Variant Creutzfeldt-Jakob disease

Update, MV case, Appendix III, blood tests, EID article

Professor Robert Will
National CJD Research and Surveillance Unit
University of Edinburgh
United Kingdom

VARIANT CREUTZFELDT-JAKOB DISEASE: CURRENT DATA (MAY 2017)

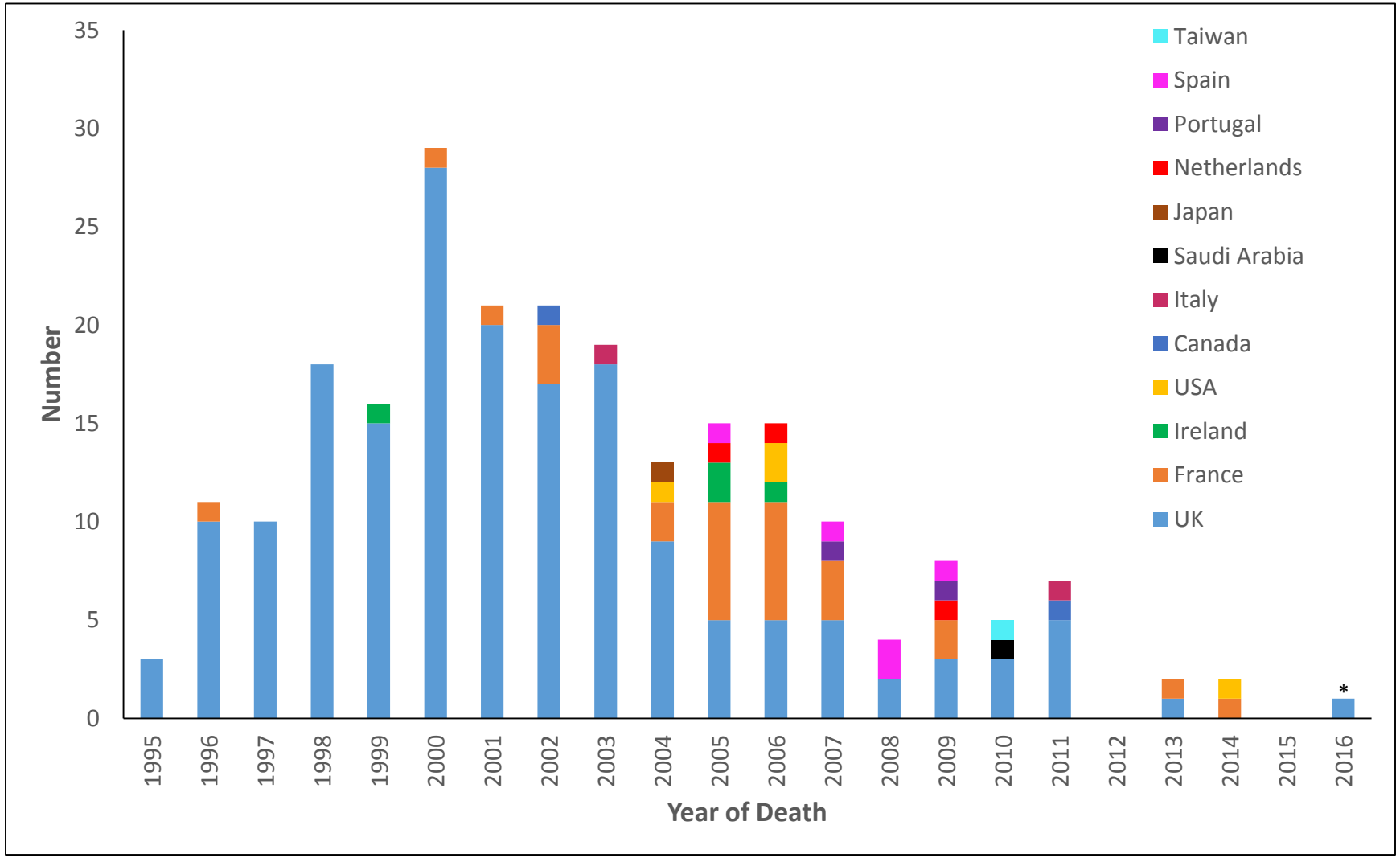
COUNTRY	TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)	TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)	RESIDENCE IN UK > 6 MONTHS DURING PERIOD 1980-1996
UK	175 (0)	3 (0)	178[1]
France	27 (0)	-	1
Republic of Ireland	4 (0)	-	2
Italy	3 (0)	-	0
USA	4[2] (0)	-	2
Canada	2 (0)	-	1
Saudi Arabia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

[1]case 178 from the UK was heterozygous at codon 129 of the *PRNP* gene

[2]the 3rd US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the USA since late 2005. According to the US case-report, the patient was most likely infected as a child when living in Saudi Arabia. In the 4th US patient, the history indicated that exposure to infection most likely occurred prior to moving to the USA.

