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

Animal & Plant Health Agency

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

Science of BSE and Food Safety Conference
Food Safety Commission Japan, Tokyo
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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

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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、グリオーシス及び空胞形成。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

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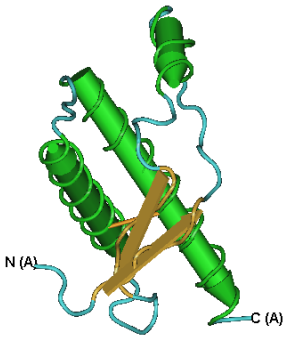
Prions and Prion Diseases

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



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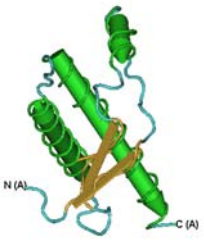
プリオン及びプリオン病

- プリオンとは？
- プリオン病とは？



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The essential daily briefing

FROM The INDEPENDENT

THURSDAY 10 SEPTEMBER 2015

ARTS

Apocalypse Slough

Rob Lowe's new comic adventure

P40

An appeal to Europe's leaders – Get a grip on the refugee crisis P4&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

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6 NEWS

COVER STORY

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

Disease trigger Prions

Q & A Should I be worried?

REACTION

Findings need further investigation, say experts

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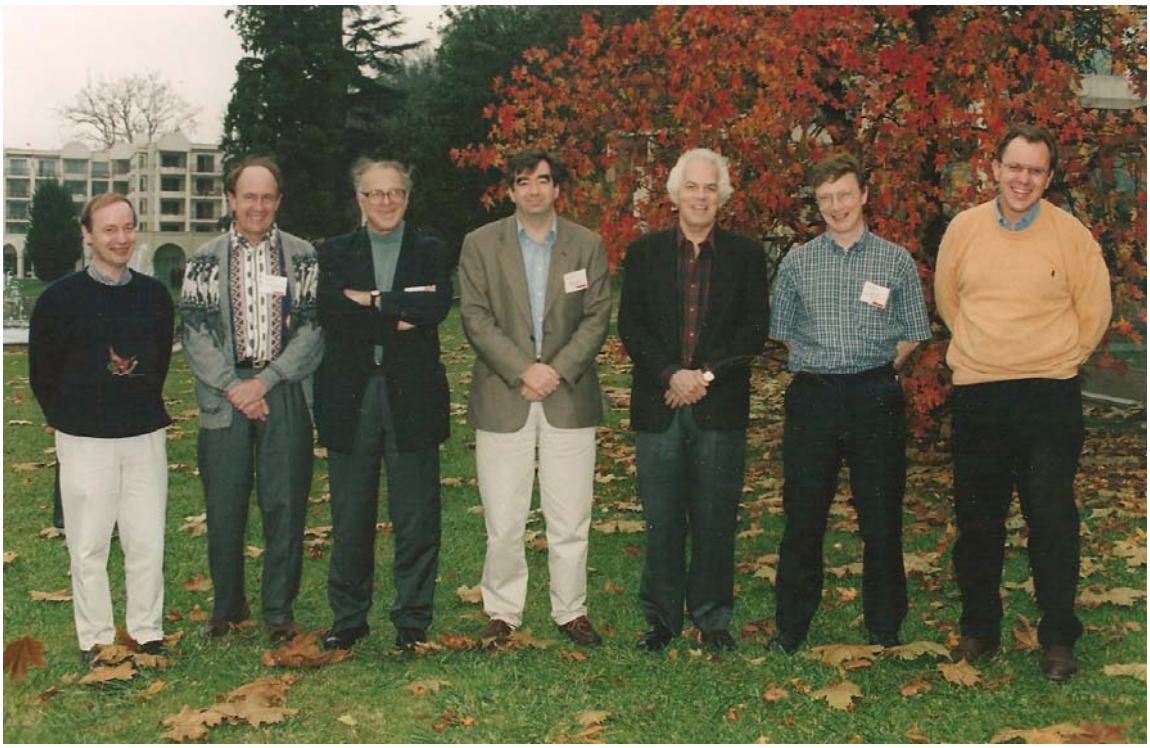

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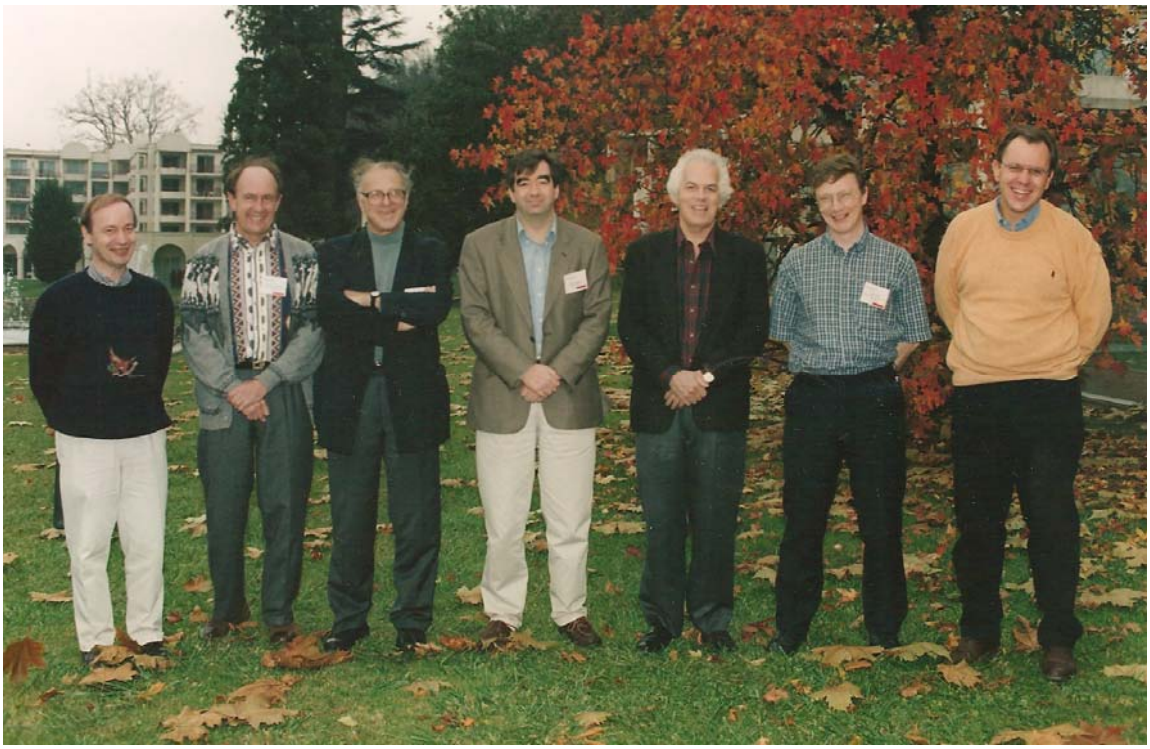

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Prions are :

- 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

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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

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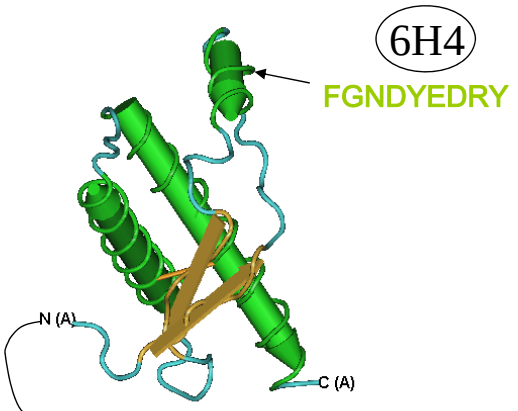
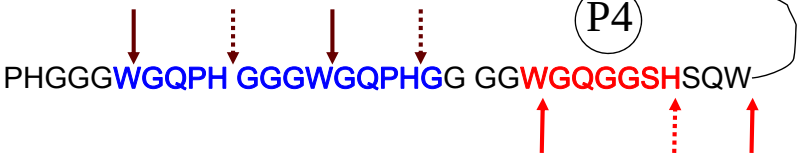
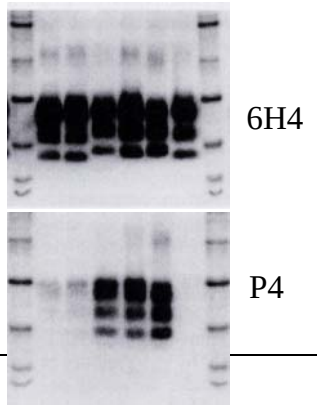
PK cleavage sites in ovine PrP^D linked to scrapie (⇓) or BSE (⇓) in sheep

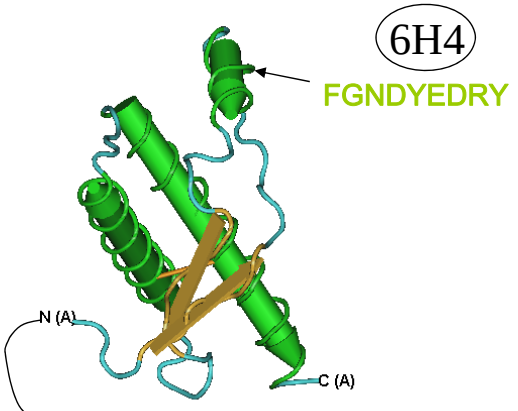


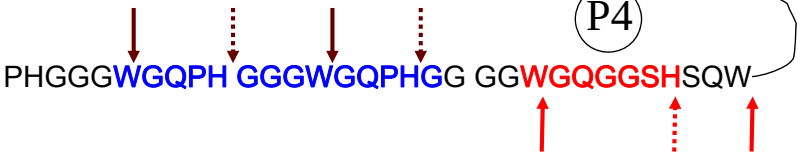


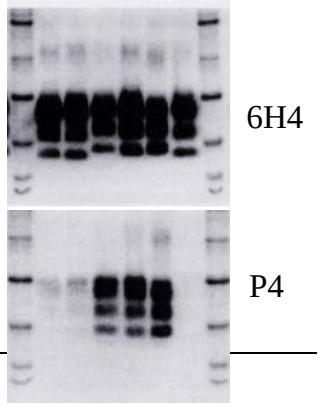


Stack et al., 2002; Thuring et al., 2004;
Baron et al., 2004;

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







Stack et al., 2002; Thuring et al., 2004;
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Bovine spongiform encephalopathy

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

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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

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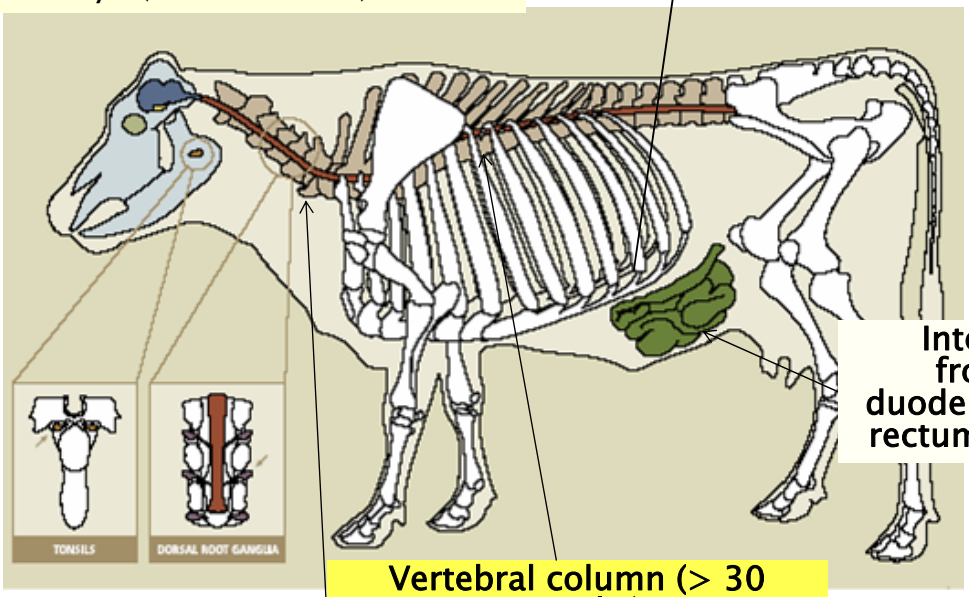
Where are the BSE prions?

