Why do people get CJD?

Bob Will

University of Edinburgh

UK

Creutzfeldt-Jakob Disease (Spongiform Encephalopathy): Transmission to the Chimpanzee

We believe that Creutzfeldt-Jakob disease has been experimentally transmitted to the chimpanzee, and that the disease is caused by a transmissible agent.

C. J. Gibbs, Jr., D. C. Gajdusek
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National Institute of Neurological Diseases and Blindness, Bethesda, Maryland 20014

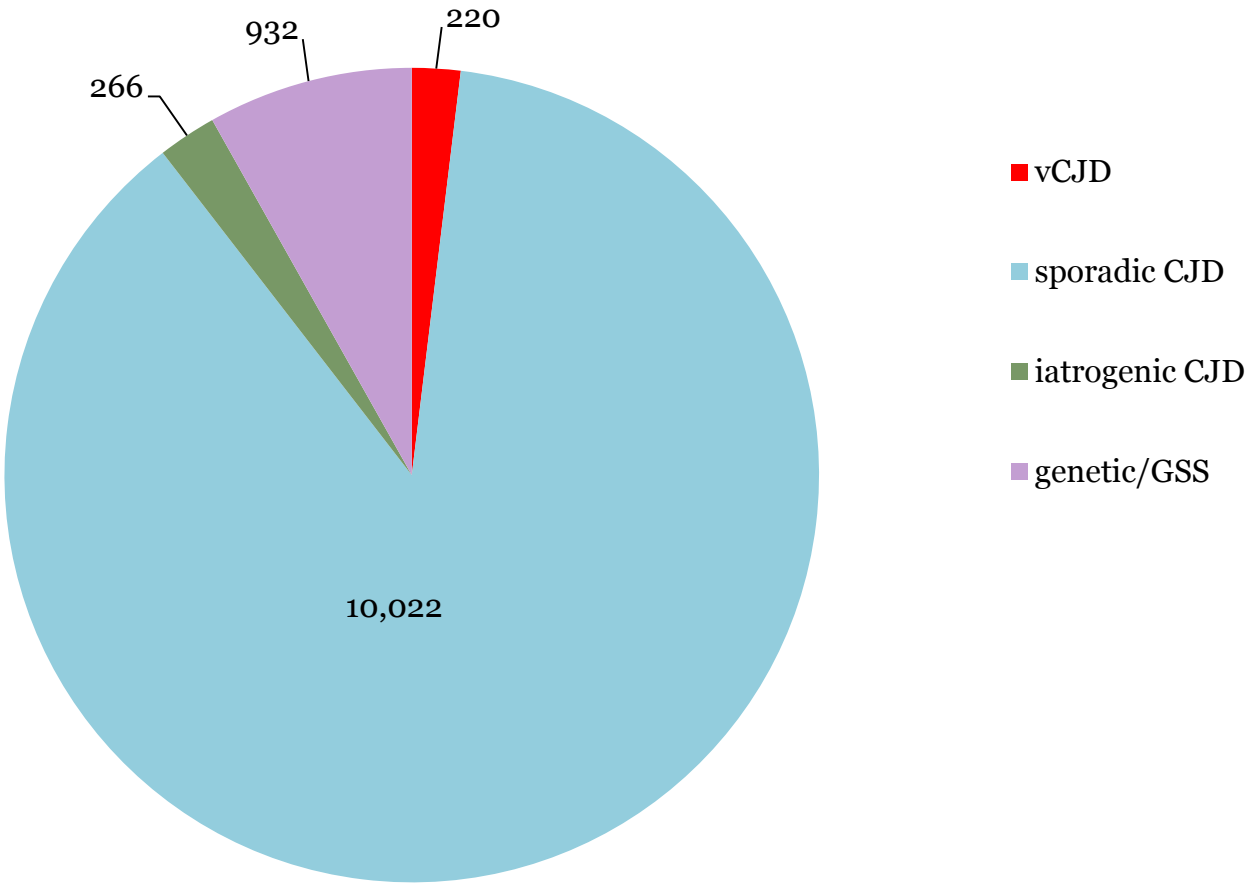
Elizabeth Beck
P. M. Daniel
Institute of Psychiatry, Department of Neuropathology, Maudsley Hospital, London, England

W. B. Matthews
Derbyshire Royal Infirmary, Derby, England

Science 1968

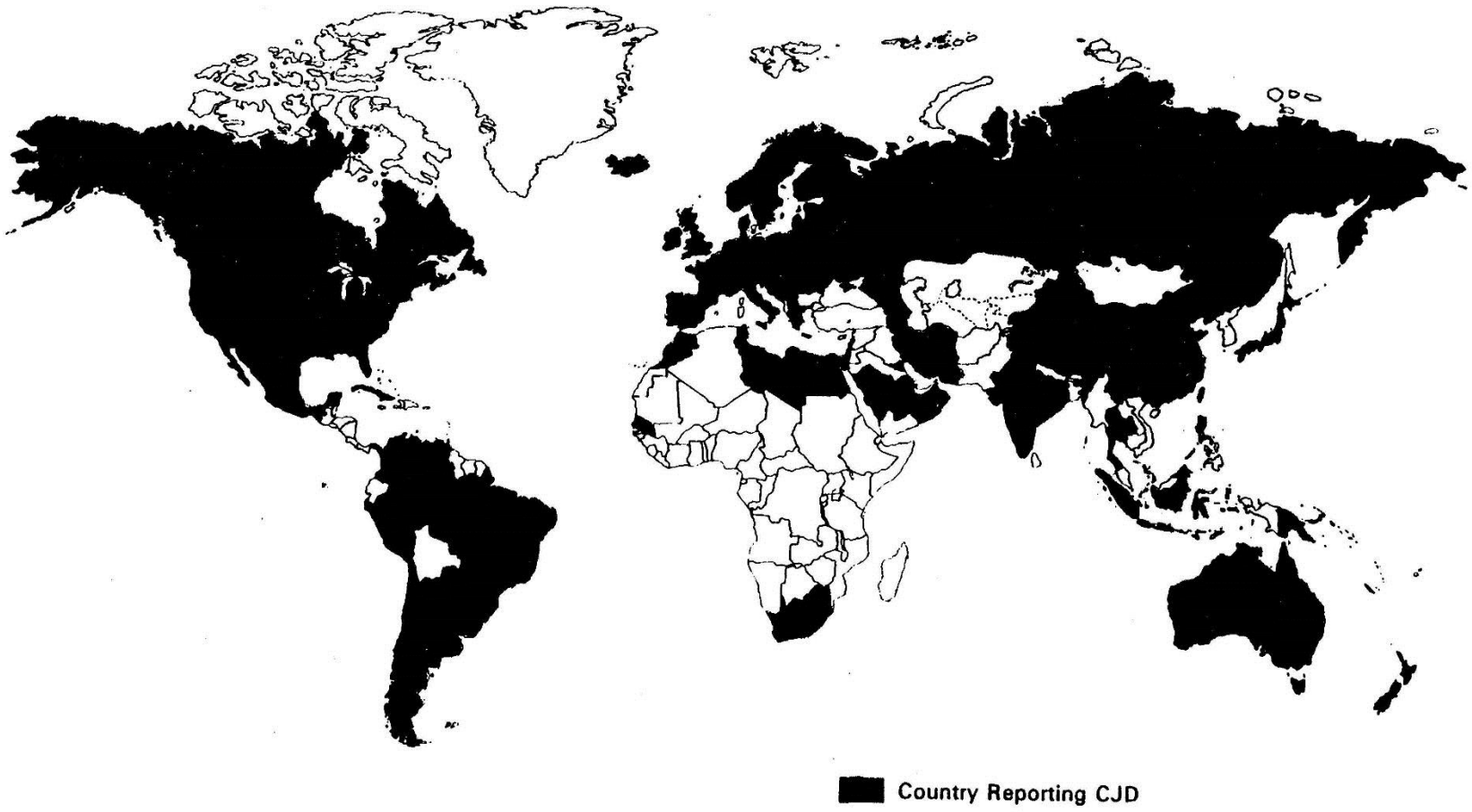
EuroCJD: CJD deaths 1993-2012

(n = 11,440)