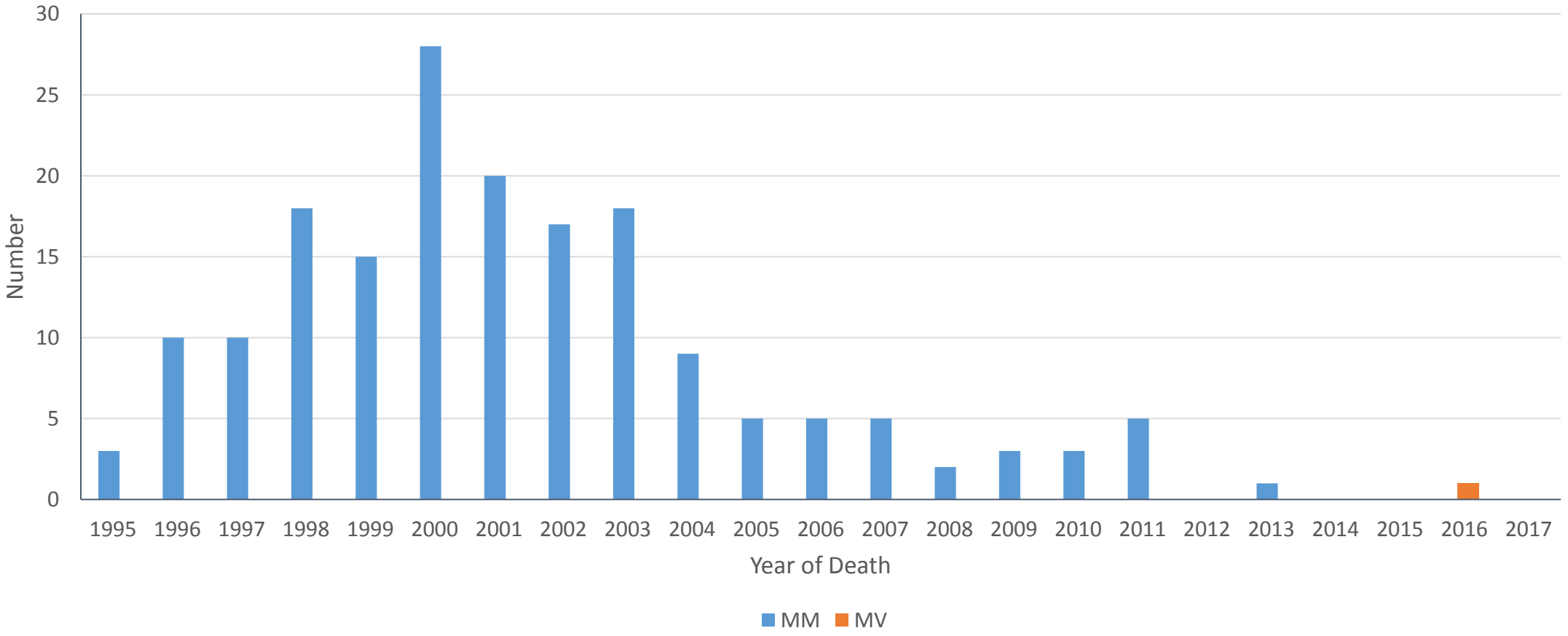
[3]the case from Japan had resided in the UK for 24 days in the period 1980-1996.

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



*MV at codon129 of the *PRNP* gene

vCJD DEATHS PER ANNUM IN THE UK



Case report

Male, aged 36 years

No significant past medical or family history

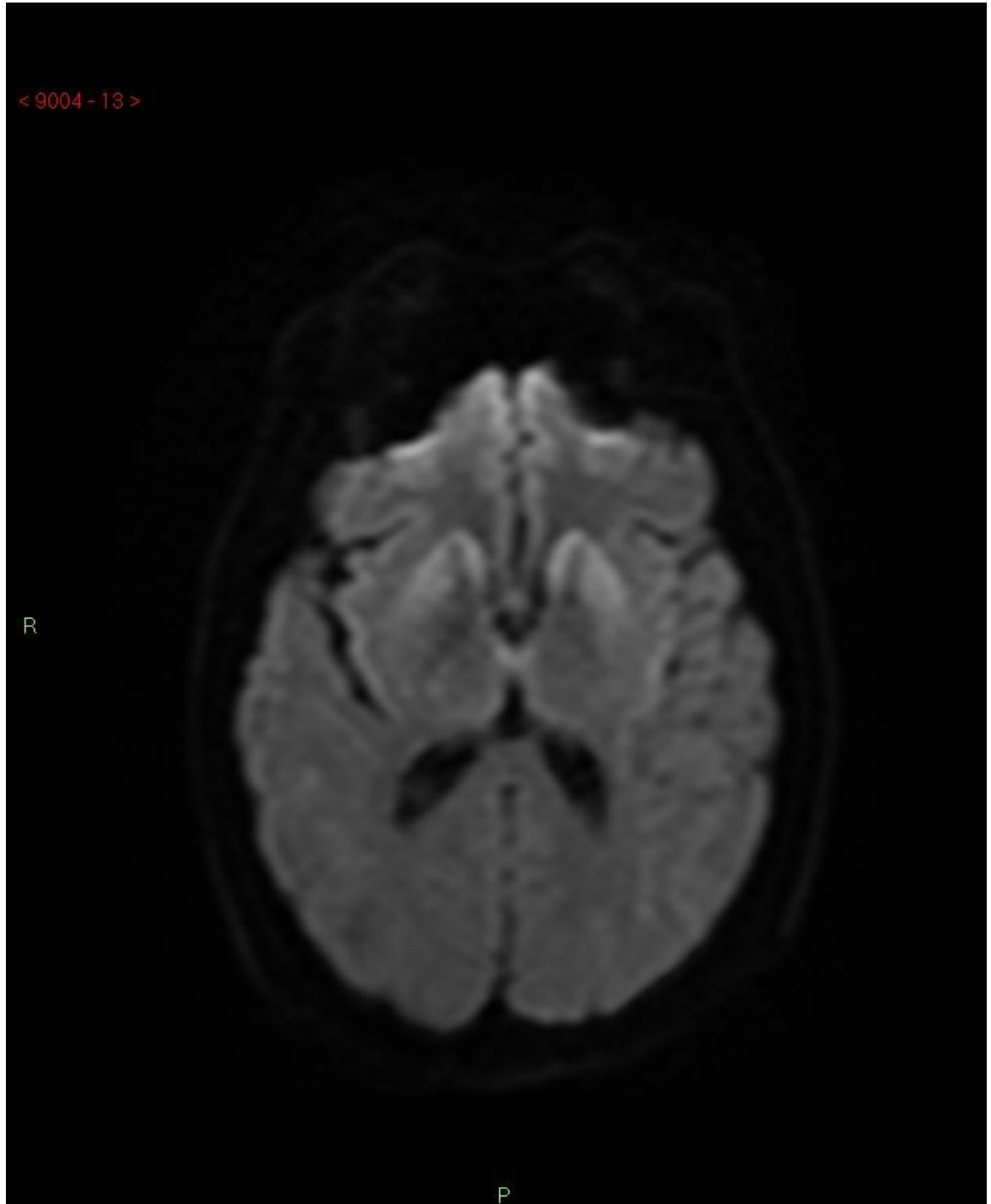
2015: apathy, depression, altered behaviour and difficulty managing at work for the preceding year
Developed ataxia, myoclonus and progressive cognitive impairment

