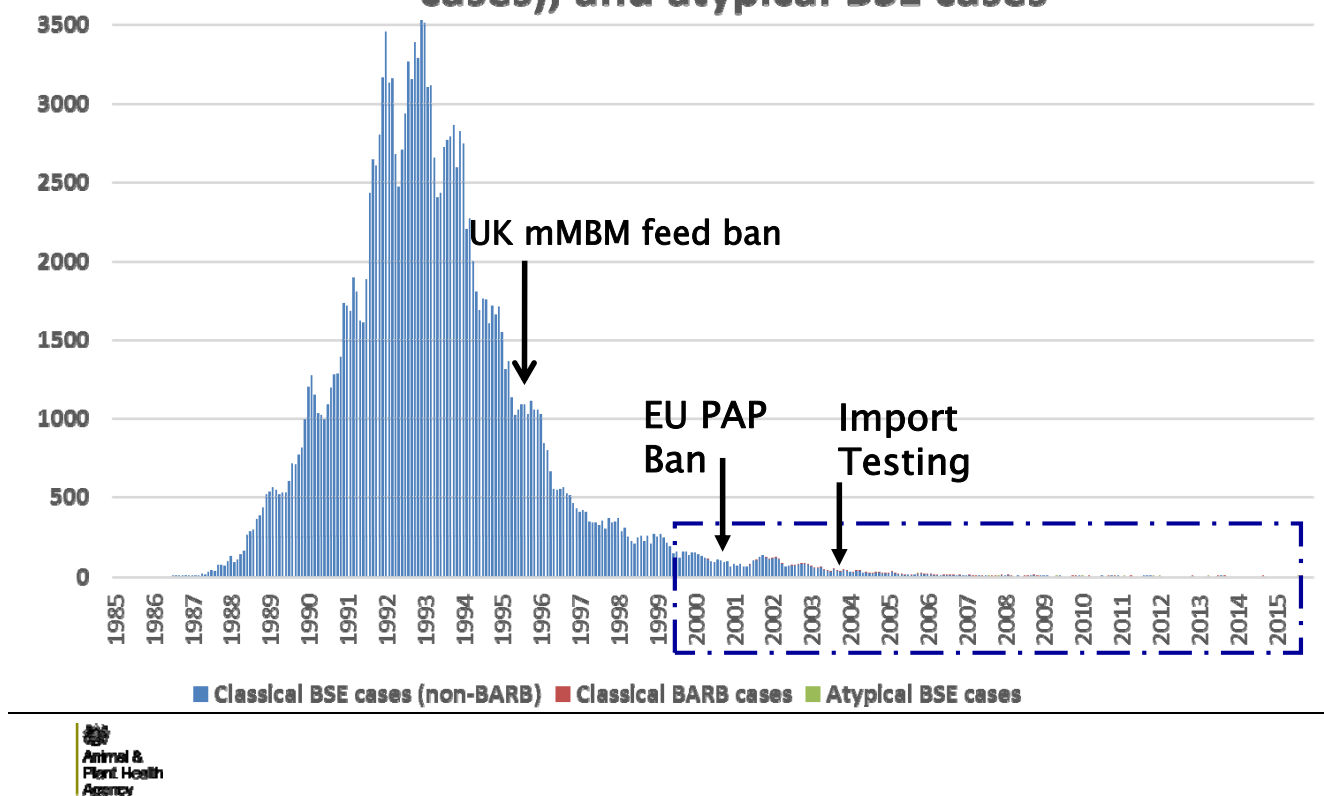
Oral dose response survival times in cattle fed BSE-infected brain