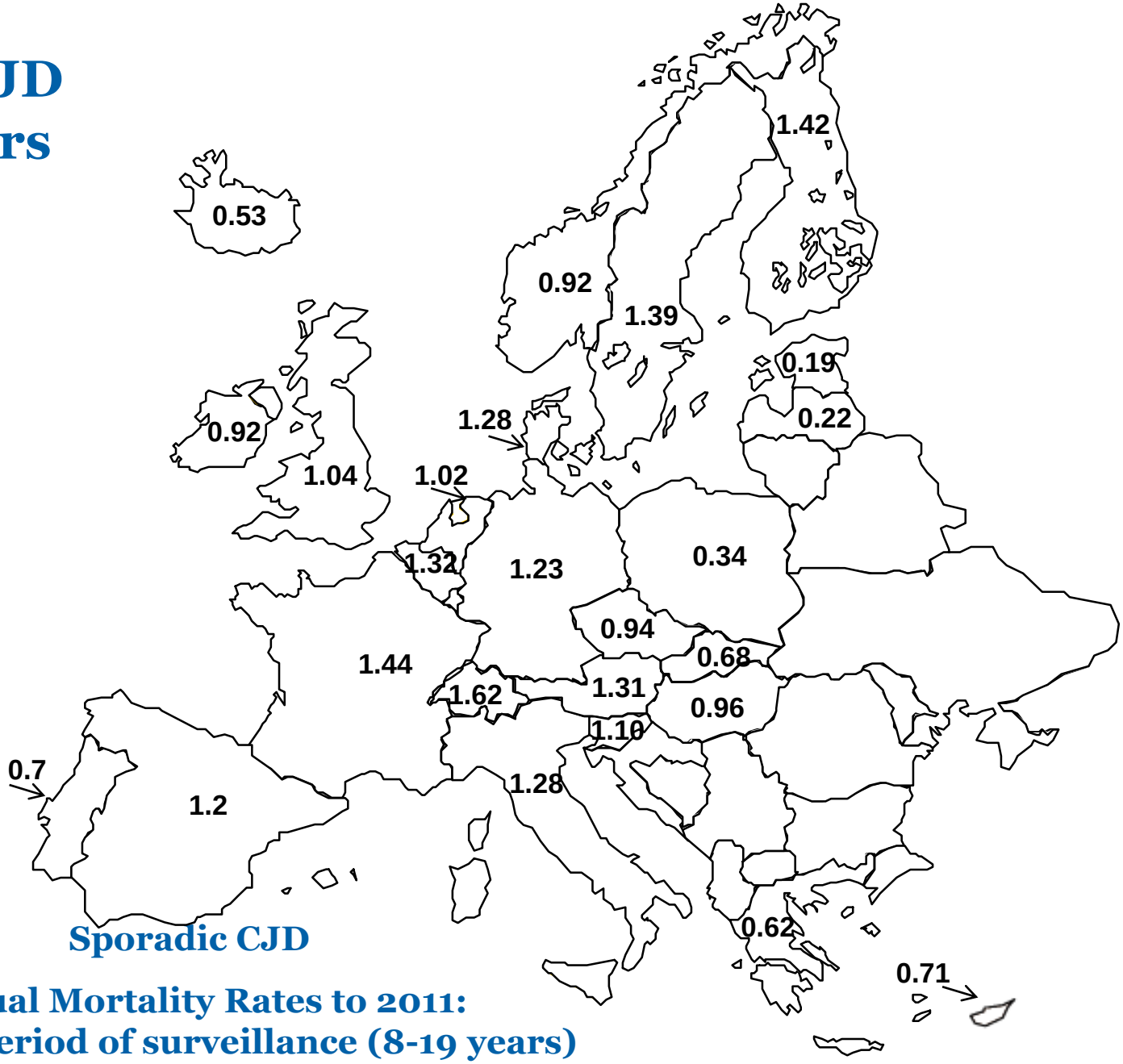


Sporadic CJD

COUNTRIES IN WHICH CJD HAS BEEN REPORTED



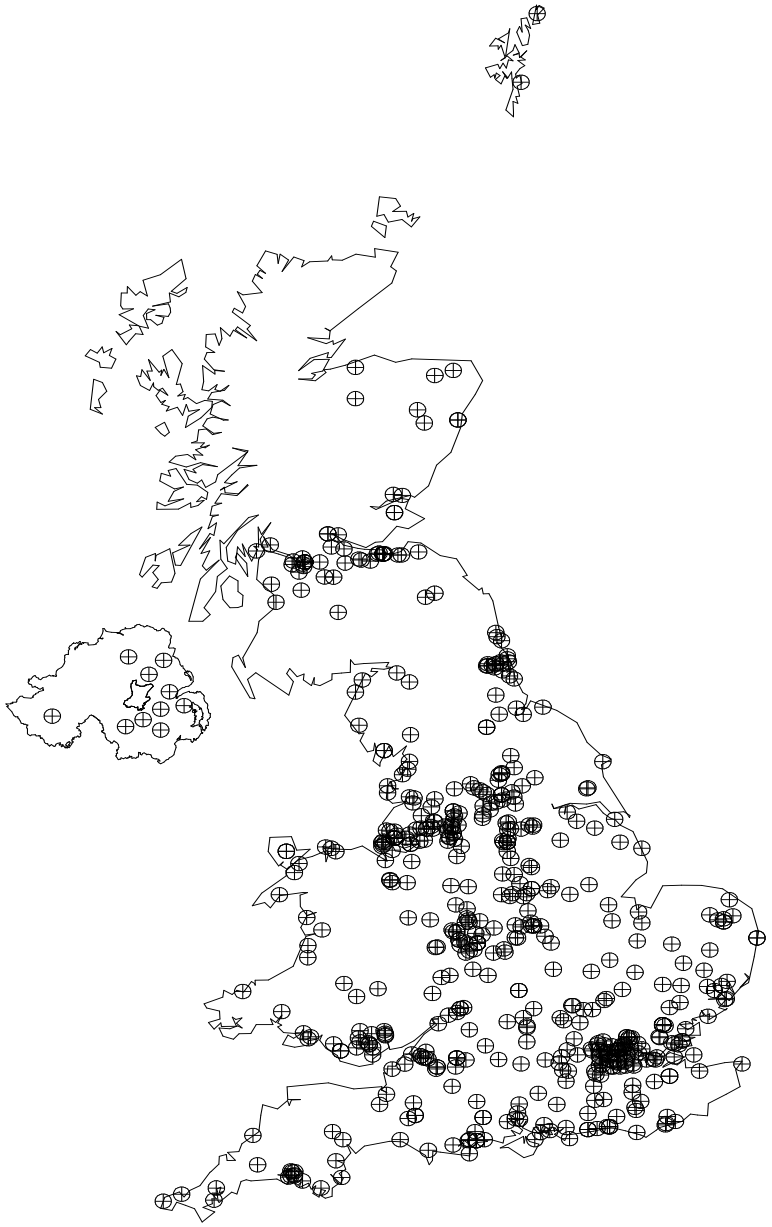
EUROCJD Members



Sporadic CJD

Annual Mortality Rates to 2011: Mean for period of surveillance (8-19 years)