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

Spinal cord (> 12 months)



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

Vertebral column (> 30 months)
Dorsal root ganglias

Tonsils (all ages)

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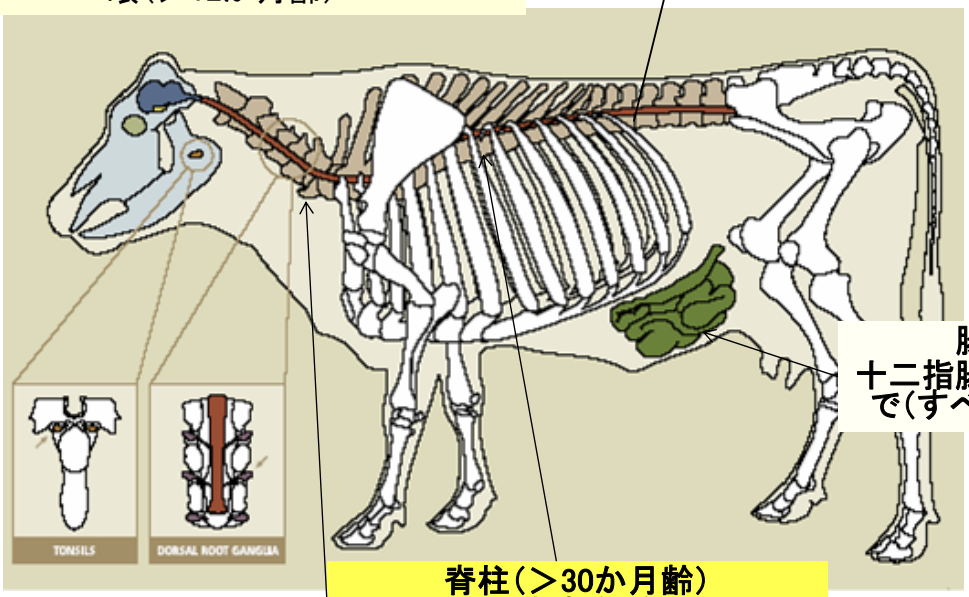
どこにBSEプリオンがあるのか?

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)

脊柱(>30か月齢)
背根神経節

扁桃(すべての月齢)

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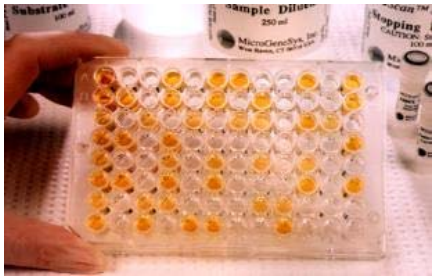
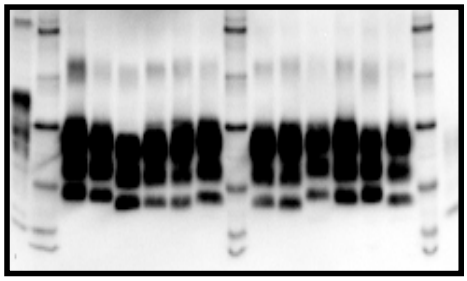
Molecular signals for BSE

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





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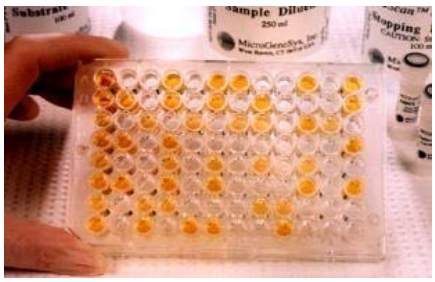
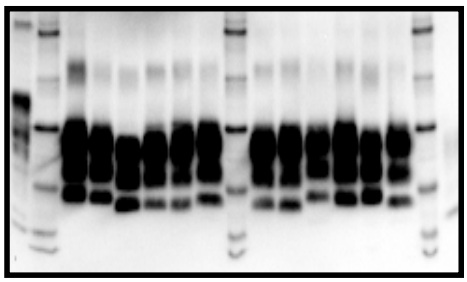
BSEの分子シグナル

- **ELISA** 法によるPrPの検出 – '迅速試験' - 通常の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





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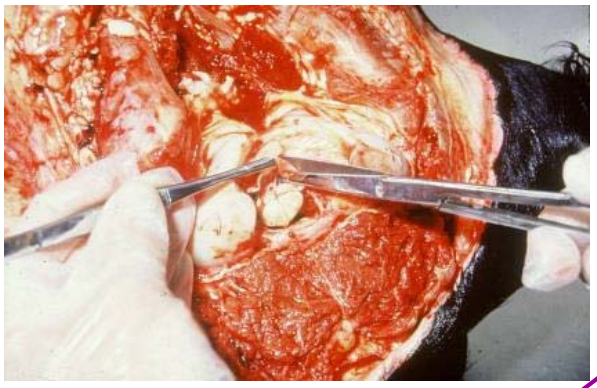
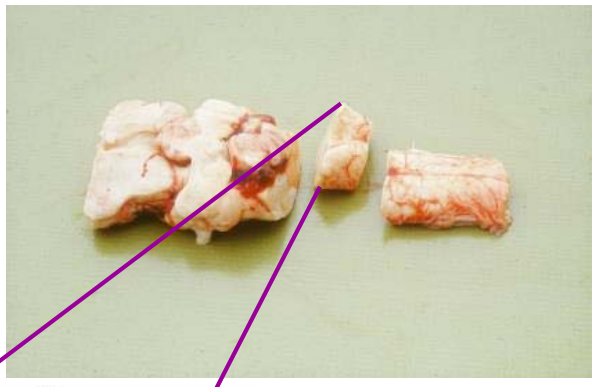
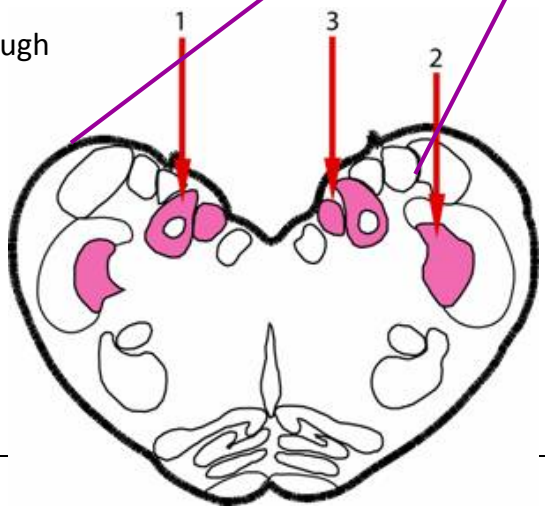




Brainstem sampled through the *foramen magnum*



Key diagnostic target areas

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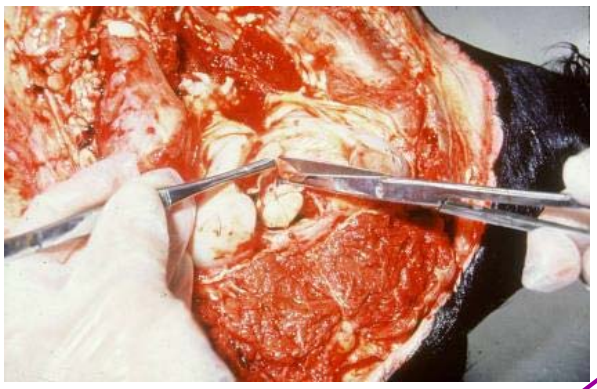
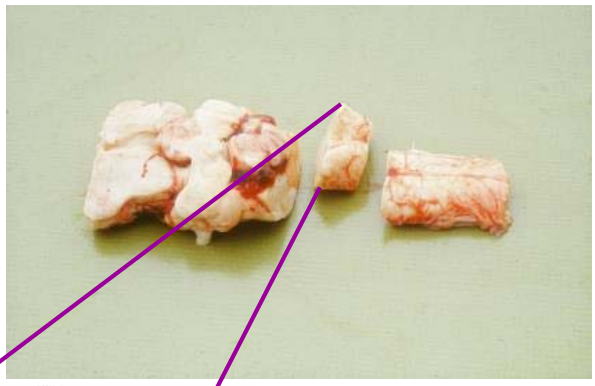
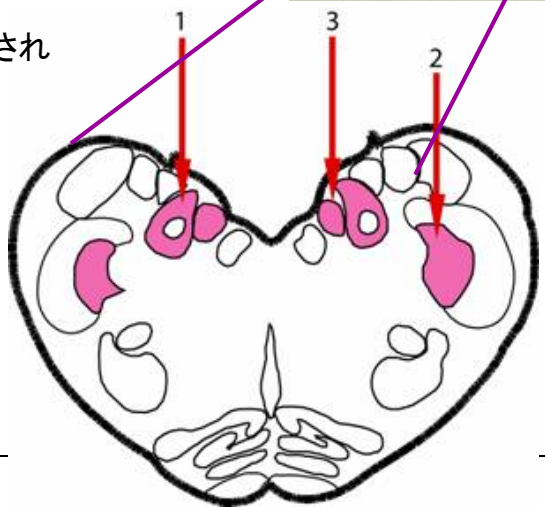




大後頭孔を通じて採取された脳幹標本



鍵となる診断上の標的領域

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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

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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

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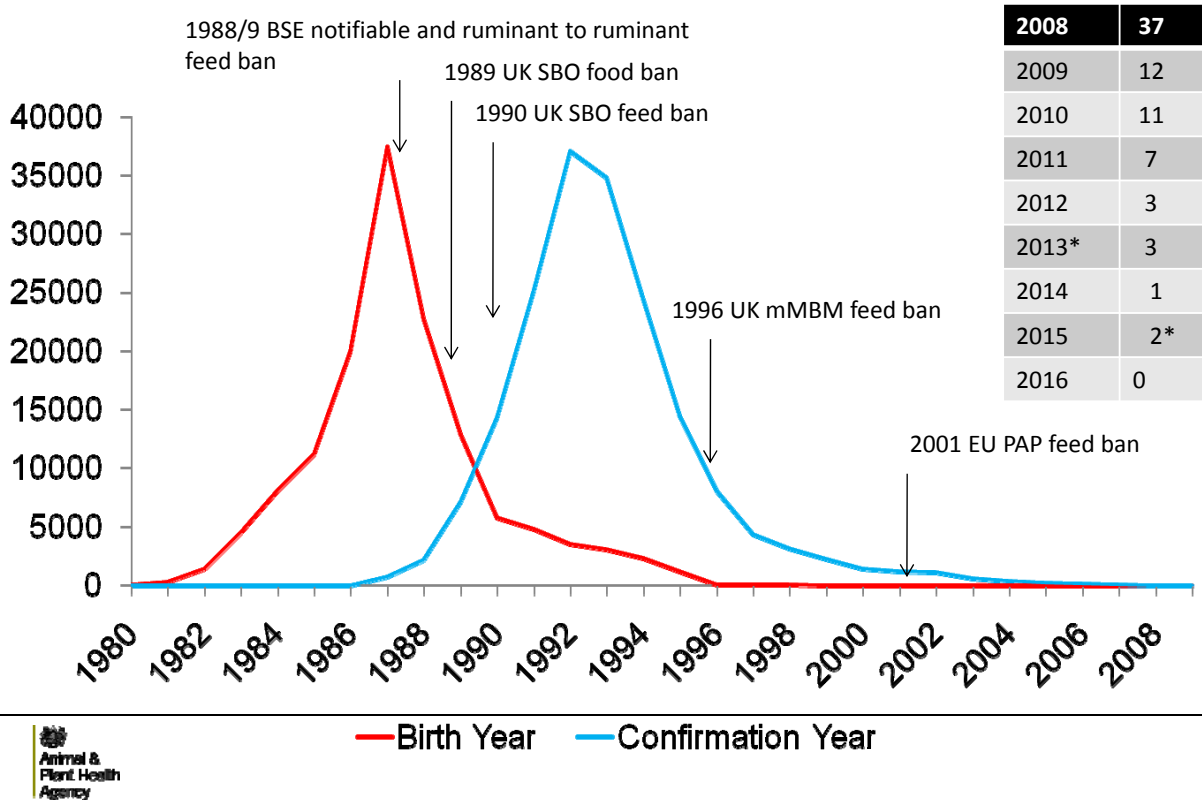
The rise and fall of the UK BSE epidemic