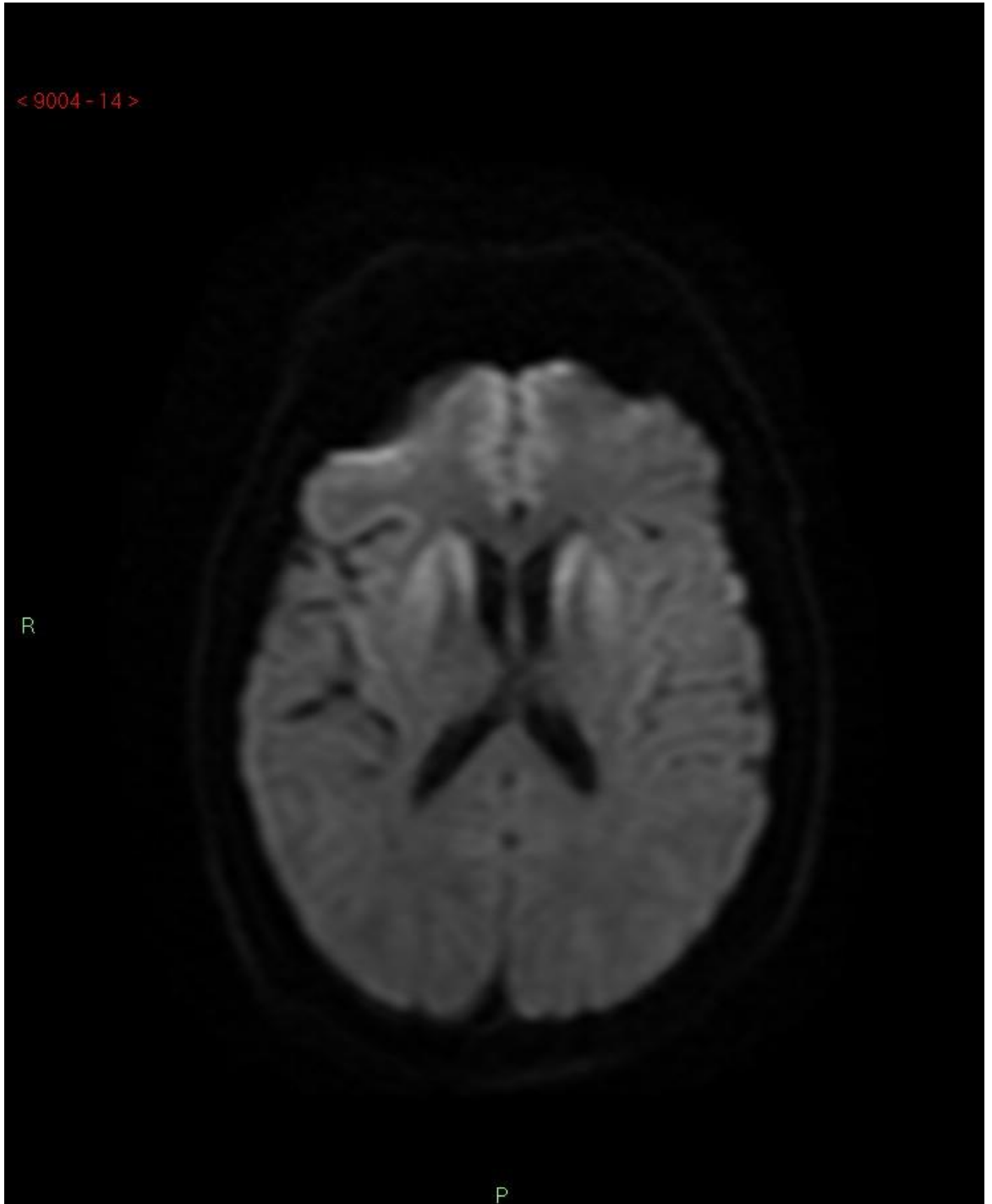
Died 2016

Duration of illness: 20 months

MRI: high signal in caudate and putamen
Codon 129 genotype: MV

Post mortem: variant CJD

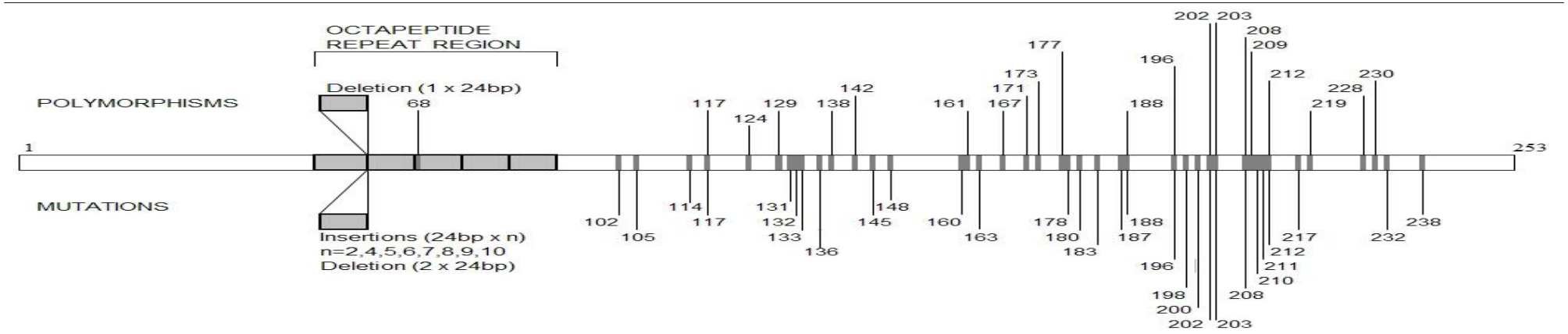