DISTRIBUTION OF SPORADIC CJD IN THE UK: 1990-2002



England and Wales

W. B. MATTHEWS

From the University Department of Neurology, Churchill Hospital, Oxford

SYNOPSIS Some aspects of the epidemiology of Creutzfeldt-Jakob disease in England and Wales in the decade 1964–73 were studied with the object of detecting evidence of natural transmission of this slow virus encephalopathy. Some geographical clustering and possibility of contact between cases was found.

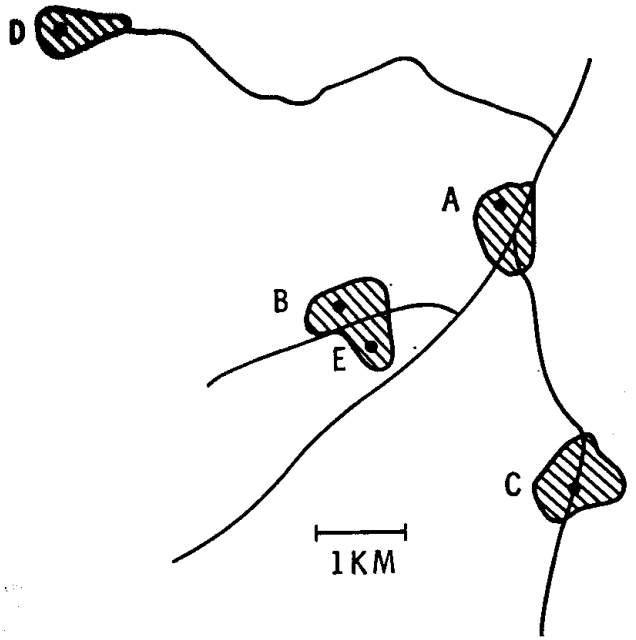


FIG. 1 *Sketch map of cluster of cases of CJD in a rural area. Shading represents villages. The lettering is explained in the text.*

JNNP 1975

BRAIN
A JOURNAL OF NEUROLOGY

Enhanced geographically restricted surveillance simulates sporadic Creutzfeldt-Jakob disease cluster

Genevieve M. Klug, Handan Wand, Alison Boyd, Matthew Law, Scott Whyte, John Kaldor, Colin L. Masters and Steven Collins

Brain 2009: 132; 493-501

Neurology®

Creutzfeldt-Jakob disease in a husband and wife

P. Brown, MD, L. Cervenáková, MD, L. McShane, PhD, L. G. Goldfarb, MD, K. Bishop, BS, F. Bastian, MD, J. Kirkpatrick, MD, P. Piccardo, MD, B. Ghetti, MD and D. C. Gajdusek, MD

ABSTRACT

A 53-year-old man died of sporadic Creutzfeldt-Jakob disease (CJD) after a 1.5-year clinical course. Four and a half years later, his then 55-year-old widow died from CJD after a 1-month illness. Both patients had typical clinical and neuropathologic features of the disease, and pathognomonic proteinase-resistant amyloid protein ("prion" protein, or PrP) was present in both brains. Neither patient had a family history of neurologic disease, and molecular genetic analysis of their PrP genes was normal. No medical, surgical, or dietary antecedent of CJD was identified; therefore, we are left with the unanswerable alternatives of human-to-human transmission or the chance occurrence of sporadic CJD in a husband and wife.

Neurology March 1998 vol. 50 no. 3 684-688

Neurology®

That calculation yields r = 1.8 per million sporadic CJD deaths per year.
Using the values of c_1, c_2, …, c_{16} and r calculated from the above table, we compute $1 - p_1 \cdot p_2 \cdot \ldots \cdot p_{16}$ to be 0.021. That is, if we observe a population of similar size and marital status composition to the U.S. population from 1979 to 1994, we estimate a 2.1% chance of observing a married couple in which both husband and wife die of sporadic CJD within 5 years of one another.

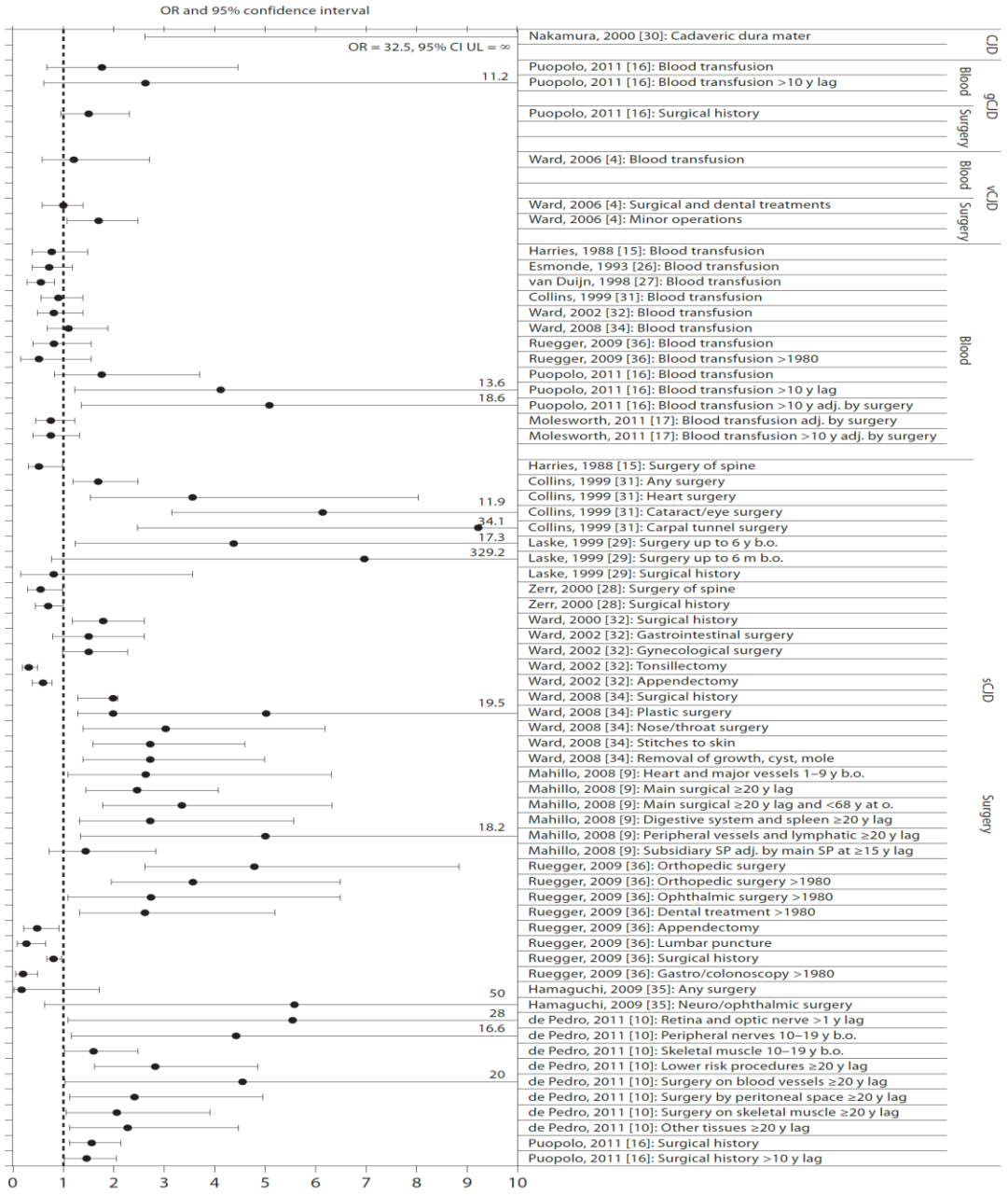
Neurology March 1998 vol. 50 no. 3 684-688