2008	37
2009	12
2010	11
2011	7
2012	3
2013*	3
2014	1
2015	2*
2016	0

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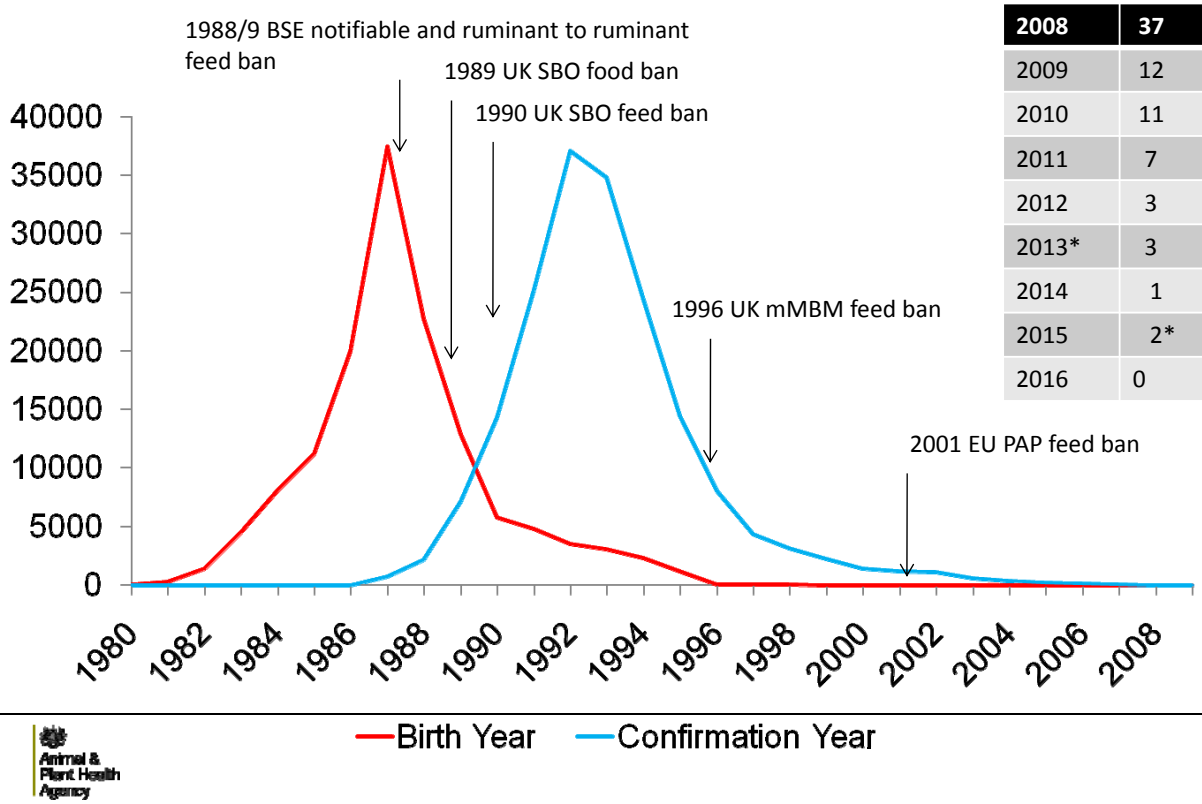
英国におけるBSE発生の増加と減少



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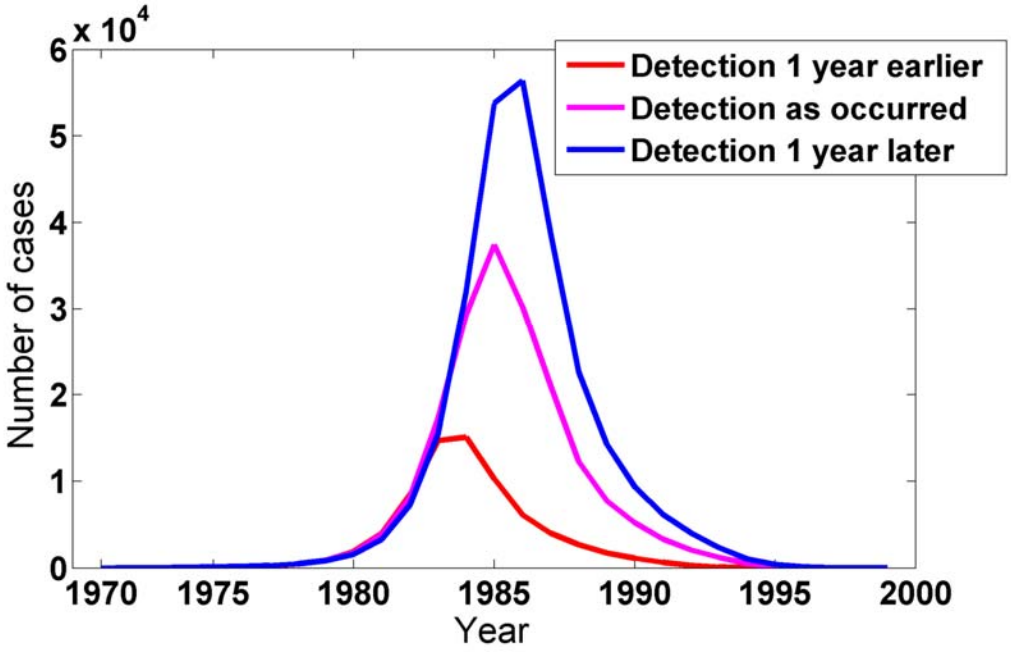
Predicted impact of earlier/later implementation of BSE control measures



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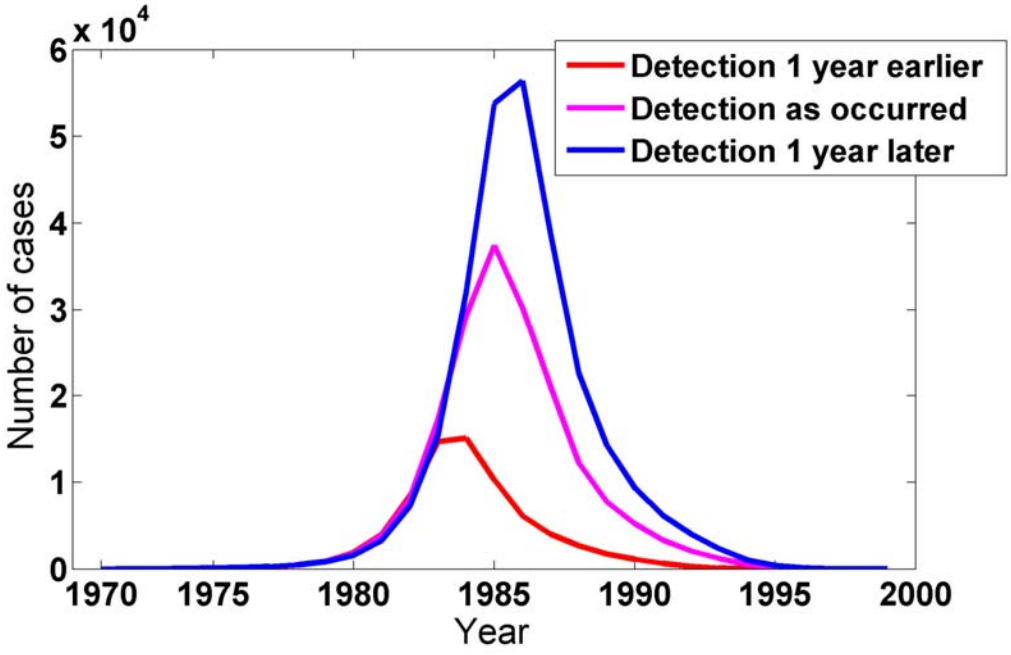
BSE管理措置を早期／後期に実行したことにより予想される効果



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Classical and Atypical types of BSE

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BSEの定型と非定型

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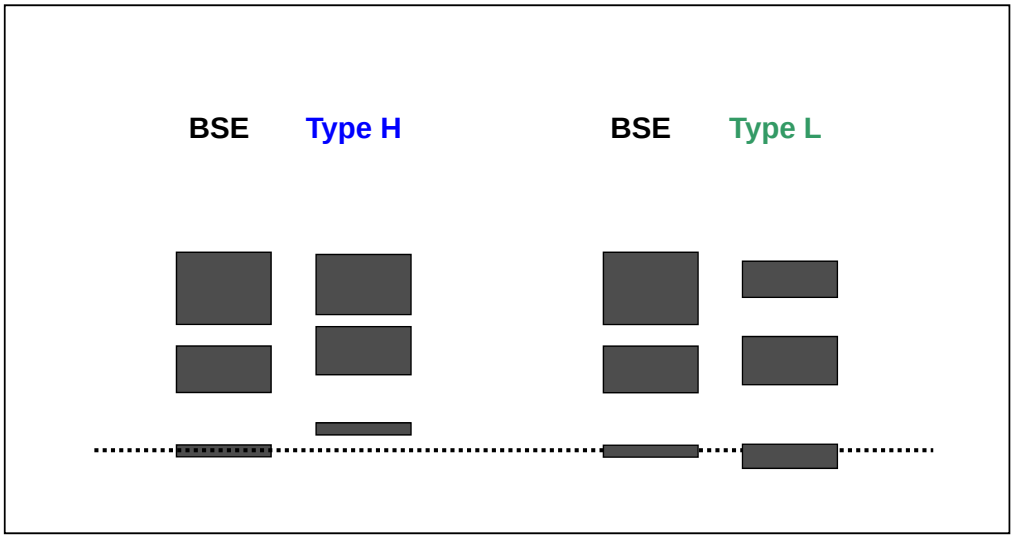
Molecular patterns of PrPres in classical and atypical BSEs



Type H (High)
France + others

Type L (Low)
Japan & Italy

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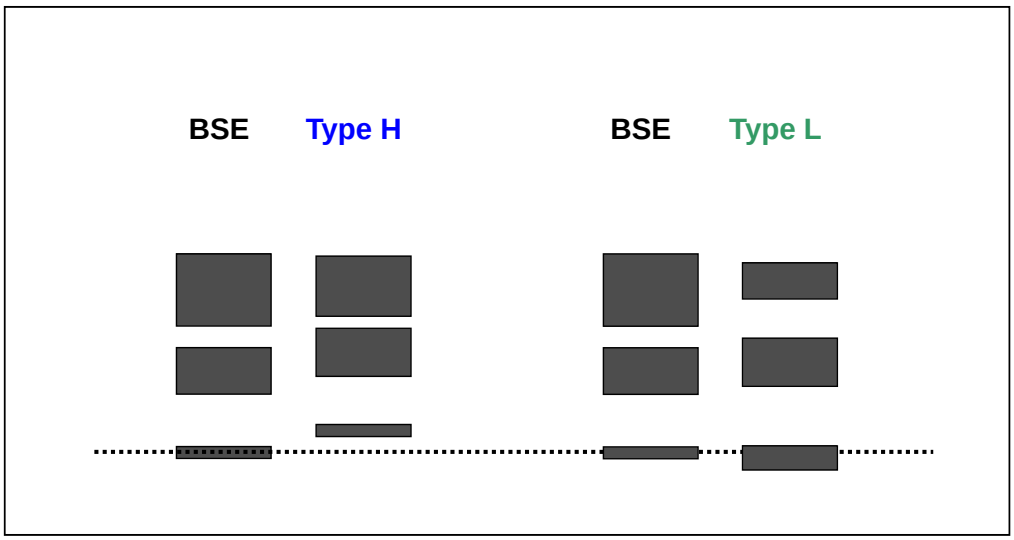
定型及び非定型BSEの PrPreの分子パターン



Type H (High)
France + others

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Japan & Italy

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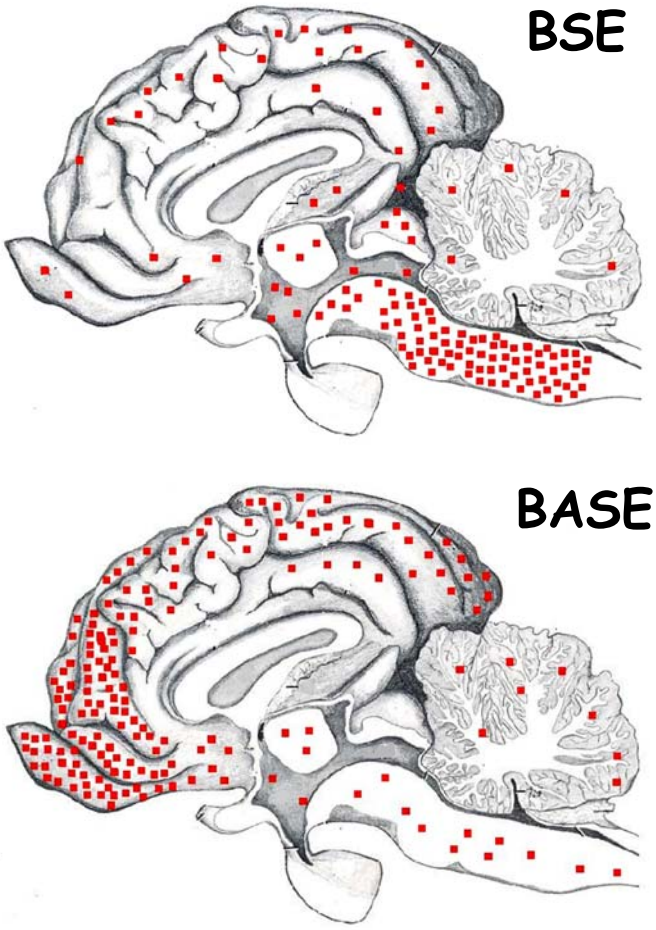
Brain regional distribution of PrP^D in BSE and BASE