< 9004 - 13 >
R
P


< 9004 - 14 >
R
P

Codon 129 genotype in vCJD

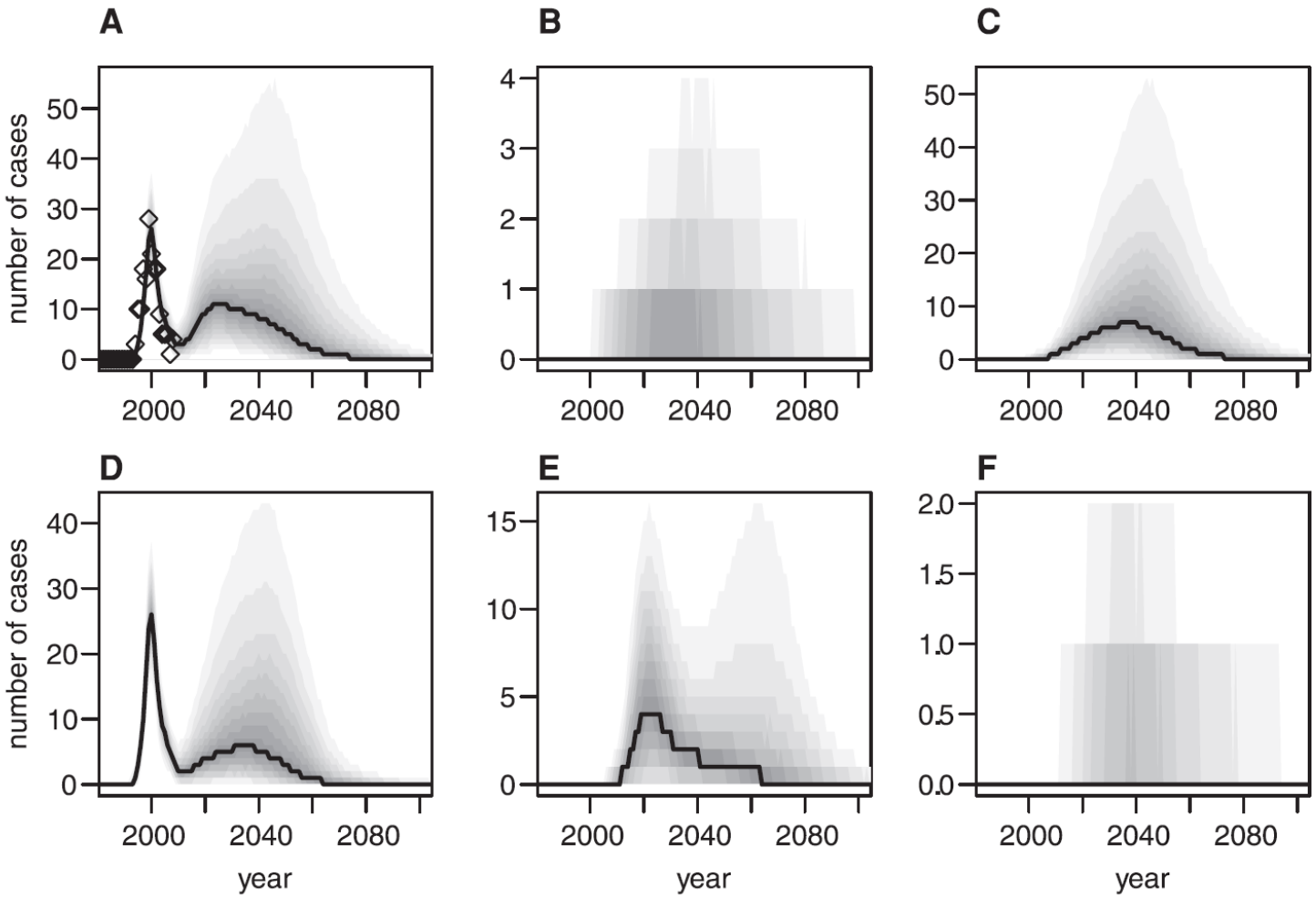
- 160/161 tested cases in UK : MM
- 1/161 tested cases in UK : MV
- 52/52 cases outside UK: MM