Neuro
epidemiology

Sensitivity to Biases of Case-Control Studies on Medical Procedures, Particularly Surgery and Blood Transfusion, and Risk of Creutzfeldt-Jakob Disease

Jesús de Pedro Cuesta María Ruiz Tovar Hester Ward Miguel Calero
Andrew Smith Concepción Alonso Verduras Maurizio Pocchiari
Marc L. Turner Frode Forland Daniel Palm Robert G. Will

Graphical representation of selected results.
M = Months;
y = years;
o. = onset;
b.o. = Before onset;
adj. = adjusted.



Eurosurveillance

Health professions and risk of sporadic Creutzfeldt–Jakob disease, 1965 to 2010

E Alcalde-Cabero[1], J Almazán-Isla[1], J P Brandel[2], M Breithaupt[3], J Catarino[4], S Collins[5], J Haybäck[6], R Höftberger[7], E Kahana[8], G G Kovacs[7,9], A Ladogana[10], E Mitrova[11], A Molesworth[12], Y Nakamura[13], M Pocchiari[10], M Popovic[14], M Ruiz-Tovar[1], A L Taratuto[15], C van Duijn[16], M Yamada[17], R G Will[12], I Zerr[3], J de Pedro Cuesta (jpedro@isciii.es)[1]

1. National Centre of Epidemiology - Consortium for Biomedical Research in Neurodegenerative Diseases (Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas – CIBERNED), Carlos III Institute of Health, Madrid, Spain
2. Institut National de la Santé et de la Recherche Médicale (INSERM) UMRS 975, National CJD Surveillance Network, Assistance publique - Hôpitaux de Paris (APHP), National Reference Centre for CJD, Pitié-Salpêtrière Hospital Group, Paris, France
3. Department of Neurology, National Reference Centre for TSE, Georg-August University, Göttingen, Germany
4. Alameda Epidemiology and Health Statistics Department, Lisbon, Portugal
5. Department of Pathology, University of Melbourne, Melbourne, Australia
6. Institute of Neuropathology, Zurich University Hospital, Zurich, Switzerland
7. Institute of Neurology, Vienna Medical University, Vienna, Austria
8. Department of Neurology, Barzilai Medical Centre, Ashkelon, Israel
9. National Reference Centre for Human Prion Diseases, Semmelweis University, Budapest, Hungary
10. Department of Cell Biology and Neurosciences, Health Institute, Rome, Italy
11. Department of Prion Diseases, Slovak Medical University Research Base, Bratislava, Slovakia
12. National CJD Research and Surveillance Unit, Western General Hospital, Edinburgh, United Kingdom
13. Department of Public Health, Jichi Medical University, Shimotsuke, Japan
14. nstitute of Pathology, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia
15. Department of Neuropathology/FLENI, Referral Centre for CJD and other TSEs, Institute for Neurological Research, Buenos Aires, Argentina
16. National Surveillance of CJD, Erasmus MC, Rotterdam, The Netherlands
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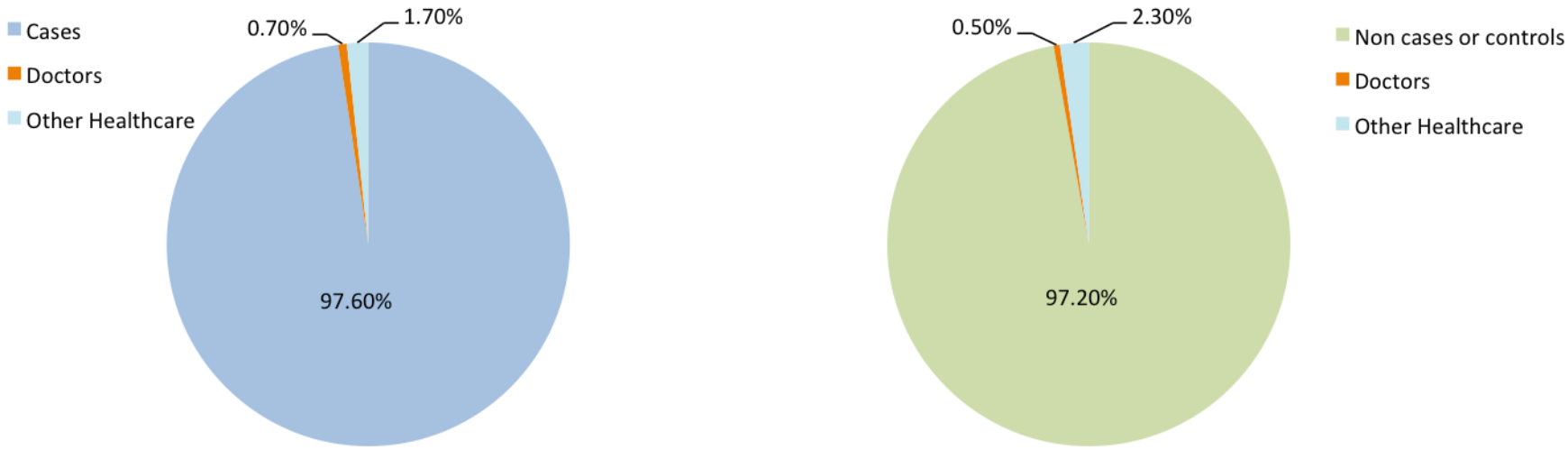
Euro Surveillance 2012;17(15) pii=20144