Casalone et al., 2004

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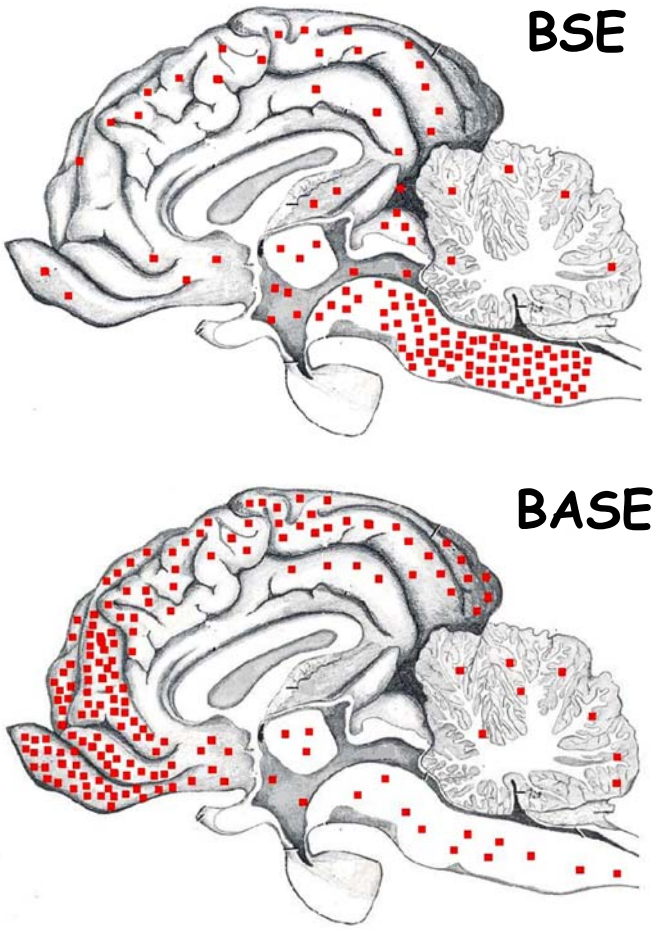
BSE及びBASEにおけるPrP^D の脳内分布



Casalone et al., 2004

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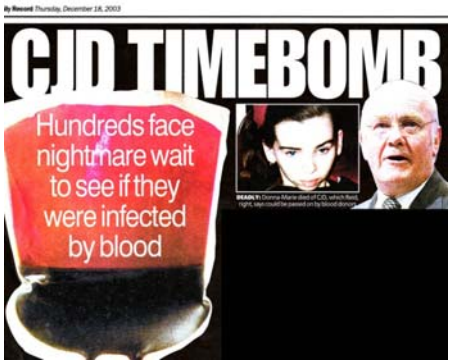
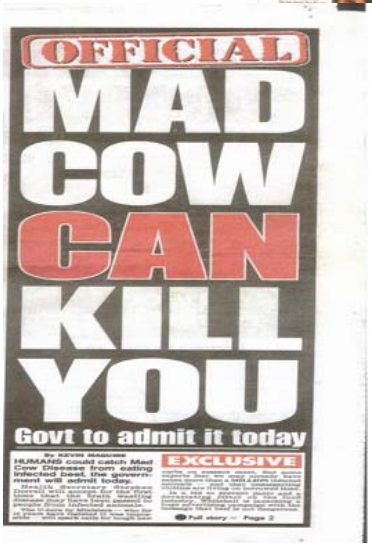
Mad Cow Disease or Bovine Spongiform Encephalopathy

↓

New variant Creutzfeldt-Jakob disease

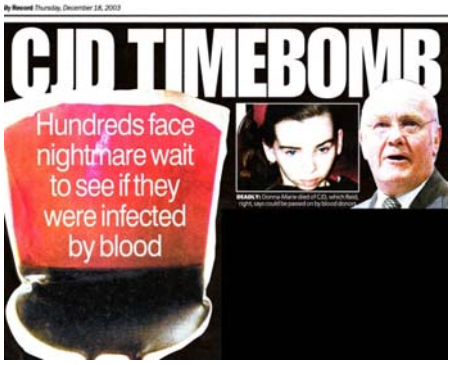


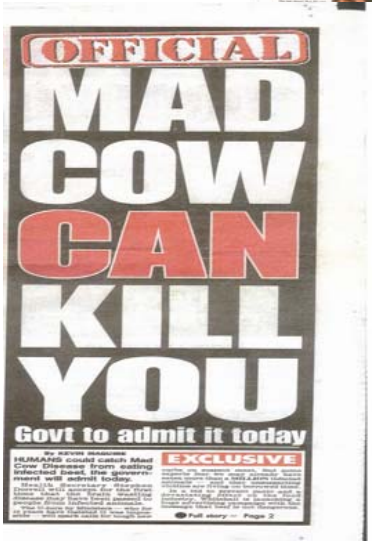


狂牛病もしくは牛海綿状脳症

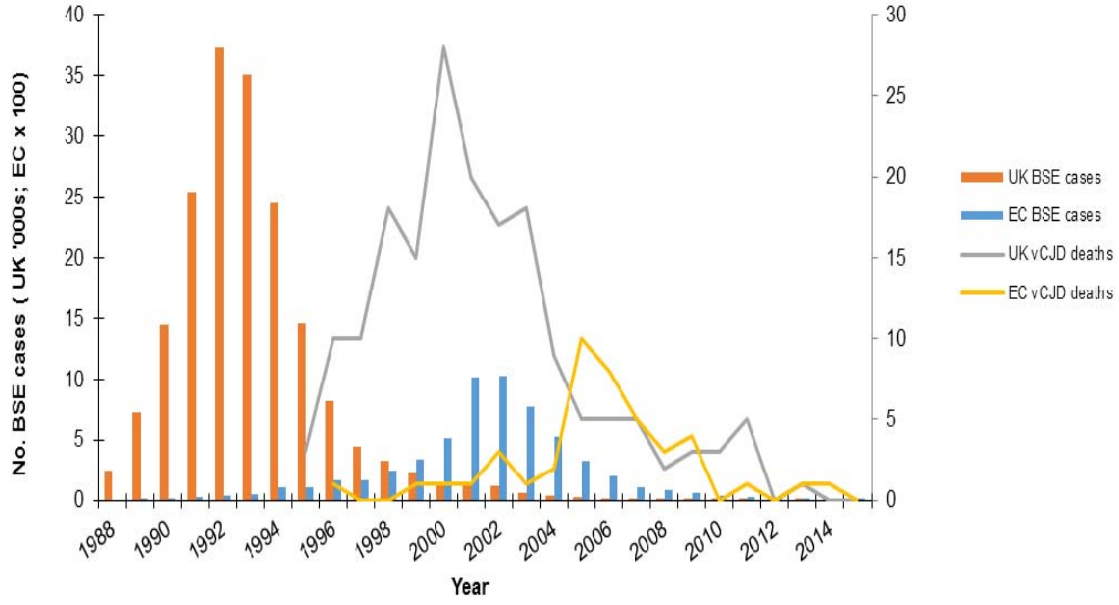
↓

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



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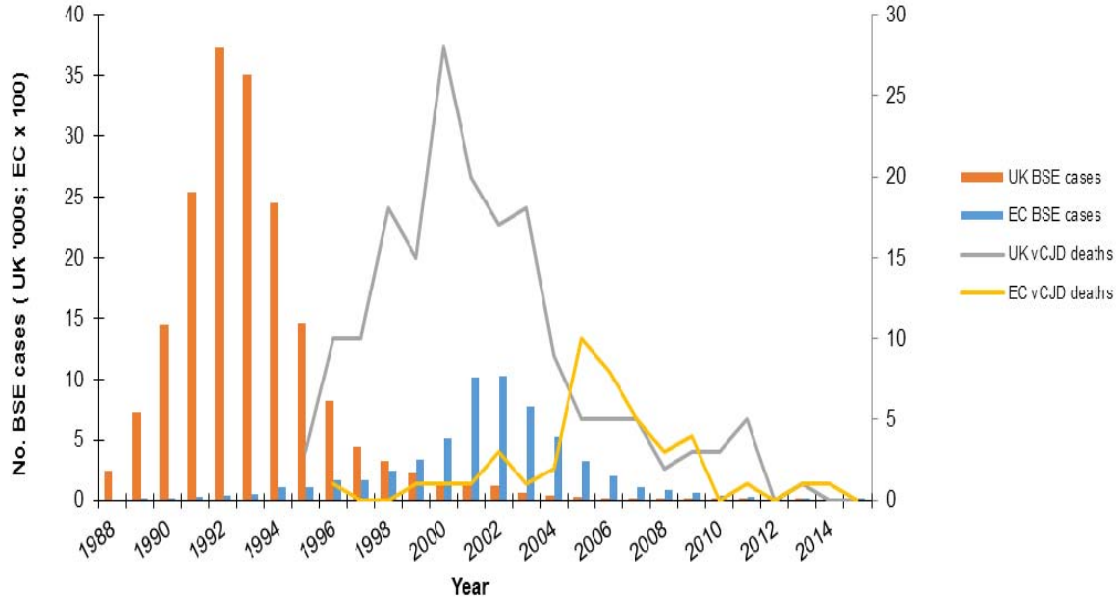
英国及びヨーロッパにおける BSE(1988-2015) 及びvCJD (1994-2015)の発生数



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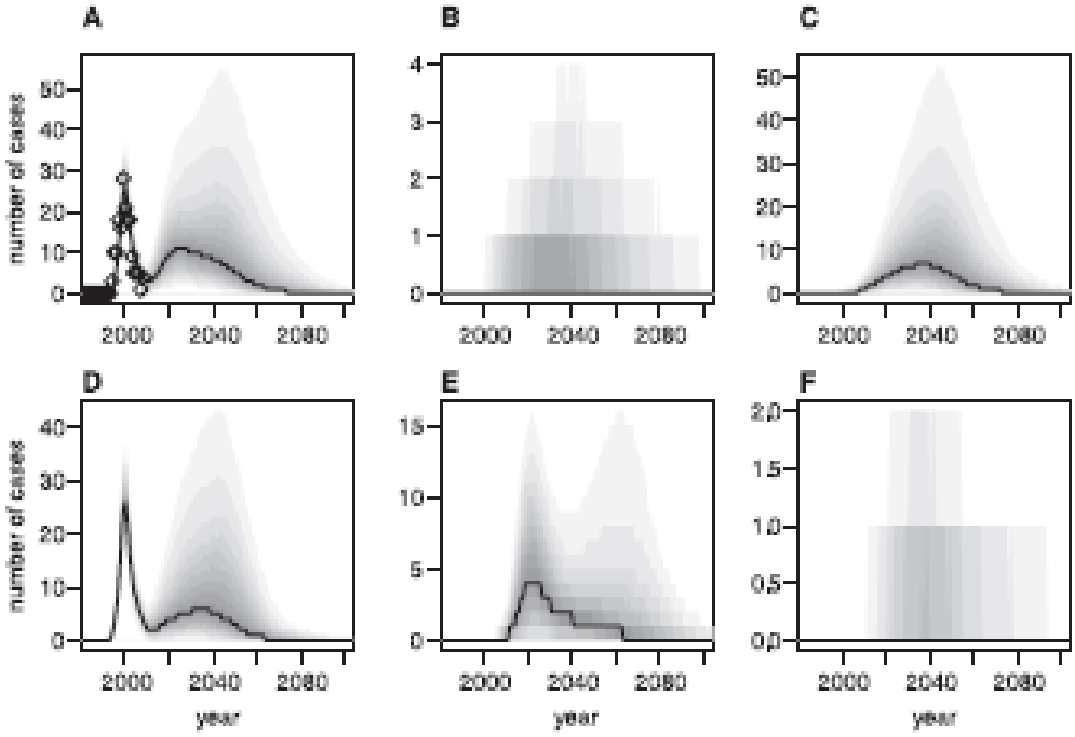
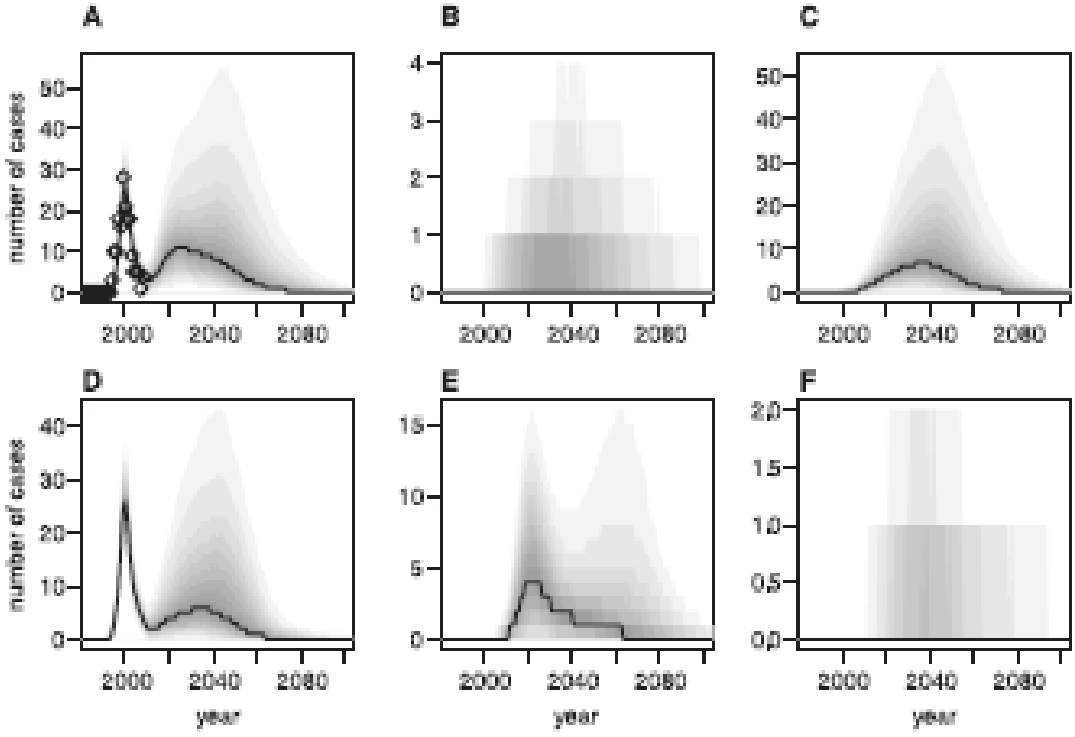
Uncertainty in the tail of the vCJD epidemic
Garske & Ghani, PLoS One, 2010