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



PLoS one

Median and posterior distributions of projected time series



Cases:

A: Total number

B: Transfusion associated

C: Unidentifiable transfusion associated

Genotypes:

D: MM

E: MV

F: VV

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

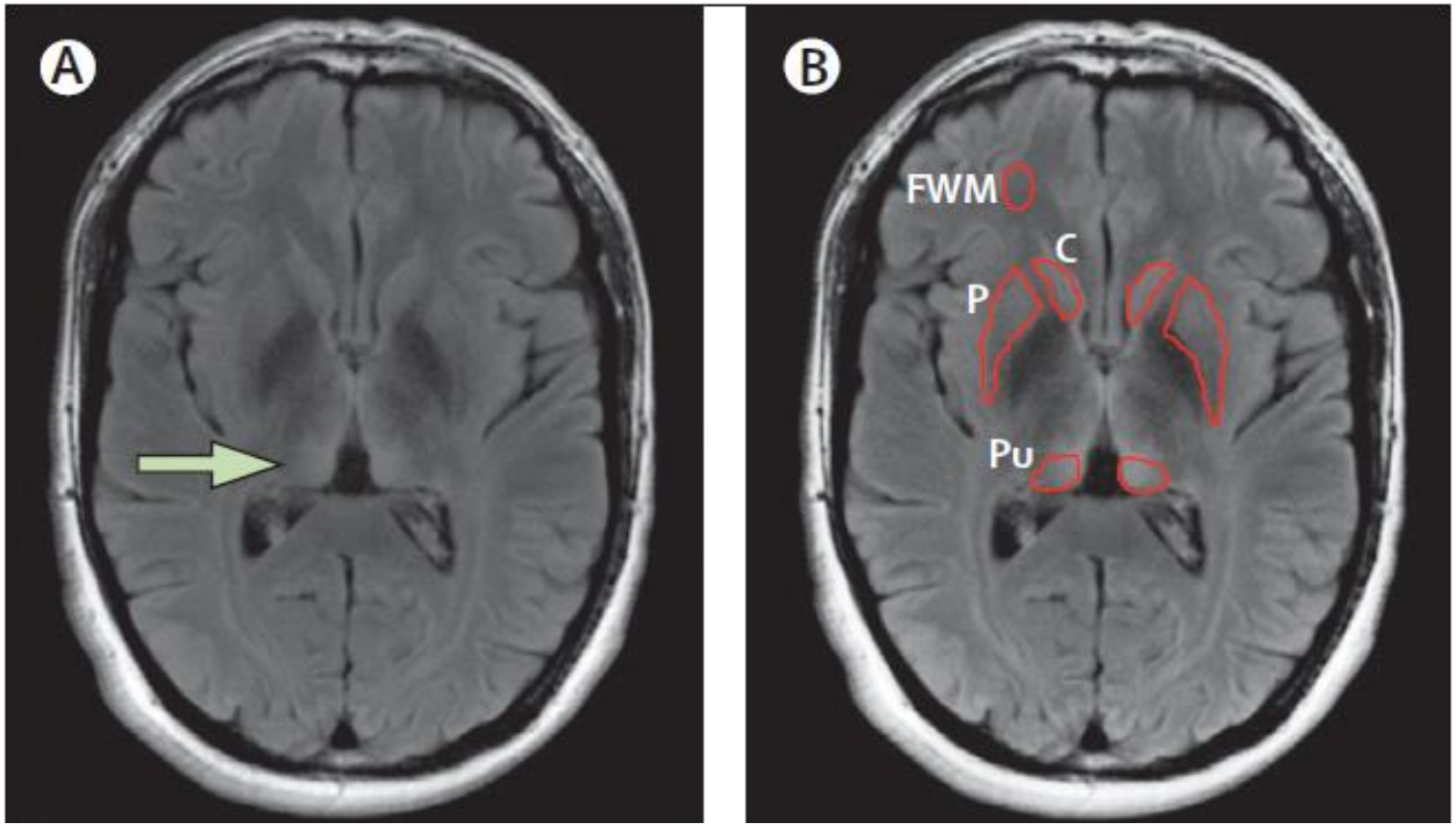


Figure: MRI
(A) Increased signal intensity in the pulvinar nucleus bilaterally (arrow).
(B) MR signal intensity in the pulvinar (Pu) is higher than in the head of the caudate nuclei (C), putamen (P), and right frontal white matter (FWM).