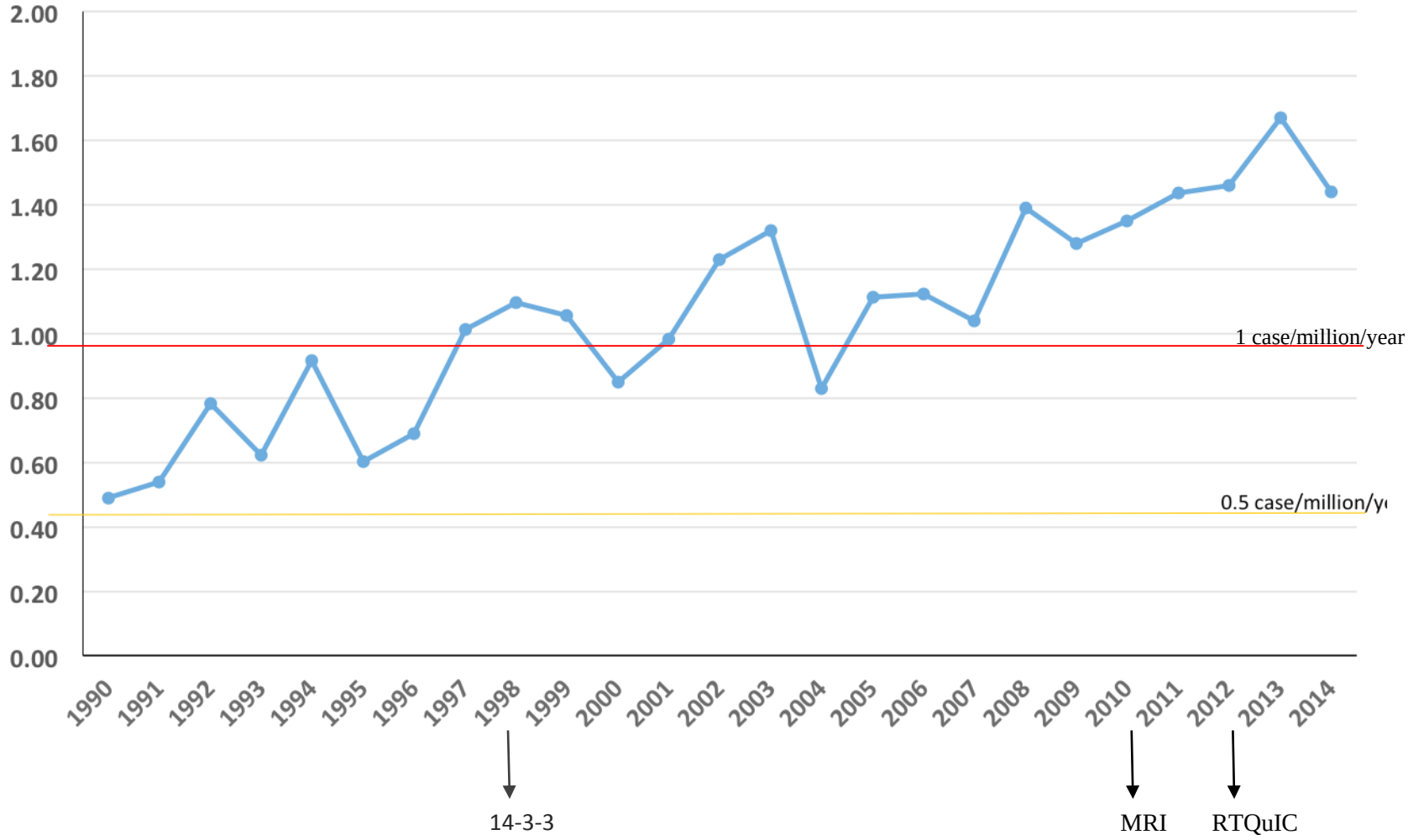
Euro Surveillance 2012;17(15) pii=20144

Occupation and Risk of Sporadic CJD: EUROCJD 1980-2010



We conclude that a wide spectrum of medical specialities and health professions are represented in sCJD cases and that the data analysed do not support any overall increased occupational risk for health professionals.

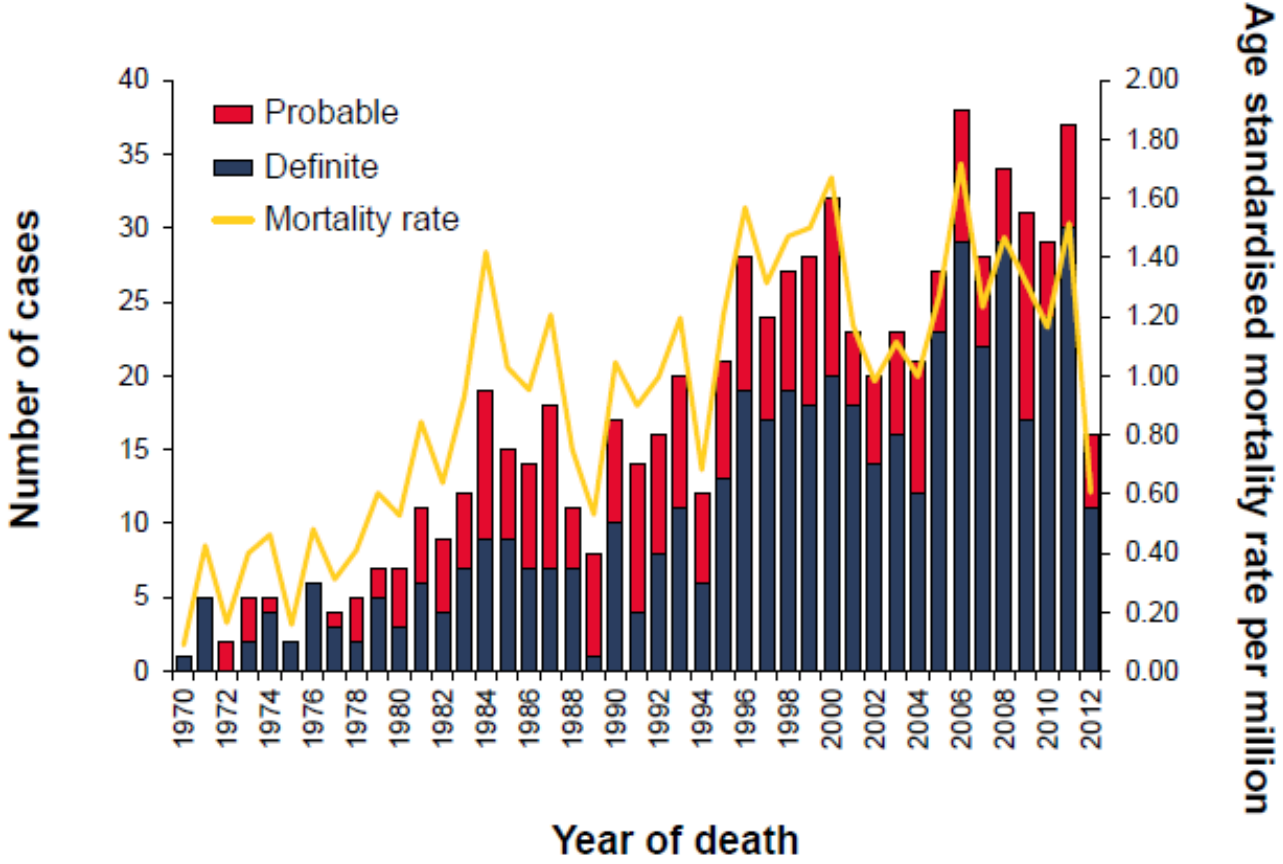
Mortality rates for definite and probable sporadic CJD in the UK
1 January 1990 - 31 December 2014



Surveillance for Creutzfeldt-Jakob disease in Australia: update to December 2012

Genevieve M Klug, Alison Boyd, Teresa Zhao, Christiane Stehmann, Marion Simpson, Catriona McLean, Colin L Masters & Steven J Collins

Number of definite and probable TSE cases and age standardised mortality rate in Australia, 1970 to 2012, by classification and year



Sporadic CJD

- No environmental risk factors for sCJD have been identified
- No link to occupation, past medical history, blood transfusion, medications, diet, etc.
- No link to scrapie in sheep
- No evidence of spread from person to person
- Cases occur randomly in space and time and occur worldwide

Sporadic CJD

- These…. studies suggest that at some point in the lives of the one in a million individuals who acquire sporadic Creutzfeldt-Jakob disease, cellular PrP may spontaneously convert to the scrapie form.