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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英国における BSEの起源、過去及び現在

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The Horn Review, 2001

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

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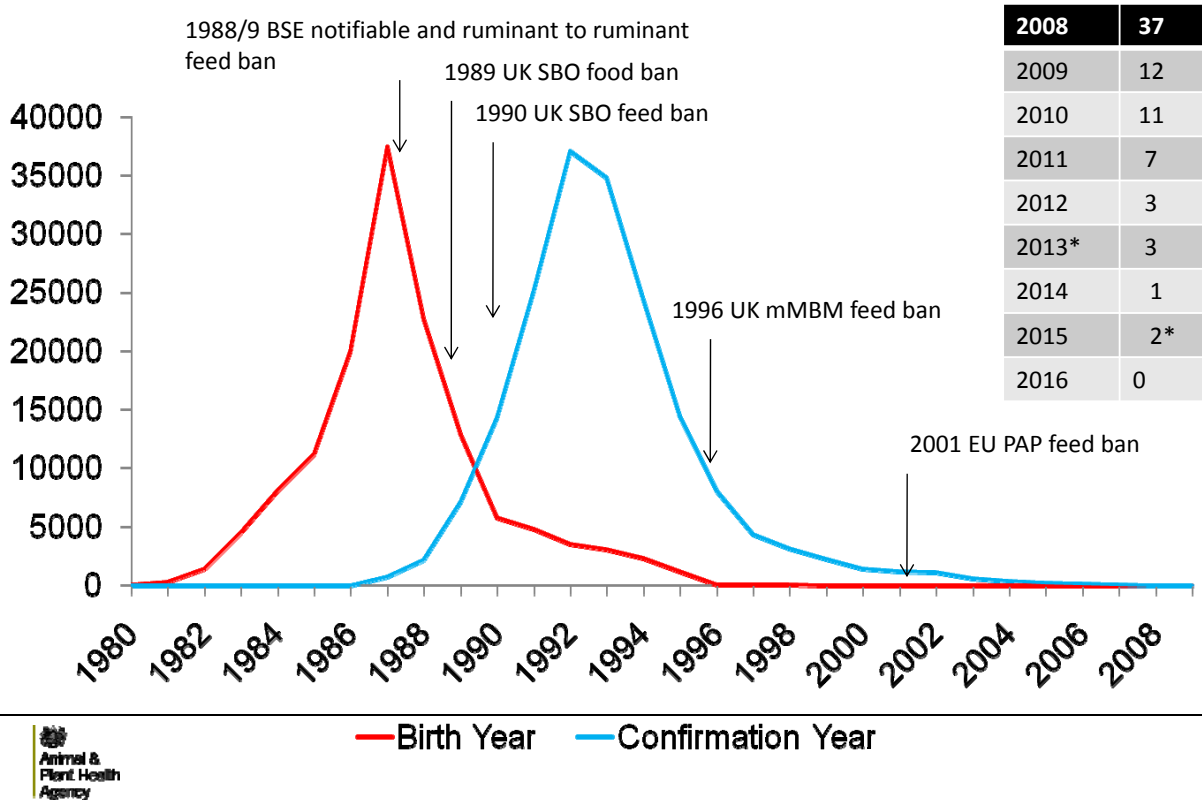
The rise and fall of the UK BSE epidemic



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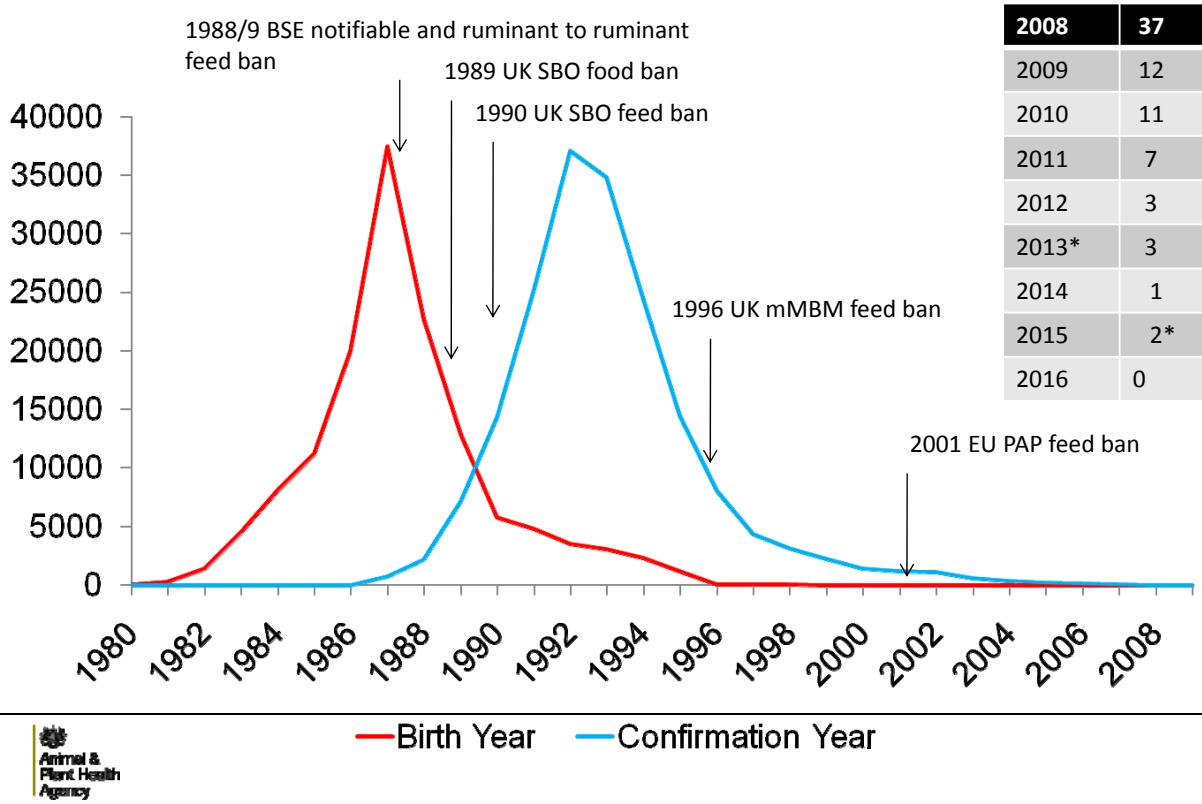
英国におけるBSE発生の増加と減少



2008	37
2009	12
2010	11
2011	7
2012	3
2013*	3
2014	1
2015	2*
2016	0

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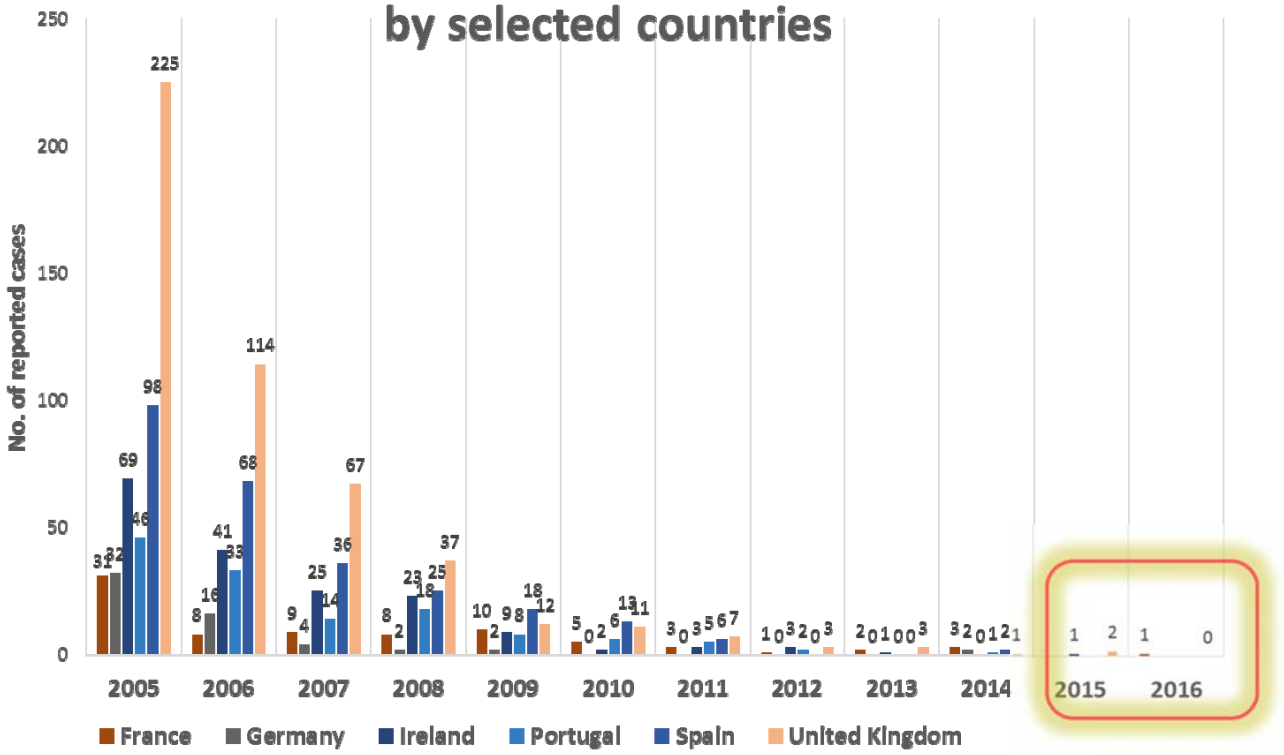
Number of BSE cases reported to OIE each year by selected countries