MV vCJD

A high index of suspicion of vCJD in individuals with:

- a vCJD phenotype
- an MV genotype
- an MRI with high signal in caudate and putamen
- a negative RT QuIC

- particularly in younger patients

A firm diagnosis requires neuropathology (or possibly tonsil biopsy)

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.

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

Public Health England

Health Protection Report
weekly report

Infection report

Volume 10 Number 26 Published on: **12 August 2016**

Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens

Public Health England

Health Protection Report
weekly report

Infection report
Volume 10 Number 26 Published on: **12 August 2016**

Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens

The Appendix-III survey examined by immunohistochemistry (IHC) appendices removed at operation and collected from 44 hospitals throughout England. Abnormal prion accumulation was detected within the follicular dendritic cells of seven appendices out of 29,516 suitable samples examined.

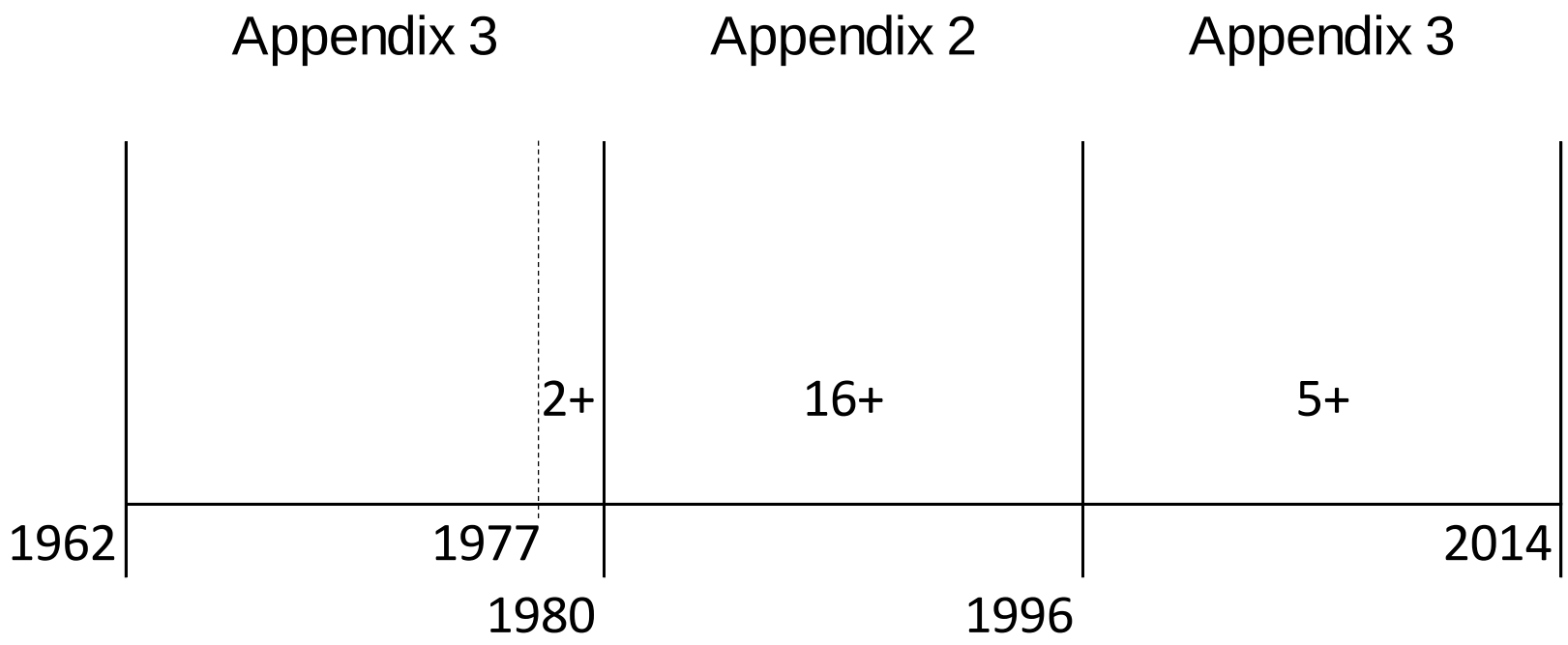
Public Health England

Health Protection Report
weekly report

Infection report

Volume 10 Number 26 Published on: **12 August 2016**

Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens



Public Health England

Health Protection Report
weekly report

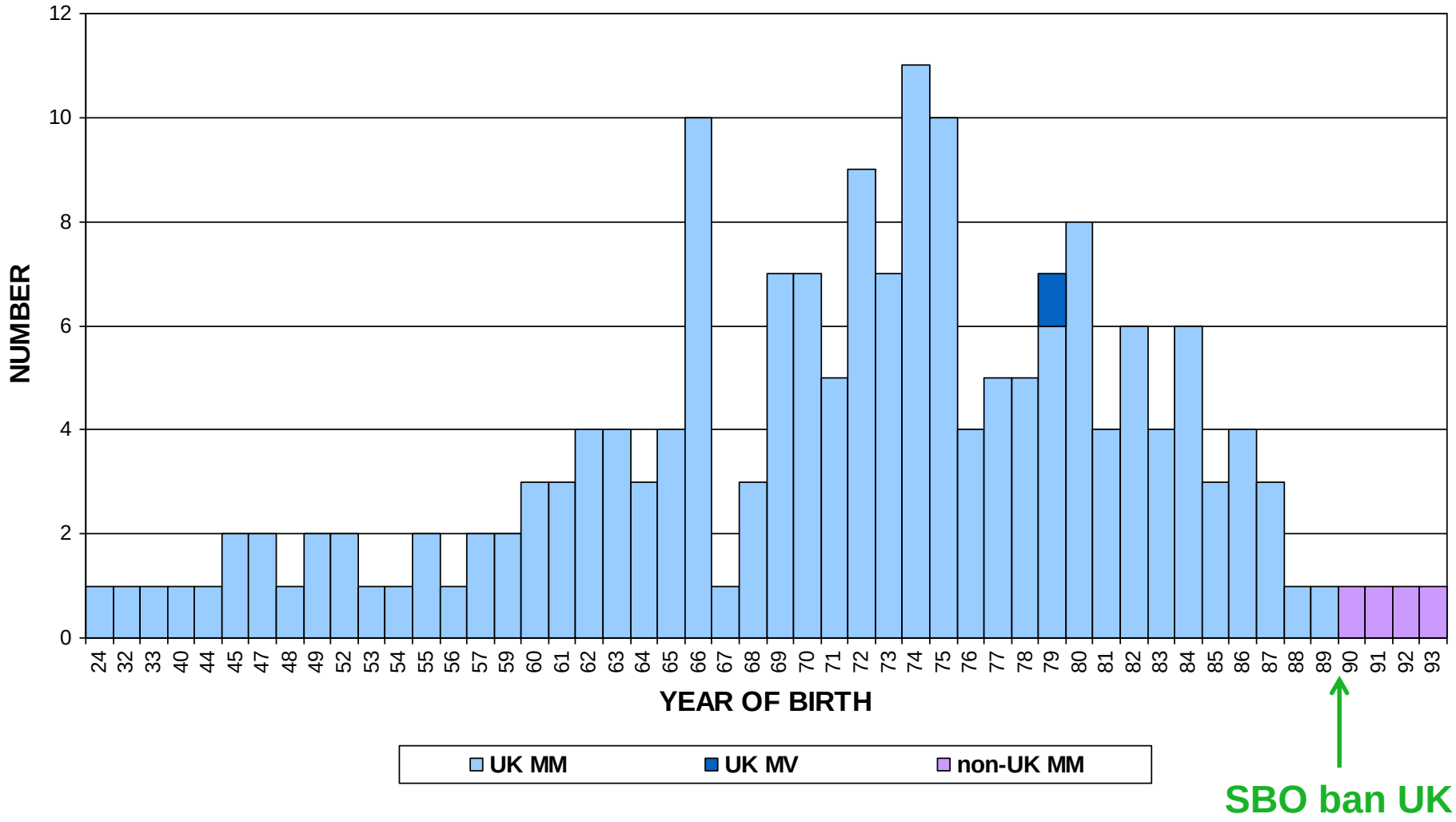
Infection report
Volume 10 Number 26 Published on: **12 August 2016**

Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens

The other five positive samples were found in the 14,824 appendices from subjects born in 1996 or later and removed at operation in 2000 through 2014: all five were in the sub-group of 10,074 born in 1996 through 2000.

[i.e. aged 4-18 years]

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



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PRION DISEASES

Detection of prions in blood from patients with variant Creutzfeldt-Jakob disease

Luis Concha-Marambio,[1,2] Sandra Pritzkow,[1] Fabio Moda,[1,3] Fabrizio Tagliavini,[3] James W. Ironside,[4] Paul E. Schulz,[1] Claudio Soto[1,2]*

Sci. Transl. Med. **8**, 370ra183 (2016)

PRION DISEASES

Detection of prions in blood from patients with variant Creutzfeldt-Jakob disease

Sci. Transl. Med. **8**, 370ra183 (2016)