- Stanley Prusiner 1995

Genetic human prion disease

Linkage of a prion protein missense variant to Gerstmann–Sträussler syndrome

Karen Hsiao*, Harry F. Baker‡, Tim J. Crow‡, Mark Poulter‡, Frank Owen‡, Joseph D. Terwilliger§, David Westaway*, Jurg Ott§‖ & Stanley B. Prusiner*†¶

MUTATIONS OF THE PRP GENE UK (n=188)

MUTATION	NUMBER
Insertions in the coding region of the PrP gene	65
E200K	44
P102L	37
D178N	14
A117V	13
V210I	4
Q212P	2
Y163X	2
D167G	1
E196K	1
E211Q	1
G54S	1
P105L	1
P84S	1
S132I	1

Quantifying prion disease penetrance using large population control cohorts

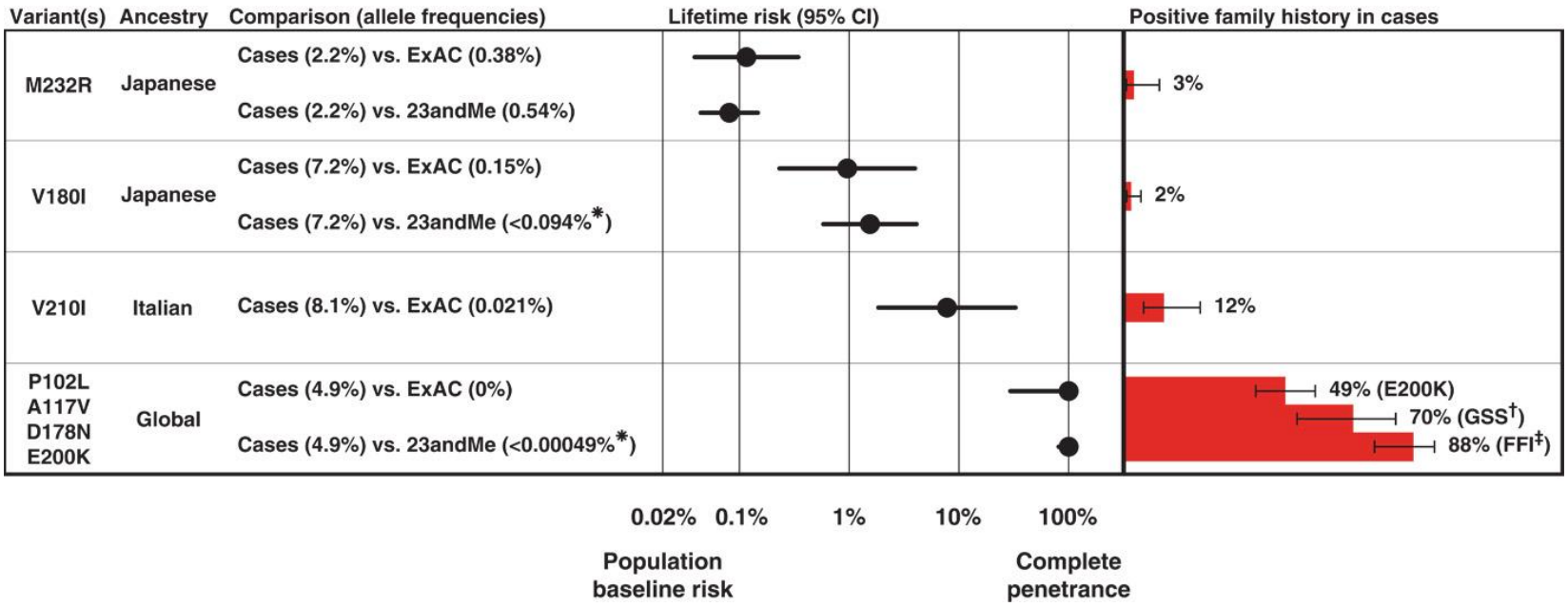
by Eric Vallabh Minikel, Sonia M. Vallabh, Monkol Lek, Karol Estrada, et al

Sci Transl Med
Volume 8(322):322ra9-322ra9
January 20, 2016

Published by AAAS

Science Translational Medicine
AAAS

Fig. 3. Variants that confer intermediate amounts of lifetime risk.



Eric Vallabh Minikel et al., Sci Transl Med 2016;8:322ra9

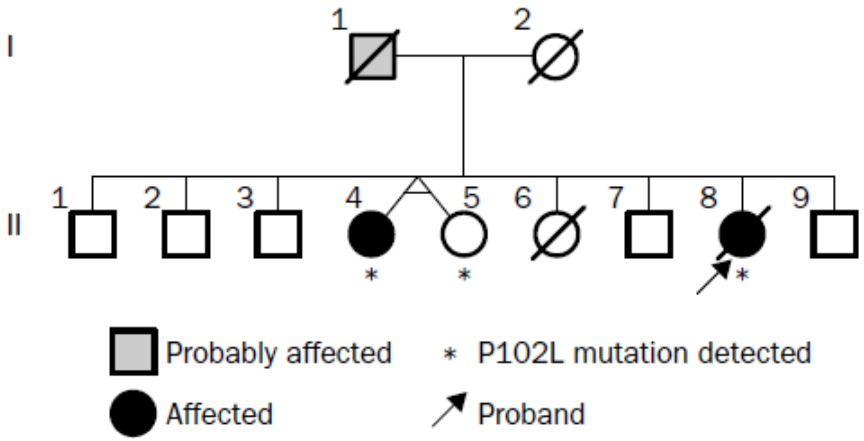
THE LANCET

Discordant Gerstmann-Sträussler-Scheinker disease in monozygotic twins

Shinji Hamasaki, Susumu Shirabe, Ryouichi Tsuda,
Toshiro Yoshimura, Tatsufumi Nakamura, Katsumi Eguchi