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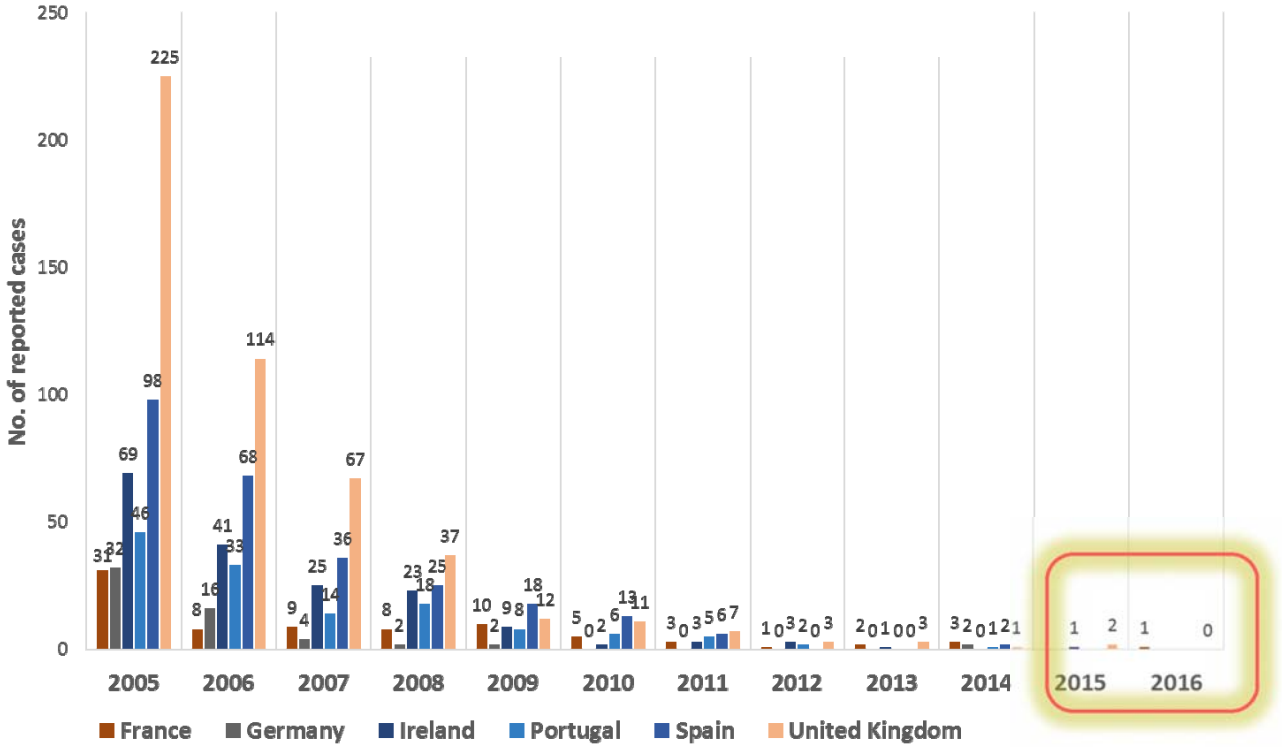
主要国がOIEに通報したBSE発生例の数（年別）



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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**)

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欧州及びカナダにおける定型BSEの最近の事例 (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**)

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How much infectivity….?

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感染性はどの程度か….?

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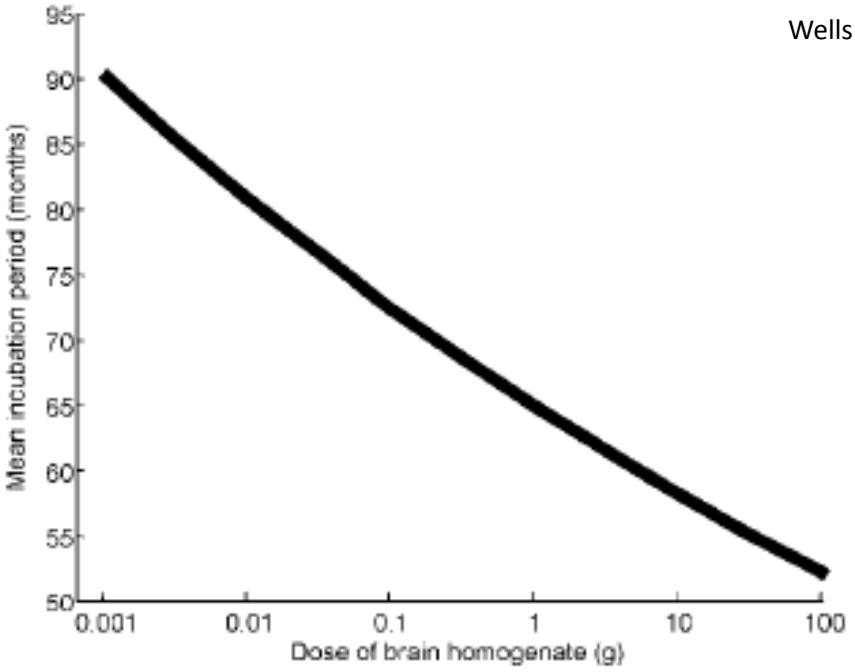
Dose-survival time curve for oral infection of cattle with classical BSE prions

Wells et al, 2007



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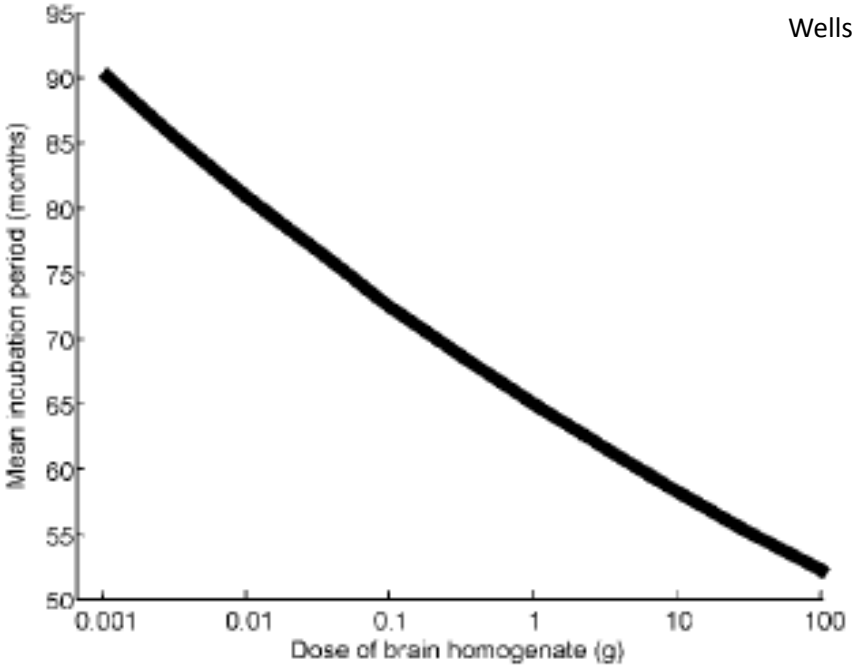
定型BSEプリオンによる牛の経口感染の投与量-生存時間曲線

Wells et al, 2007



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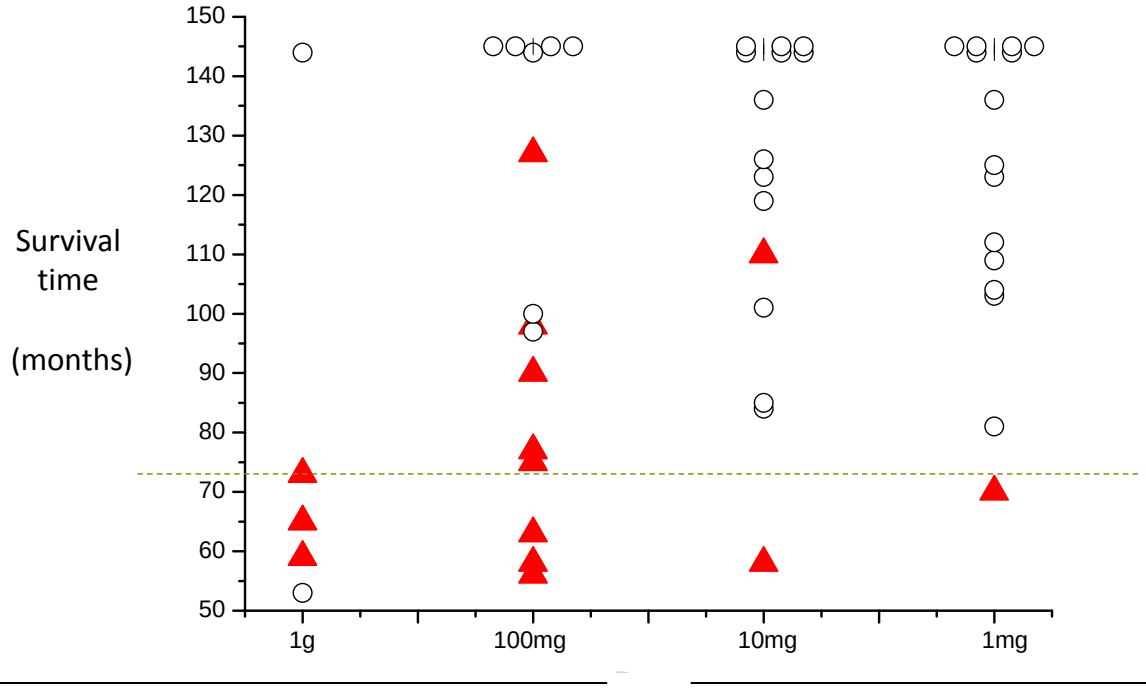
Oral dose response survival times in cattle fed BSE-infected brain



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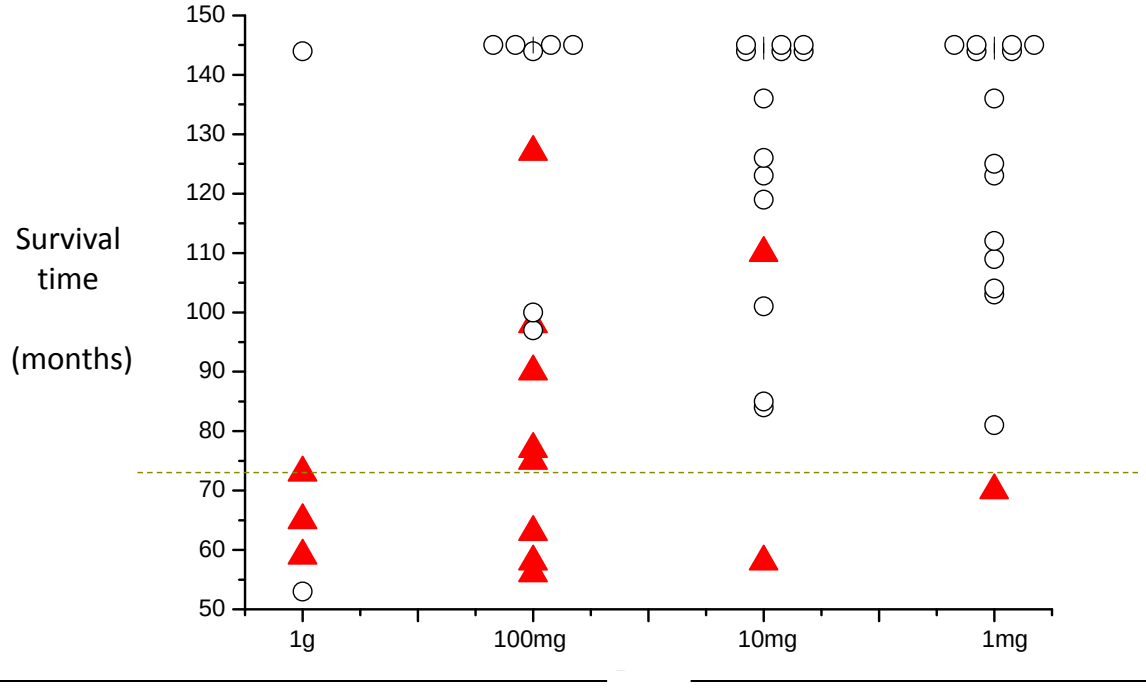
BSE感染牛脳組織を投与された牛における経口投与反応生存時間