We used the protein misfolding cyclic amplification (PMCA) technique to analyze blood samples from 14 cases of vCJD and 153 controls, including patients affected by sCJD and other neurodegenerative or neurological disorders as well as healthy subjects. Our results showed that PrP^{Sc} could be detected with 100% sensitivity and specificity in blood samples from vCJD patients. Detection was possible in any of the blood fractions analyzed and could be done with as little as a few microliters of sample volume.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PRION DISEASES

Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease

Daisy Bougard,[1]* Jean-Philippe Brandel,[2,3,4] Maxime Bélondrade,[1] Vincent Béringue,[5] Christiane Segarra,[1] Hervé Fleury,[6] Jean-Louis Laplanche,[4,7] Charly Mayran,[1] Simon Nicot,[1] Alison Green,[8] Arlette Welaratne,[3] David Narbey,[9] Chantal Fournier-Wirth,[1] Richard Knight,[8] Robert Will,[8] Pierre Tiberghien,[9,10] Stéphane Haïk,[2,3,4] Joliette Coste[1,9]*

Sci. Transl. Med. **8**, 370ra182 (2016)

PRION DISEASES

Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease

Sci. Transl. Med. **8**, 370ra182 (2016)

This assay allowed the blinded identification of 18 patients with clinical vCJD among 256 plasma samples from the two most affected countries, with 100% sensitivity [95% confidence interval (CI), 81.5 to 100%], 99.2% analytical specificity (95% CI, 95.9 to 100%), and 100% diagnostic specificity (95% CI, 96.5 to 100%). This assay also allowed the detection of silent carriage of prions 1.3 and 2.6 years before the clinical onset in two blood donors who later developed vCJD.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products

London, 23 June 2011

2. Human TSEs current status

2.1. Sporadic, genetic and iatrogenic forms of human TSEs

There is no evidence that sporadic, genetic or iatrogenic forms of human TSEs have been transmitted from person to person through exposure to plasma products or urinary derived medicinal products. Systematic surveillance for CJD of all types has been undertaken in a number of countries, including a collaborative study in the EU since 1993,[12,13] and no case of sporadic, genetic or iatrogenic CJD has been causally linked to prior treatment with plasma products.