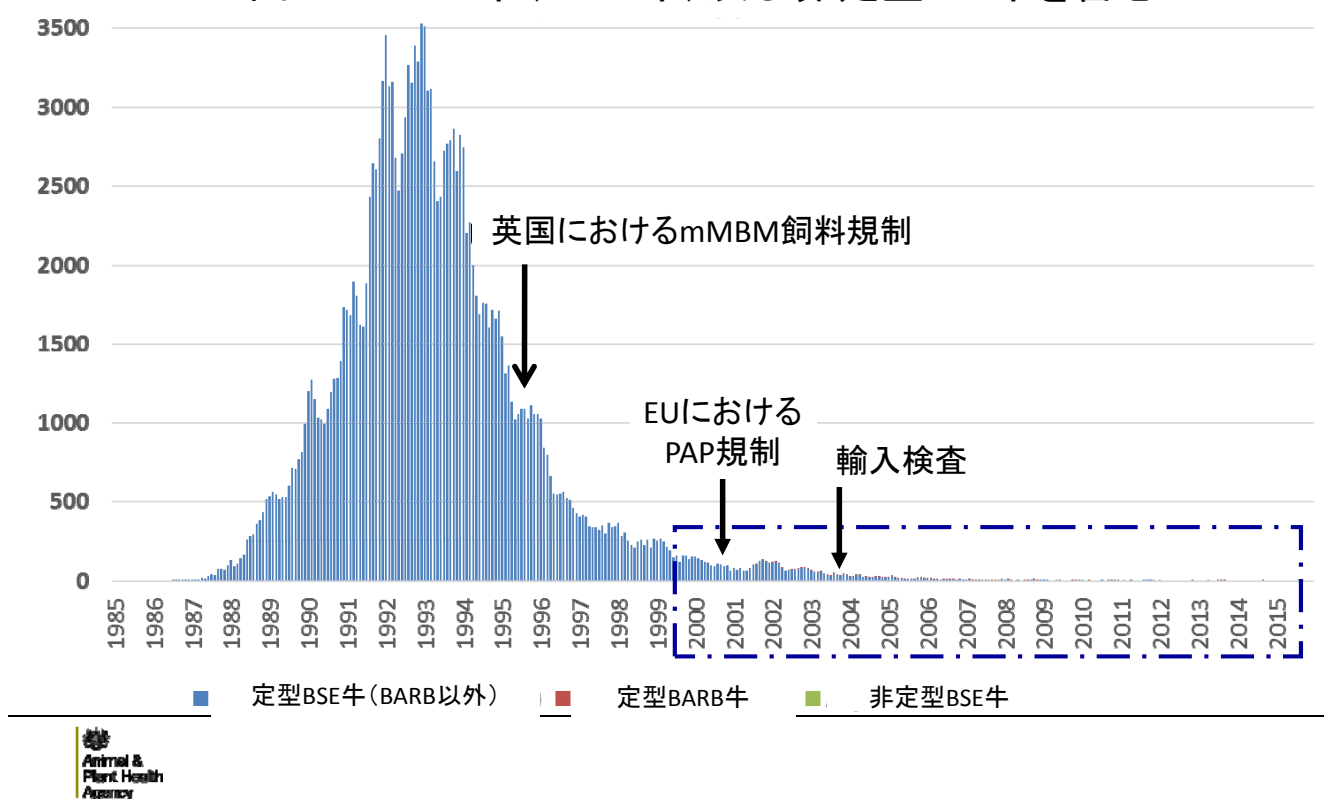
BSE感染牛脳組織を投与された牛における経口投与反応生存時間



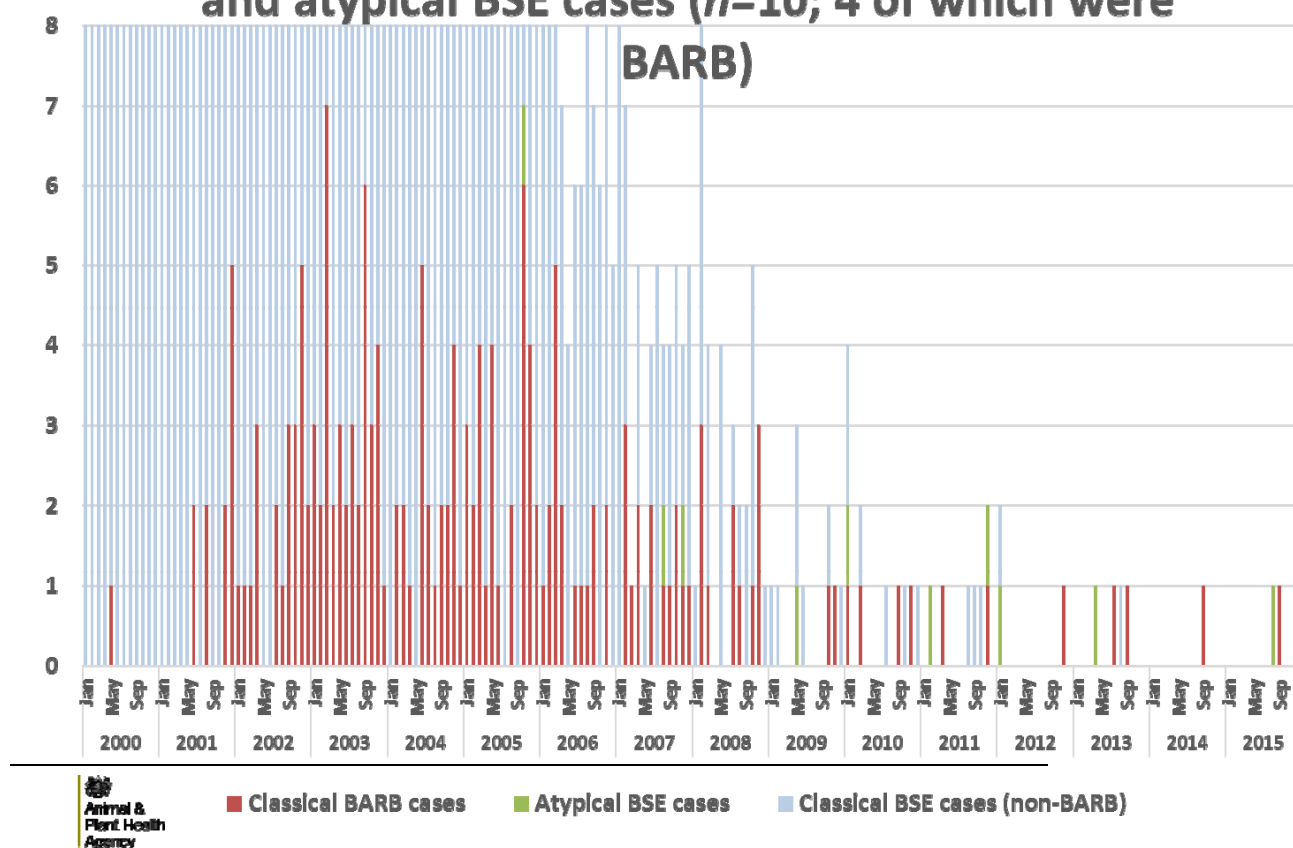
BSE epidemic curve for GB; including cases born after the 