THE LANCET • Vol 352 • October 24, 1998

Family pedigree

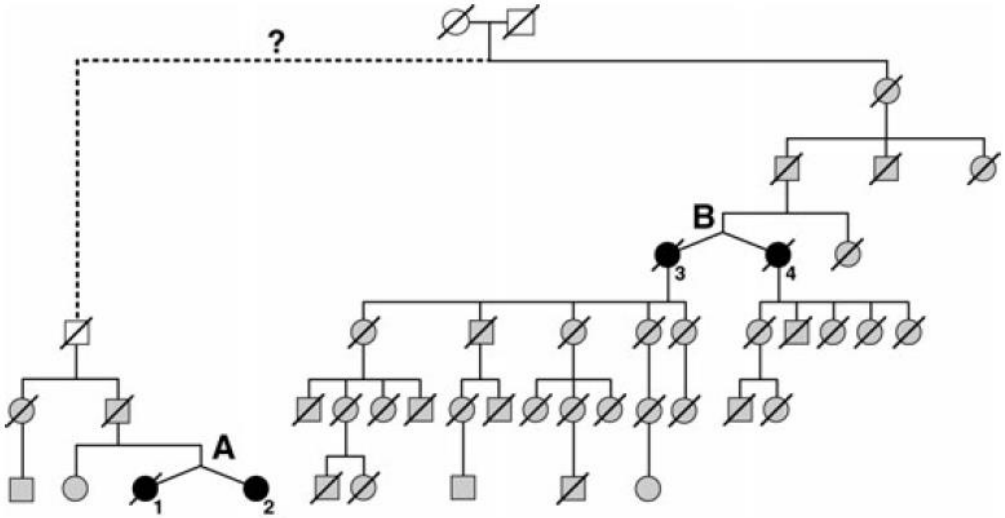


Neuropathology and Applied Neurobiology

Seven-year discordance in age at onset in monozygotic twins with inherited prion disease (p102L)

Neuropathology and Applied Neurobiology (2009), **35**, 427–432

T. Webb*†
S. Mead*†
J. Beck†
J. Uphill†
S. Pal*†
S. Hampson*
J. D. F. Wadsworth†
I. Dalmau Mena†
C. O'Malley†
S. Wroe*†
A. Schapira‡
S. Brandner†
J. Collinge*†



Genetic Prion Disease

- We suspect that mutation in the PrP gene render the resulting proteins susceptible to flipping from an alpha-helical to a beta-sheet shape. Presumably, it takes time until one of the molecules spontaneously ßips over and still more time for scrapie PrP to accumulate and damage the brain enough to cause symptoms.

- Stanley Prusiner 1995

Iatrogenic CJD

EMERGING
INFECTIOUS DISEASES

Incubation periods and clinical presentations of iatrogenic Creutzfeldt-Jakob disease, according to source of infection

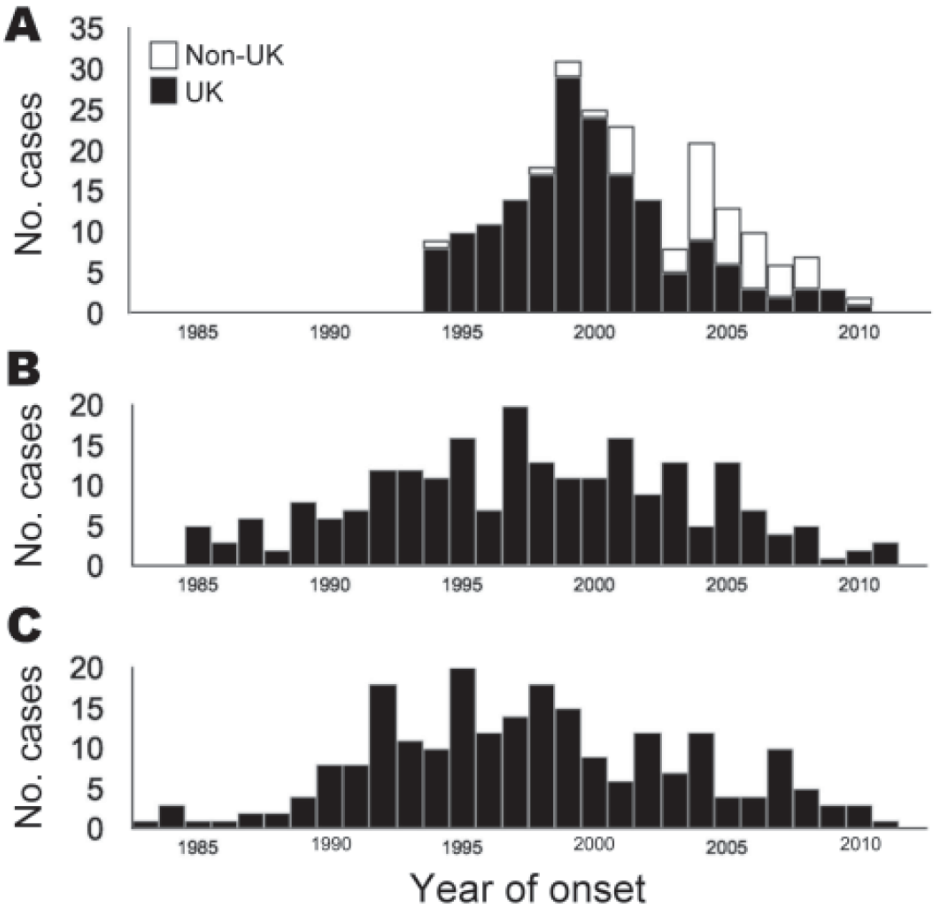
Source of Infection	No. cases	Mean incubation period, y (range)	Clinical signs†
Dura mater graft	228	12 (1.3–30)	Cerebellar, visual, dementia
Neurosurgical instruments*	4	1.4 (1–2.3)	Visual, dementia, cerebellar
Stereotactic EEG needles	2	1.3, 1.7	Dementia, cerebellar
Corneal transplant	2	1.5, 27	Dementia, cerebellar
Growth hormone	226	17 (5–42)‡	Cerebellar
Gonadotropin	4	13.5 (12–16)	Cerebellar
Packed red blood cells§	3	6.5, 7.8, 8.3	Psychiatric, sensory, dementia, cerebellar

*EEG, electroencephalogram.
†In order of decreasing frequency.
‡Averages and ranges were 13 (5–24) y in France; 20 (7–39) y in the United Kingdom; and 22 (10–42) y in the United States.
§An additional asymptomatic but infected red-cell recipient died of an unrelated illness; another asymptomatic infected hemophilia patient who had been exposed to potentially contaminated factor VIII also died of an unrelated illness (neither is included in the table).