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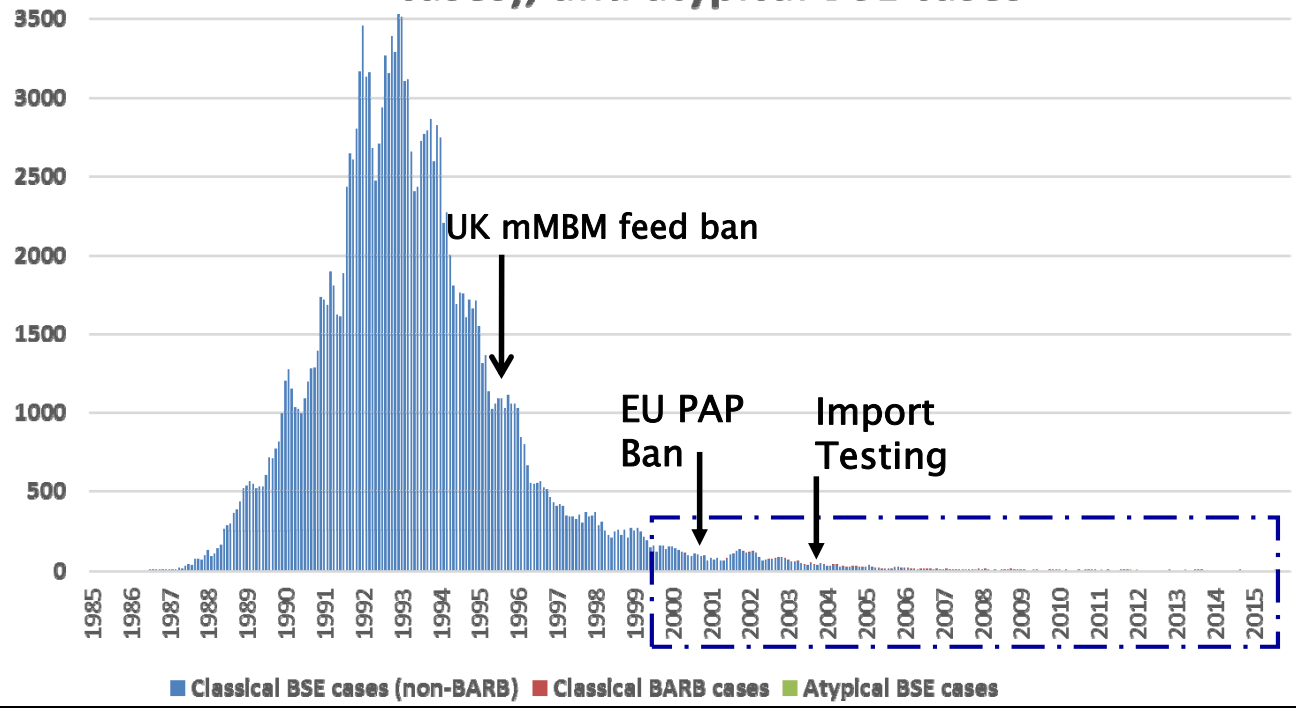
BSE epidemic curve for GB; including cases born after the 1996 GB mMBM feed ban (BARB cases), and atypical BSE cases



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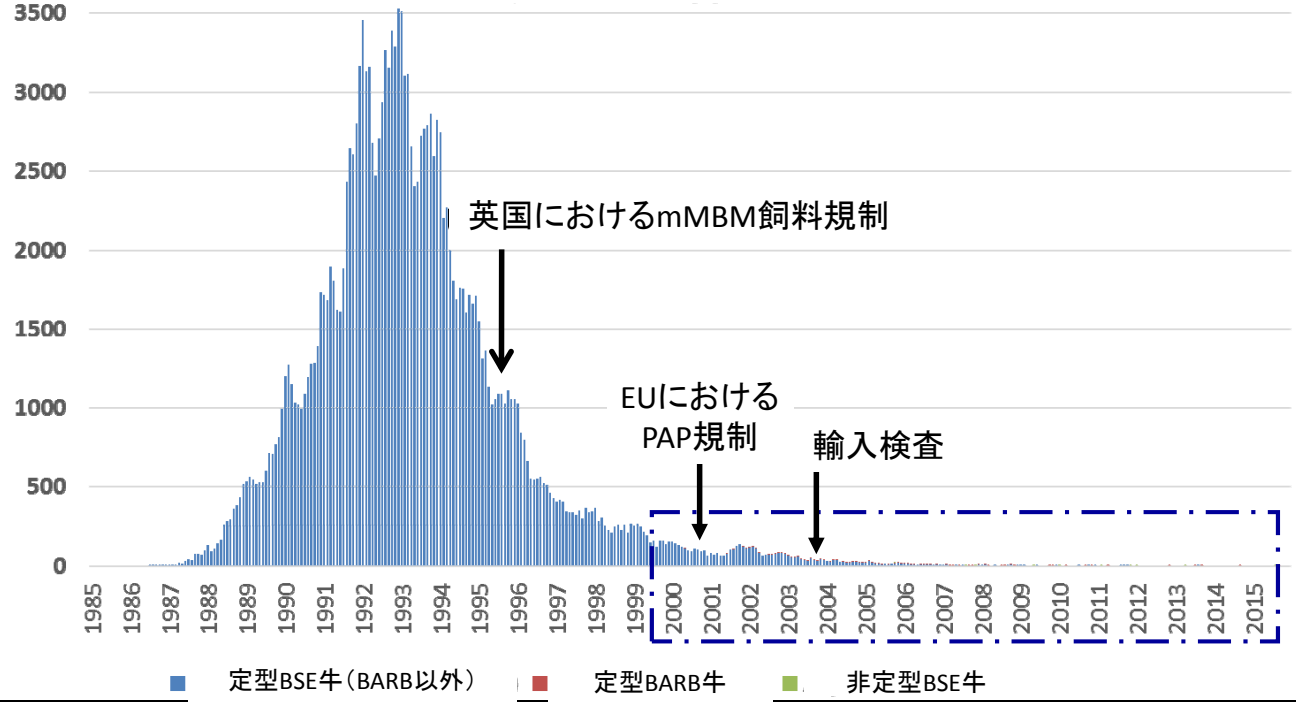
英国のBSE流行曲線：1996年の英国における哺乳類動物肉骨粉（mMBM）飼料規制後に出生したBSE牛（BARB牛）及び非定型BSE牛を含む



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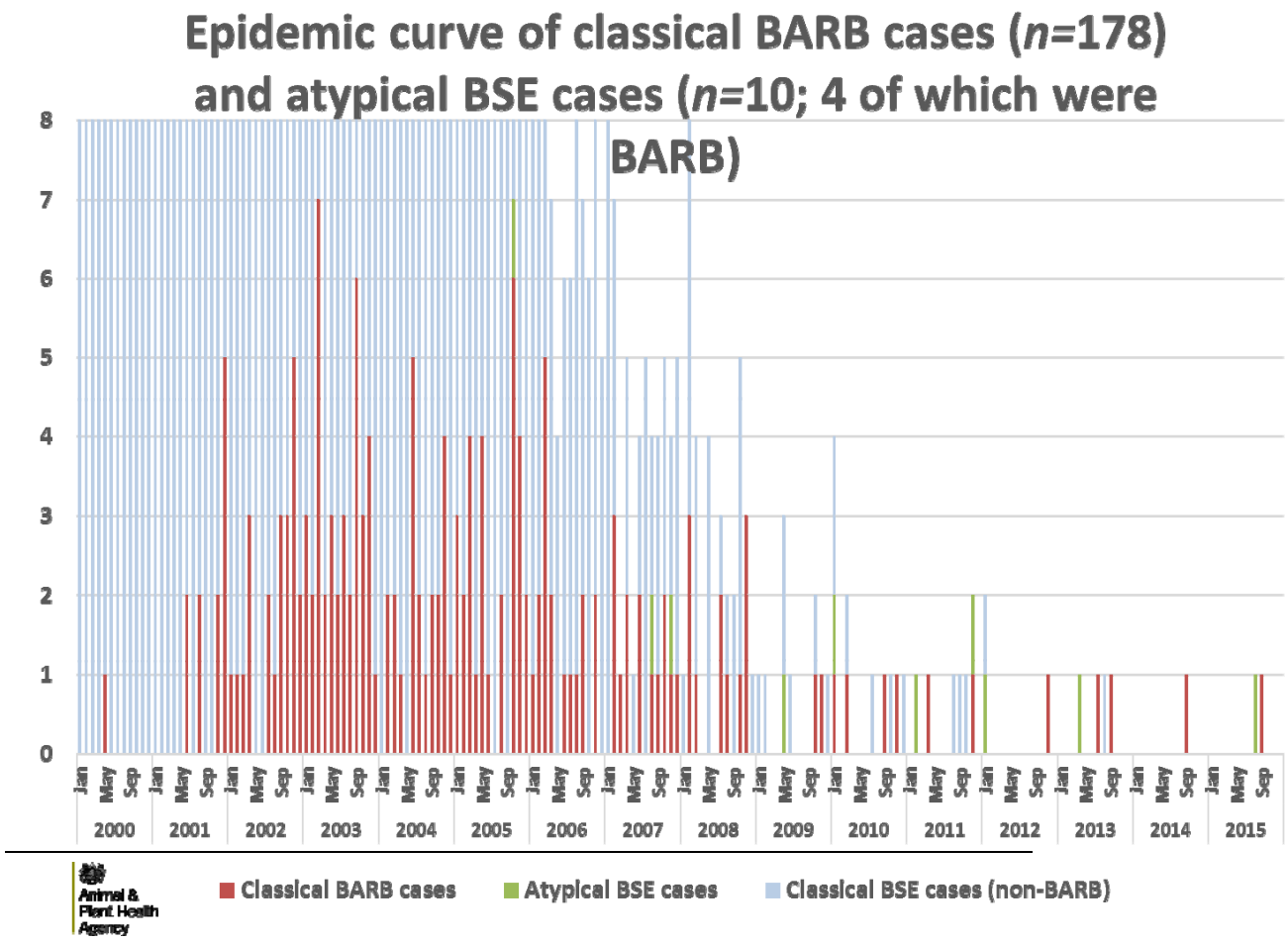
Epidemic curve of classical BARB cases (n=178) and atypical BSE cases (n=10; 4 of which were BARB)
0
1
2
3
4
5
6
7
8
Jan May Sep
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
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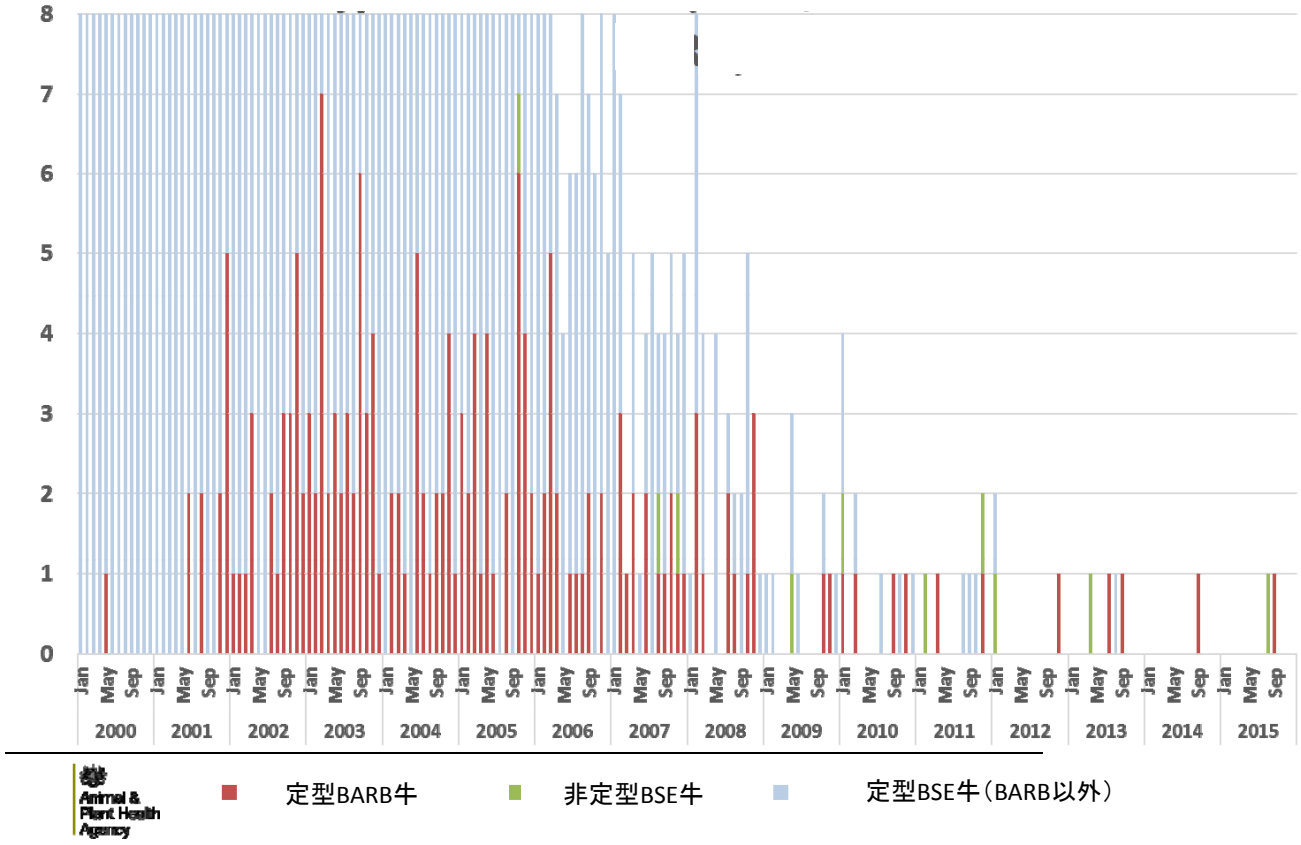
Classical BARB cases
Atypical BSE cases
Classical BSE cases (non-BARB)