1996 GB mMBM feed ban (BARB cases), and atypical BSE cases



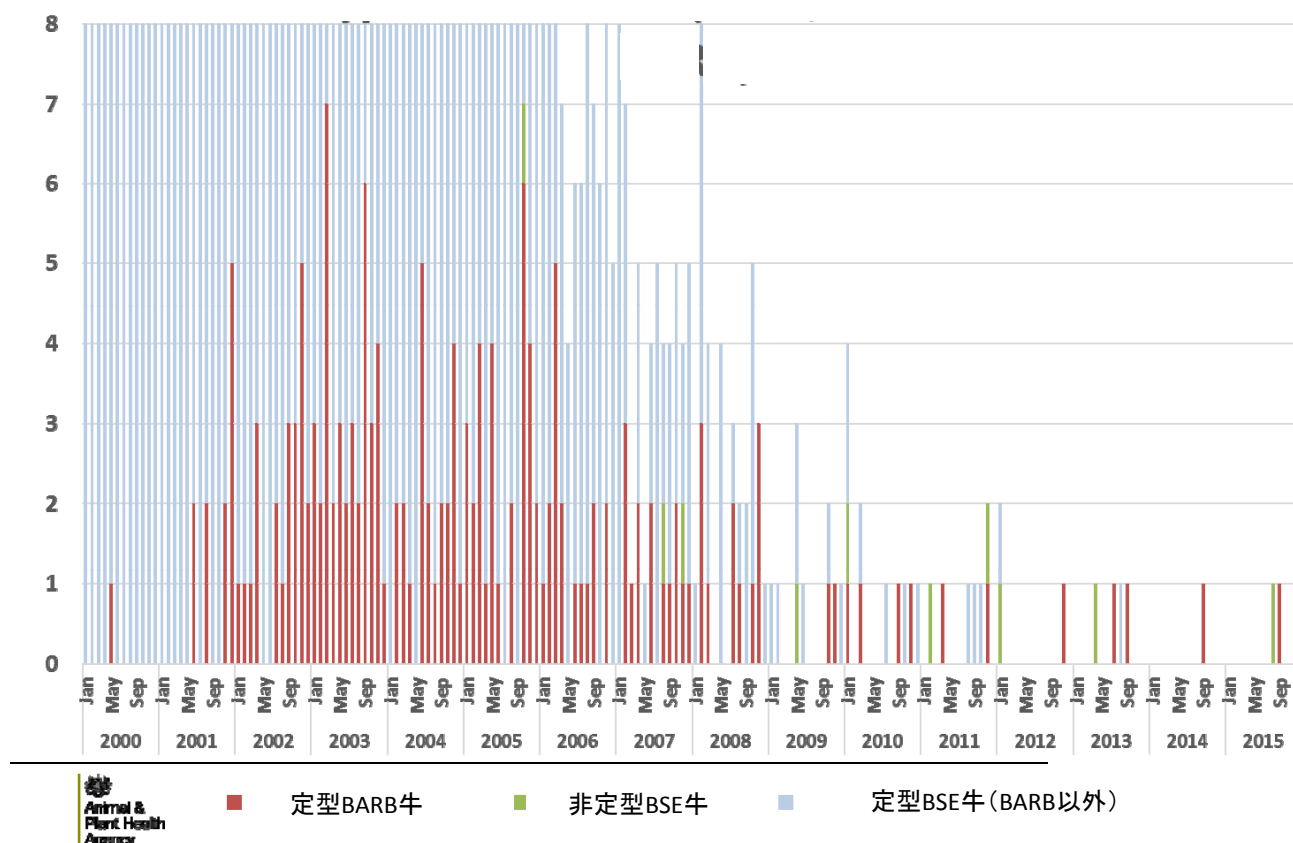
英国のBSE流行曲線： 1996年の英国における哺乳類動物肉骨粉(mMBM)飼料規制後 に出生したBSE牛 (BARB牛) 及び非定型BSE牛を含む