EMERGING INFECTIOUS DISEASES

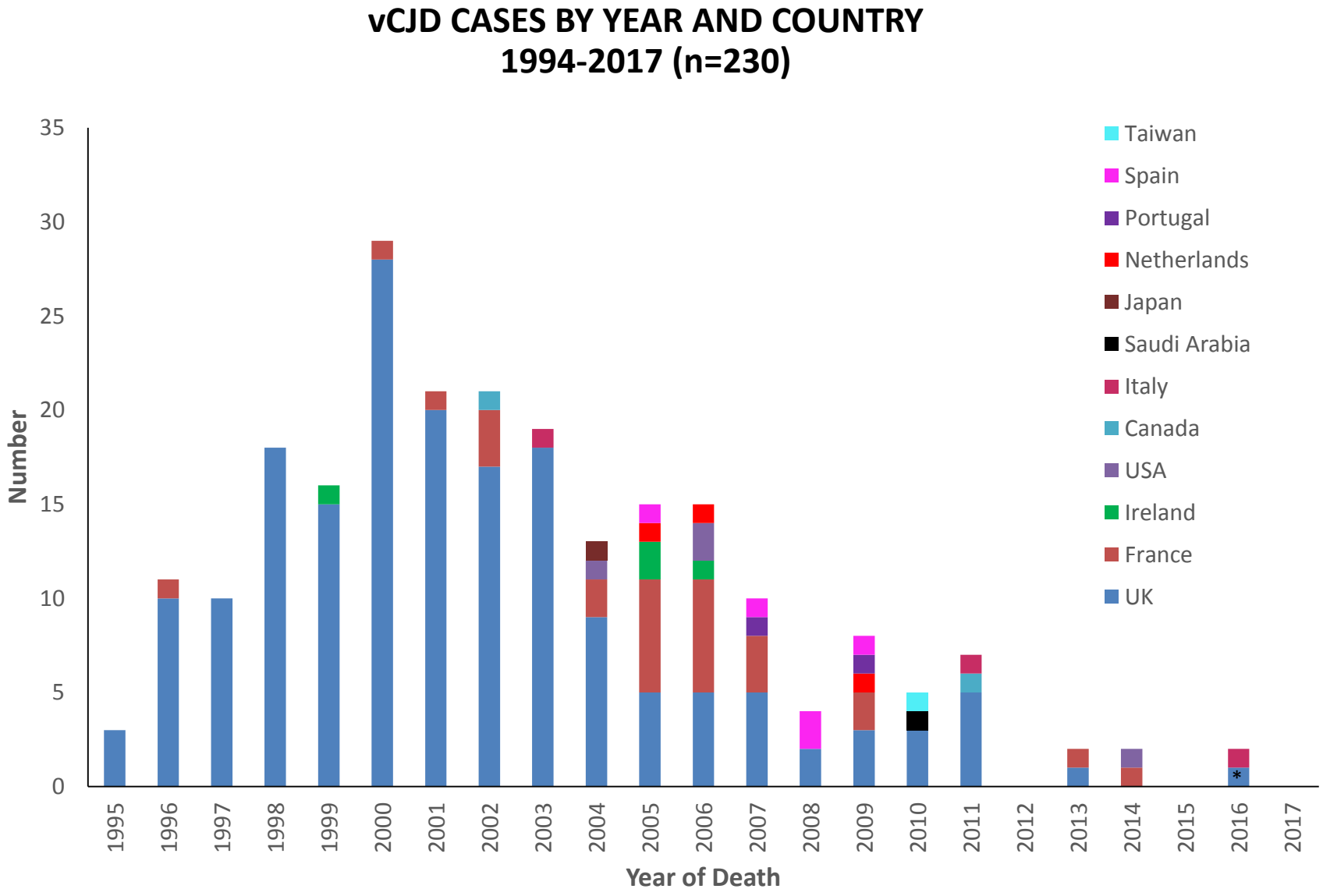
Iatrogenic Creutzfeldt-Jakob Disease, Final Assessment

Paul Brown, Jean-Philippe Brandel, Takeshi Sato, Yosikazu Nakamura, Jan MacKenzie, Robert G. Will, Anna Ladogana, Maurizio Pocchiari, Ellen W. Leschek, and Lawrence B. Schonberger

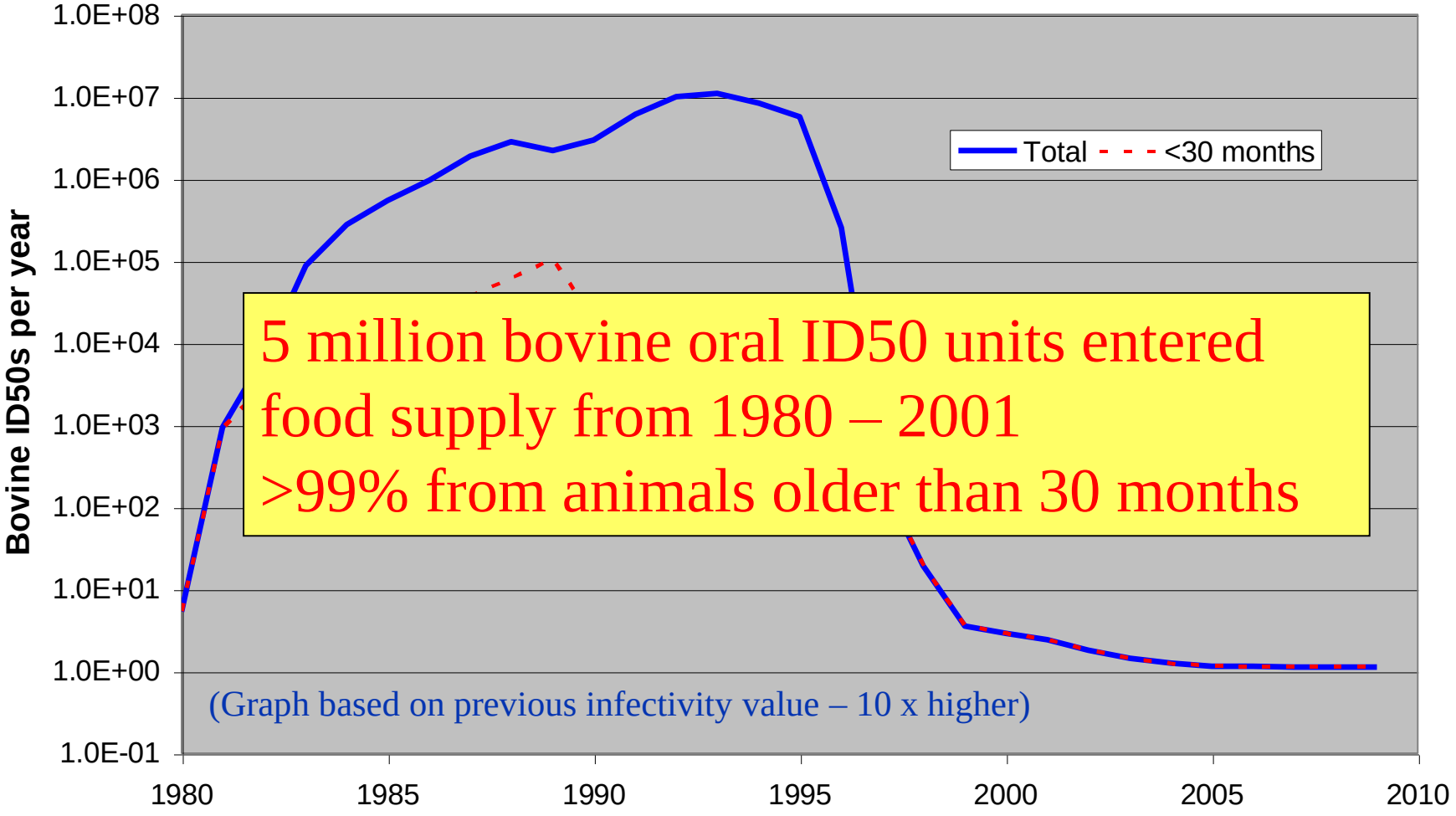


Annual incidence of variant Creutzfeldt-Jakob disease (vCJD) caused by ingestion of meat products contaminated with bovine spongiform encephalopathy agent (A) and iatrogenic CJD caused by contaminated dura mater (B) and cadaveric human growth hormone (C), 1982-2011.

Variant CJD


vCJD CASES BY YEAR AND COUNTRY
1994-2017 (n=230)
Number
Year of Death
0
5
10
15
20
25
30
35
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
*
Taiwan
Spain
Portugal
Netherlands
Japan
Saudi Arabia
Italy
Canada
USA
Ireland
France
UK

Infectious Units Entering Food supply



Base case with 3 months test sensitivity