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
0
1
2
3
4
5
6
7
8
Jan May Sep
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
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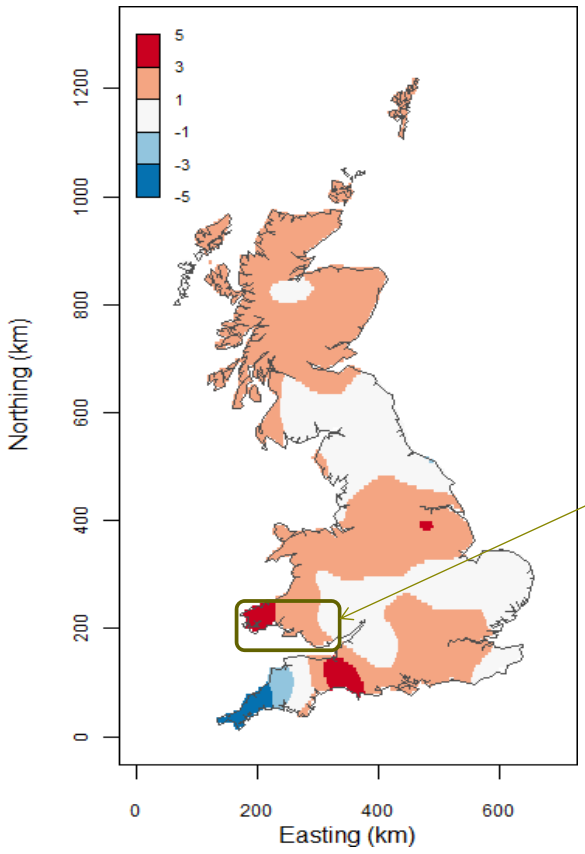
定型BARB牛
非定型BSE牛
定型BSE牛（BARB以外）



GB case : 15/0002, September 2015

Classical BSE, DoB: May 2009

Location of case : 15/0002

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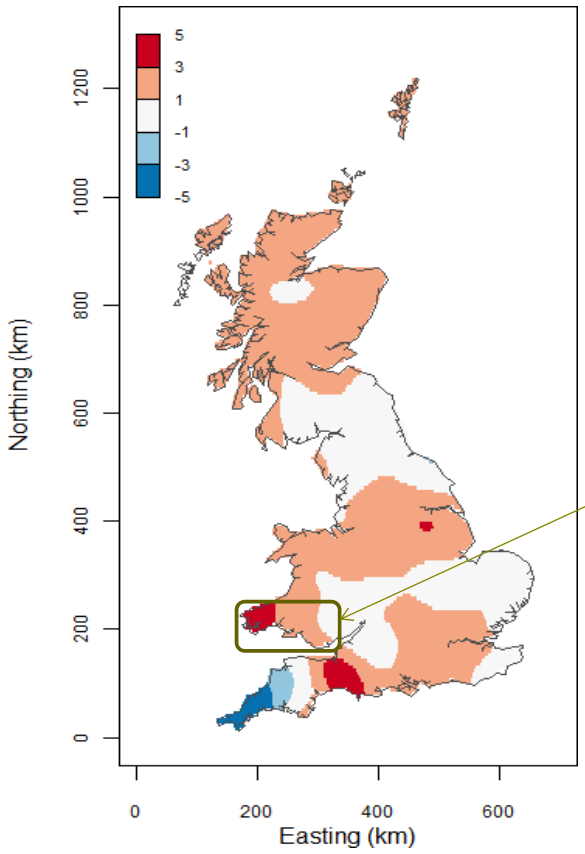

GB case : 15/0002, September 2015

Classical BSE, DoB: May 2009

Location of case : 15/0002

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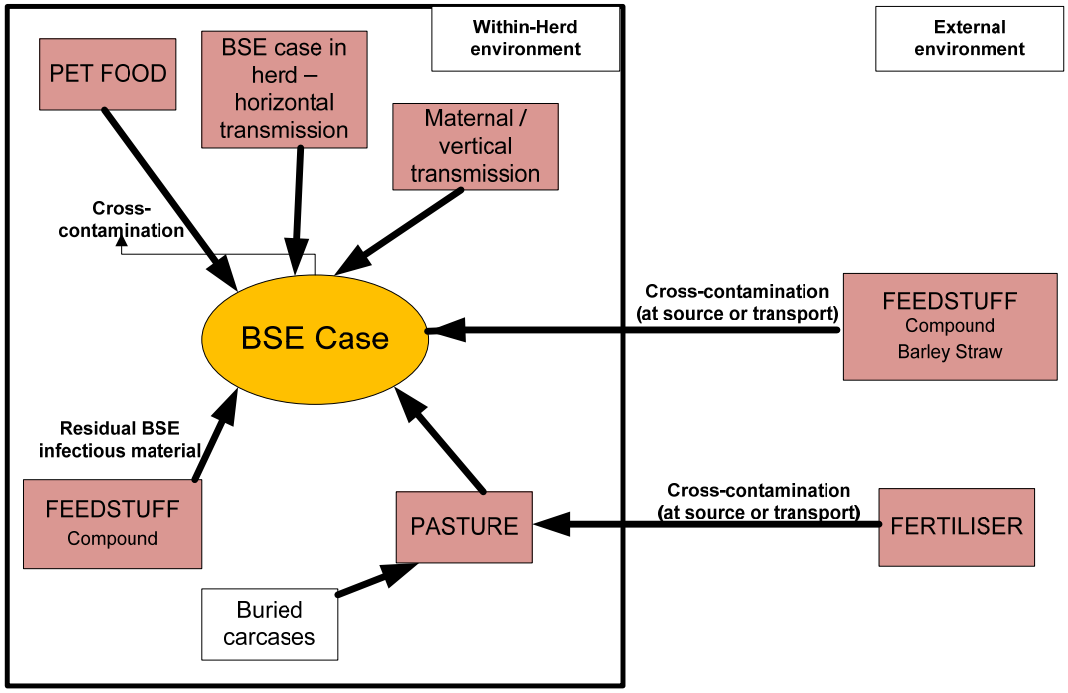
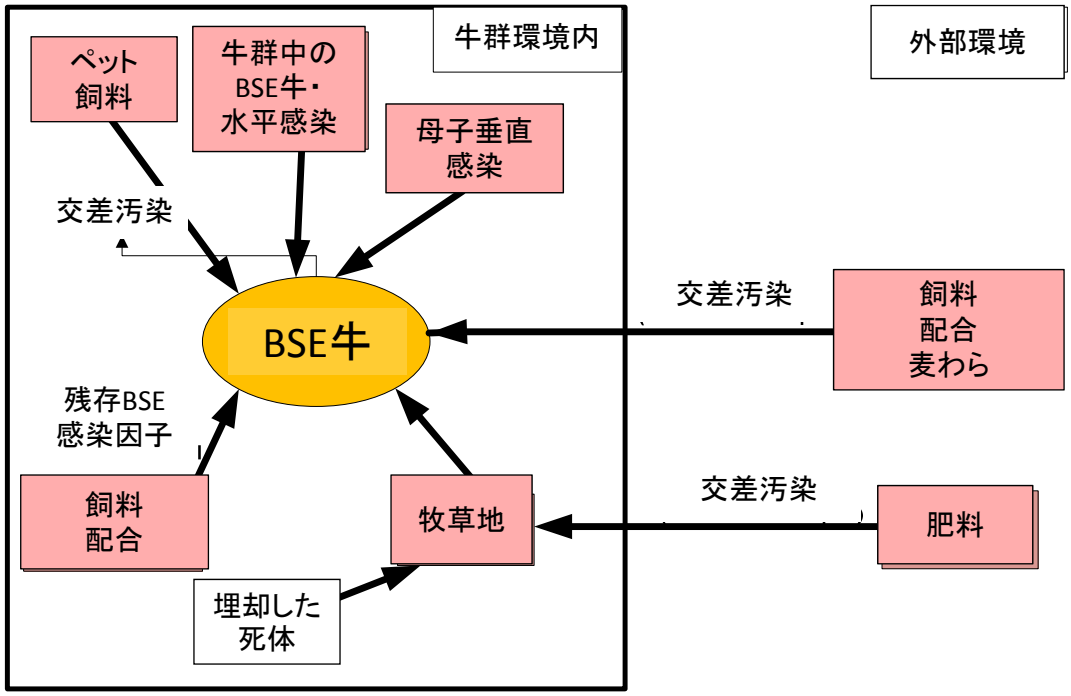
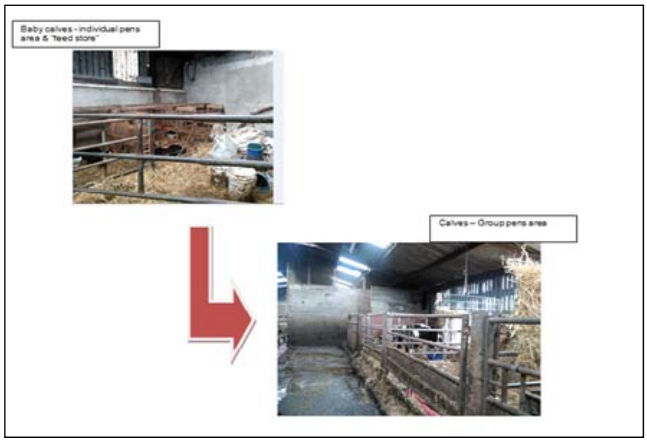
Risk Pathways



リスク・パスウェイ





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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)

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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)

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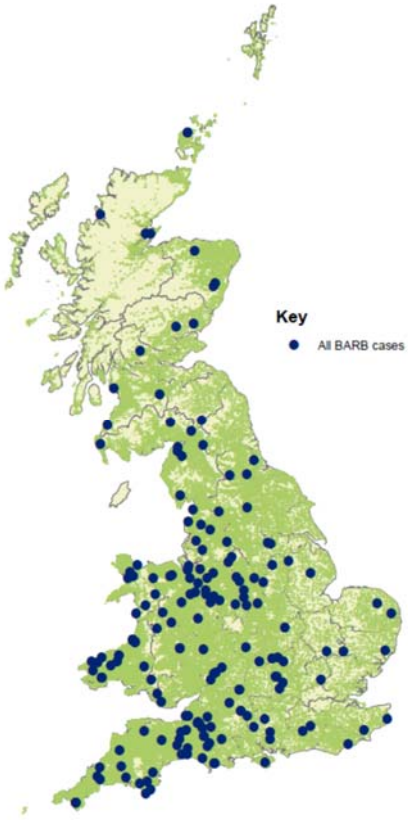
There have been 178 classical BSE BARB cases to date.
13 of these occurred since the 2009 case control analysis.



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.

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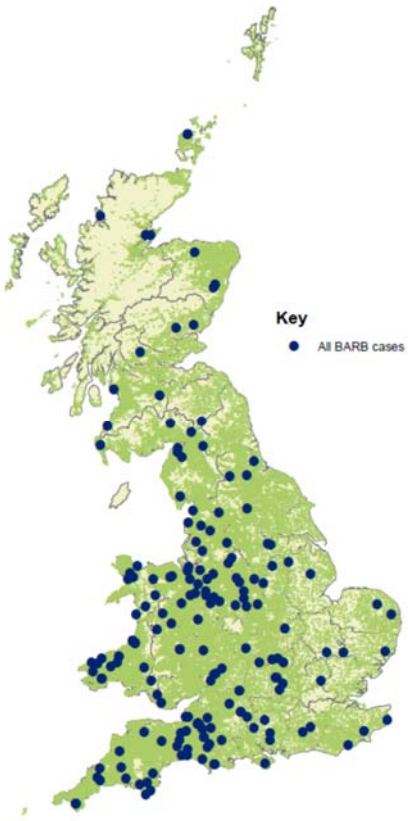
現在までに178例の定型BARB牛が発生している。
そのうち13例は、2009年の症例対照分析以降発生している。



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。

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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**.

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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。

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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.

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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。

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Thank you

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ご清聴
ありがとうございました

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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

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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

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