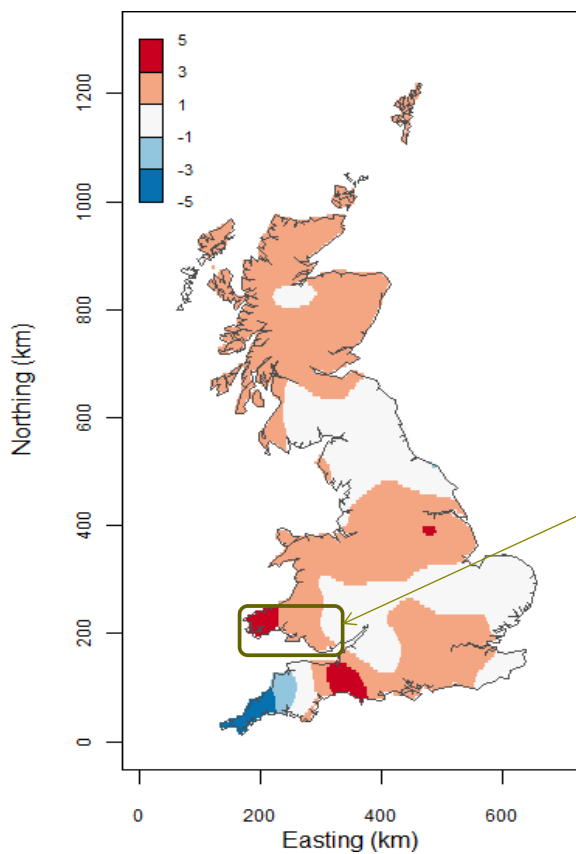


Epidemic curve of classical BARB cases ($n=178$) and atypical BSE cases ($n=10$; 4 of which were BARB)