EMERGING
INFECTIOUS DISEASES

Sporadic Creutzfeldt-Jakob Disease in 2 Plasma Product Recipients in the United Kingdom

Patrick Urwin, Kumar Thanigaikumar, James W. Ironside, Anna Molesworth, Richard S Knight, Patricia E. Hewitt, Charlotte Llewelyn, Jan Mackenzie, Robert G. Will

Emerging infectious diseases, In press 2017

EMERGING
INFECTIOUS DISEASES

Sporadic Creutzfeldt-Jakob disease (sCJD) has not been previously reported in patients with clotting disorders treated with fractionated plasma products. We report 2 cases of sCJD identified in the United Kingdom in patients with a history of extended treatment for clotting disorders; 1 patient had hemophilia B and the other von Willebrand disease. Both patients had been informed previously that they were at increased risk for variant CJD because of past treatment with fractionated plasma products sourced in the United Kingdom.

Emerging infectious diseases, In press 2017

Case 1

Von Willebrand's Disease

Rx: Since aged 9
Blood transfusions
Platelet transfusions
Factor VIII (UK sourced and recombinant)

Notified to be at risk of vCJD

No history of iatrogenic exposure

No family history of dementia/CJD

Case 2

Haemophilia B

Rx: Since early 40s
6 units FFP
Factor IX (UK sourced and recombinant)

Notified to be at risk of vCJD

No history of iatrogenic exposure

Vascular dementia

EMERGING
INFECTIOUS DISEASES

However, both cases had clinical and investigative features suggestive of sCJD. This diagnosis was confirmed in both cases on neuropathologic and biochemical analysis of the brain. A causal link between the treatment with plasma products and the development of sCJD has not been established, and the occurrence of these cases may simply reflect a chance event in the context of systematic surveillance for CJD in large populations.

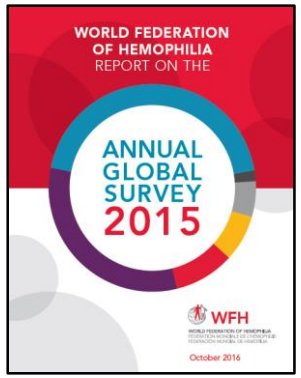
Emerging infectious diseases, In press 2017

bjh British Journal of Haematology

Patients with inherited bleeding disorders registered in the National Haemophilia Database on 1st March 2011 by diagnosis and sub-groups at risk of vCJD for public health purposes.

Patient group and subgroups	Number of patients with bleeding disorders by diagnostic subgroups				
	Haemophilia A	Haemophilia B	Von Willebrand disease	Other	Total
a. Total registered in the National Haemophilia Database (NHD)	5337	1140	9125	6863	22 465
b. Registered patients designated 'at risk' of vCJD: (treated with UK-sourced coagulation factor concentrates between 1980 and 2001)	2246	562	518	409	3735
c. Registered patients at risk of vCJD known to have received implicated FVIII and FIX batches	556	168	39	24	787*

British Journal of Haematology, 2012, **158,** 442–452



KEY NUMBERS FROM THE 2015 REPORT ON THE ANNUAL GLOBAL SURVEY

111 COUNTRIES REPRESENTED

304,362
People with bleeding disorders identified

FROM 2014 TO 2015

5.6%
(17,296)
Increase in number of people with bleeding disorders identified

187,183 People with Hemophilia

74,819 People with von Willebrand disease (VWD)

42,360 People with Other Bleeding Disorders

FACTOR VIII

Factor VIII
Usage per capita
0.53 IU
(0.05–3.52)
Median (IQR)
(81 countries, 63% of world population)

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

TRANSFUSION

BRIEF REPORT

Creutzfeldt-Jakob disease lookback study: 21 years of surveillance for transfusion transmission risk

Lauren A. Crowder,[1] Lawrence B. Schonberger,[2] Roger Y. Dodd,[3] and Whitney R. Steele[1]

RESULTS: To date, 65 CJD donors have been enrolled along with 826 of their blood recipients. These recipients have contributed 3934 person-years of follow-up and no transfusion-transmitted cases of CJD have been recognized.

CONCLUSION: From this study, as well as other epidemiologic studies, there is no evidence of CJD transfusion transmission; this risk remains theoretical.

Staff at the NCJDRSU

- Jan Mackenzie
- James Ironside
- Richard Knight
- Alison Green
- Mark Head
- Matthew Bishop
- Patrick Urwin
- Michelle Gillies
- Gurjit Chohan
- Louise Davidson

Transfusion Medicine Epidemiology Review

- Patricia Hewitt
- Charlotte Llewelyn
- National Blood Services
- Health and Social Care Information Centre

Clinicians throughout the UK

Patients and their families

The Roslin Institute

- Jean Manson
- Abigail Diack

Public Health England

- Katy Sinka