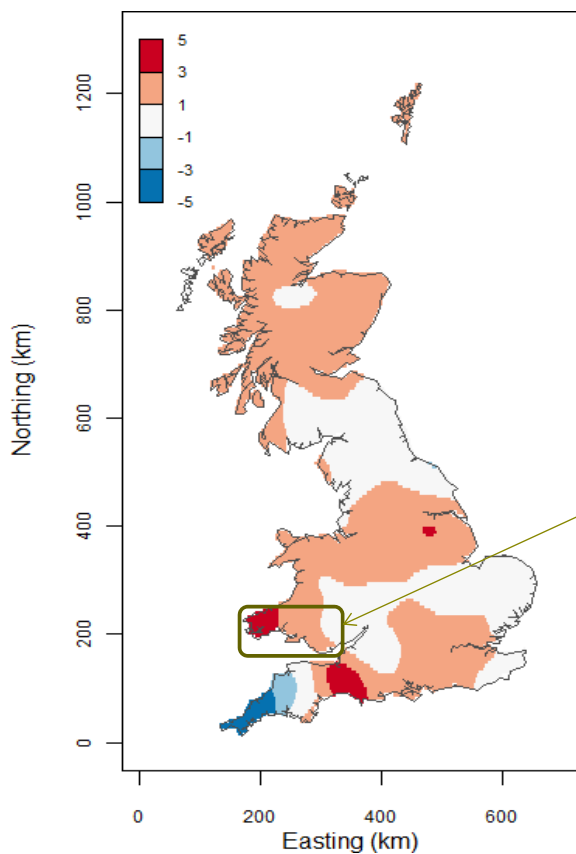
定型BARB牛(178例)及び非定型BSE牛(10例;うち4例はBARB)の流行曲線





GB case : 15/0002, September 2015
Classical BSE, DoB: May 2009

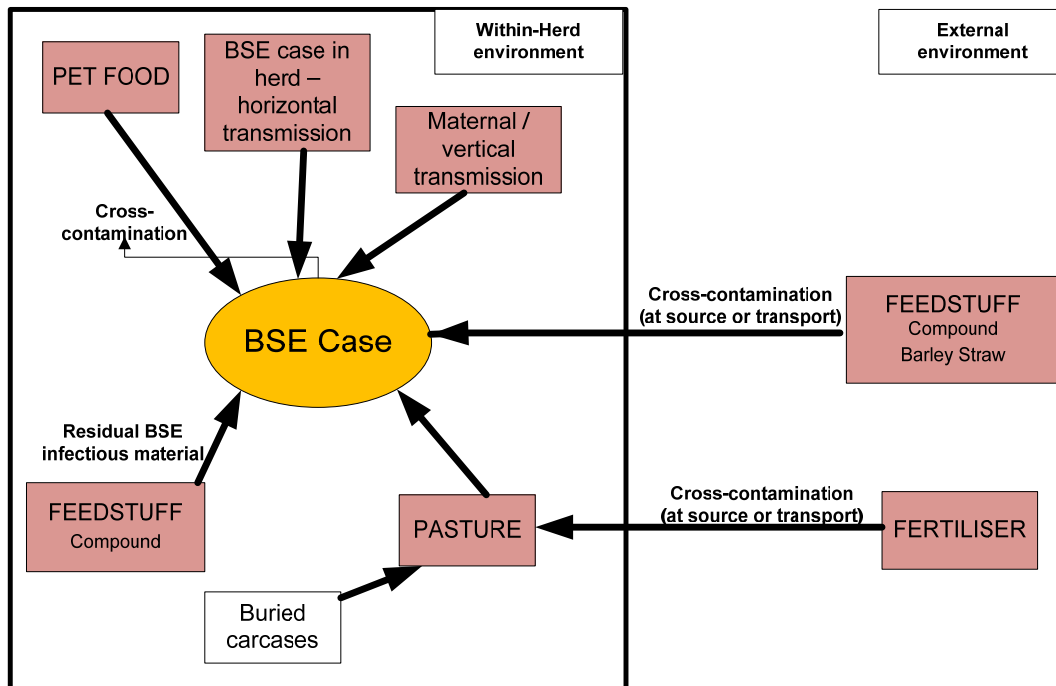
Location of case :
15/0002



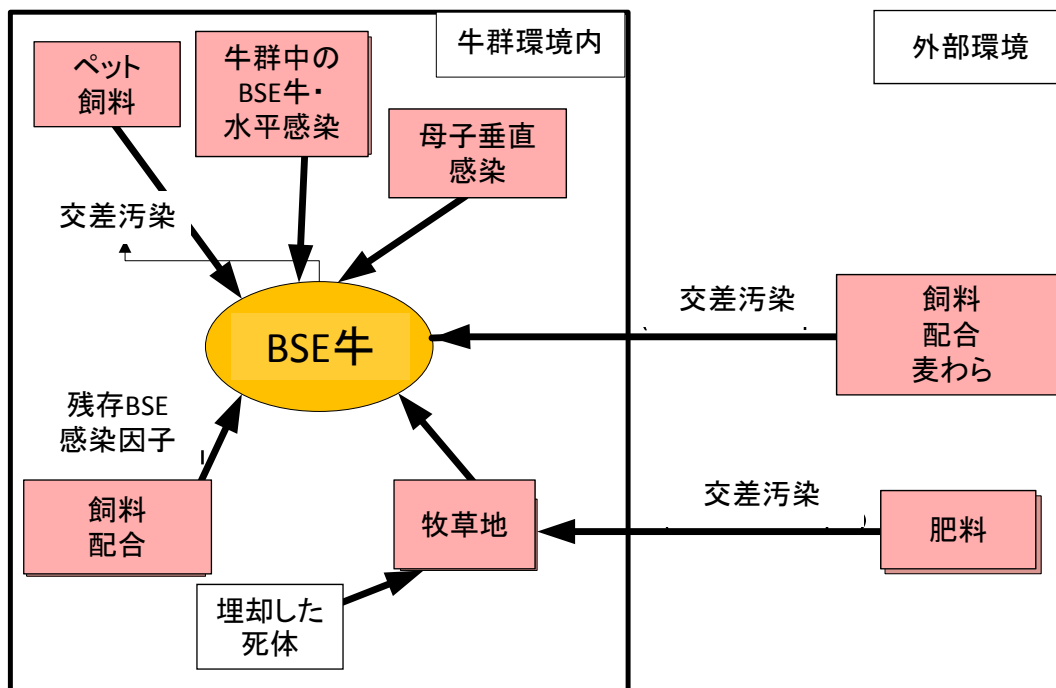
GB case : 15/0002, September 2015
Classical BSE, DoB: May 2009

Location of case :
15/0002

Risk Pathways



リスク・パスウェイ





Baby calves - individual pens area & feed store



Calves - Group pens area



Baby calves - individual pens area & feed store



Calves - Group pens area



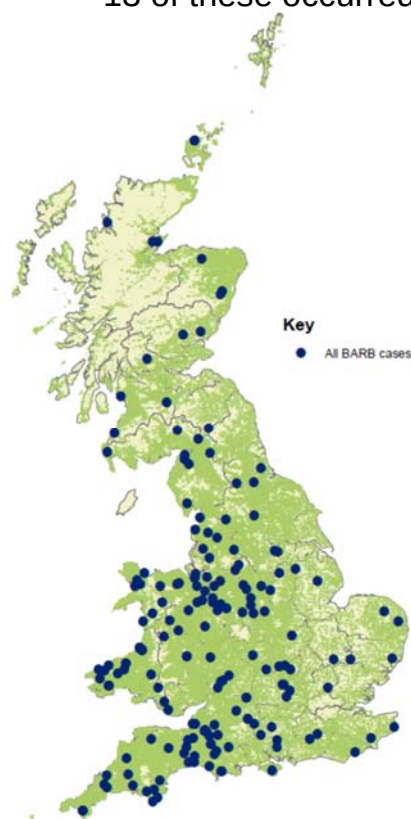
Spatial cluster analysis and descriptive epidemiology of BARB cases in GB (an update of the 2012 study)

- 17 new BARB cases since the 2009 study, of which 4 are atypical
- New spatial cluster analysis using the whole cattle population at risk as the denominator
- In addition, a descriptive epidemiological analysis of the new cases
- Data sources:
 - BSE database (VLA)
 - Cattle Tracing System (CTS)
 - BSE01 forms (epidemiological info)

英国におけるBARB牛の空間的クラスター分析及び記述疫学 (2012年の研究のアップデート)

- 2009年の研究以降、17例の新たなBARB牛、そのうち4例は非定型
- リスクのある全ての牛を分母として用いた新たな空間的クラスター分析
- 加えて、新たな事例の記述疫学的分析
- データソース:
 - BSE database (VLA)
 - Cattle Tracing System (CTS)
 - BSE01 forms (epidemiological info)

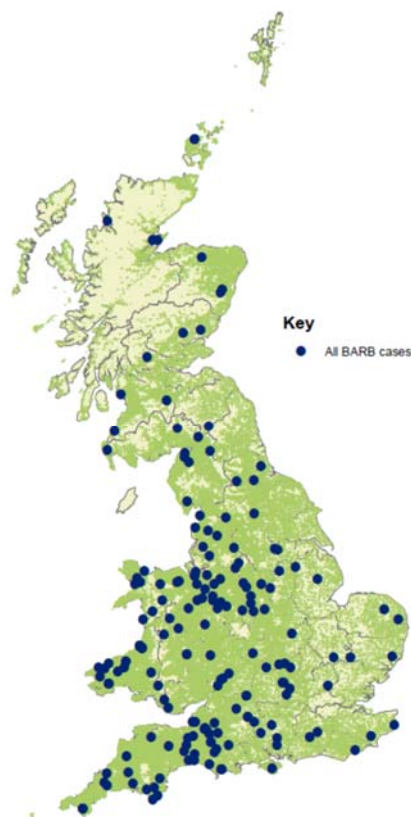
There have been 178 classical BSE BARB cases to date.
13 of these occurred since the 2009 case control analysis.



A Poisson spatial cluster analysis of all 166 holdings with BARB cases to date shows a homogeneous distribution, with **no significant spatial clustering** compared with the general population.

The 166 affected holdings are mapped, along with the cattle population at risk (location of cattle holdings) which was used as the denominator.

現在までに178例の定型BARB牛が発生している。
そのうち13例は、2009年の症例対照分析以降発生している。



現在までにBARB牛が確認された166農場のポアソン空間的クラスター分析。
その結果、一般集団と比較し、特に顕著な空間的クラスターは確認されなかった。

166戸の汚染農場が、分母として用いられたリスクのある牛群（農場の場所）とともにマッピングされている。

There has been a reduction in spatial clustering since the 2009 analysis (which identified 3 areas of excess BARB density), supporting the hypothesis that **the risk of infection in the BARB phase is more geographically homogeneous** than in previous phases of the epidemic.

This spatial distribution provides support to the suggestion that **exposure from a single feedborne source of infection is unlikely**; and does not refute the hypothesis that **exposure was from an exogenous source**.

2009年の分析以降、空間集積性は減少しており、（同分析では、BARB密度が過剰になっている3つの地域が同定された）、以前のBSE流行時期に比して、**BARBフェーズにおける感染リスクの方がより地理的に均一である**という仮説を裏付けている。

この空間的分布は、**単一の飼料由来の感染源からのばく露ではなさそうであることを支持している**；**外的な感染源からのばく露**という仮説を否定するものではない。

Farms with multiple BARB cases

- Of 166 farms with classical BARB cases, **ten** had had more than one case.
- One farm had three cases (two were detected on the same day, by cohort surveillance), and the rest each had two cases.
- For two of the ten farms, the second BARB case was detected as a result of clinical suspicion. For five out of ten, the subsequent BARB cases were detected by cohort surveillance.
- On nine out of the ten farms, the second cases were detected within a short time period of the first, i.e. approximately a year.

The existence of one BARB case may increase the likelihood of finding another BARB case on the same farm, due to increased farmer awareness and active surveillance measures.

複数のBARB牛が発生した農場

- 定型BARB牛が発生した166戸の農場のうち**10戸**では、1例以上の事例が発生した。
- 1戸の農場では3例発生しており(2例は、コホート・サーベイランスにより、同日に検出)、残りの農場では各戸2例発生している。
- 10農場のうち2戸では、2例目のBARB牛は、臨床的に疑われた結果、検出された。10農場中5戸では、コホート・サーベイランスにより、後続のBARB牛が検出された。
- 10農場のうち9戸では、2例目の事例は、1例目の確認から短い期間(約1年)で検出された。

1例のBARB牛の存在は、その農場におけるさらなるBARB牛の発見につながる可能性を高める。それは、農場主の注意が喚起され、アクティブ・サーベイランス措置が強化されることによる。

Thank you



ご清聴
ありがとうございました



Cases of atypical BSE in Great Britain

Year	H-type	L-type
2005	1	1
2006	0	1
2007	2	2
2008	0	2
2009	1	0
2010	0	1
2011	1	1
2012	0	1
2013	1	0
2014	0	0
2015	1	0
2016	0	0
Total	7	9

英国における非定型BSE牛

Year	H-type	L-type
2005	1	1
2006	0	1
2007	2	2
2008	0	2
2009	1	0
2010	0	1
2011	1	1
2012	0	1
2013	1	0
2014	0	0
2015	1	0
2016	0	0
Total	7	9