L’impatto della ricerca e delle teorie eziologiche sulla sorveglianza epidemiologica della malattia di Creutzfeldt-Jakob

Maurizio Pocchiari

CJD Epidemiology and Research

Before the 60s

- No much interest
- No understanding of pathogenesis
- Isolated case reports

After the 60s

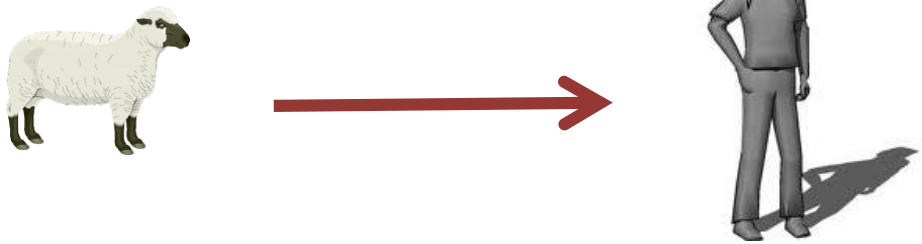
- Link between Kuru and scrapie

- Transmission of kuru to chimpanzees

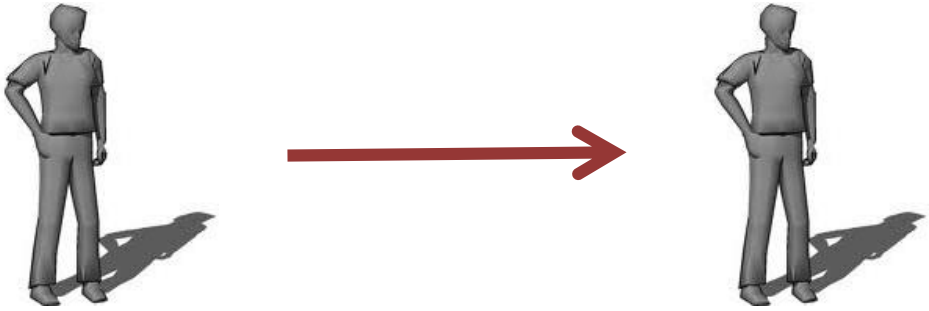
- Transmission of CJD to chimpanzees

CJD EPIDEMIOLOGY: WORKING HYPOTHESES AFTER THE 70S

All forms of human TSE diseases are considered transmissible



No strong evidences



A few cases of iatrogenic CJD reported since 1960 (Nevin et al, 1960)

Possible cluster cases (familial and sporadic forms) (Brown et al, 1979; Masters et al, 1979)

START OF SYSTEMATIC CJD EPIDEMIOLOGICAL STUDIES

Italy

UK

France

CJD Epidemiology

- **CJD is a rare disease (about 1 case per million people)**
- **CJD is randomly distributed all over the World**
- **Although CJD is transmissible, most cases occur sporadically**

Masters et al, 1979; Ladogana et al., 2012; updated Sept 2017

IATROGENIC CASES

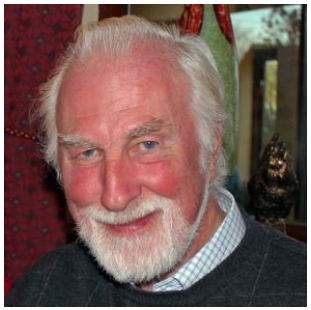
HUMAN-TO-HUMAN TRANSMISSION OF SPORADIC AND FAMILIAL CJD

Source of infection	Mean incubation period (yrs)	n	Year
Neurosurgical instruments	1.4	4	1950s
Corneal transplant	1.5, 2.7	2	1974
Stereotactic EEG needles	1.3, 1.7	2	1977
Growth hormone	17	226	1985
Dura mater graft	12	228	1987
Gonadotropin	13.5	4	1990
Transfusion (variant CJD)	7.5	3 (4)	2004
Therapy with plasma-derived products	(12-14)	(1v) +2s (?)	2010

Adapted and updated (2017) from Brown et al, 2012

CJD Epidemiology and Research

The 80s - BSE



Gerard Wells

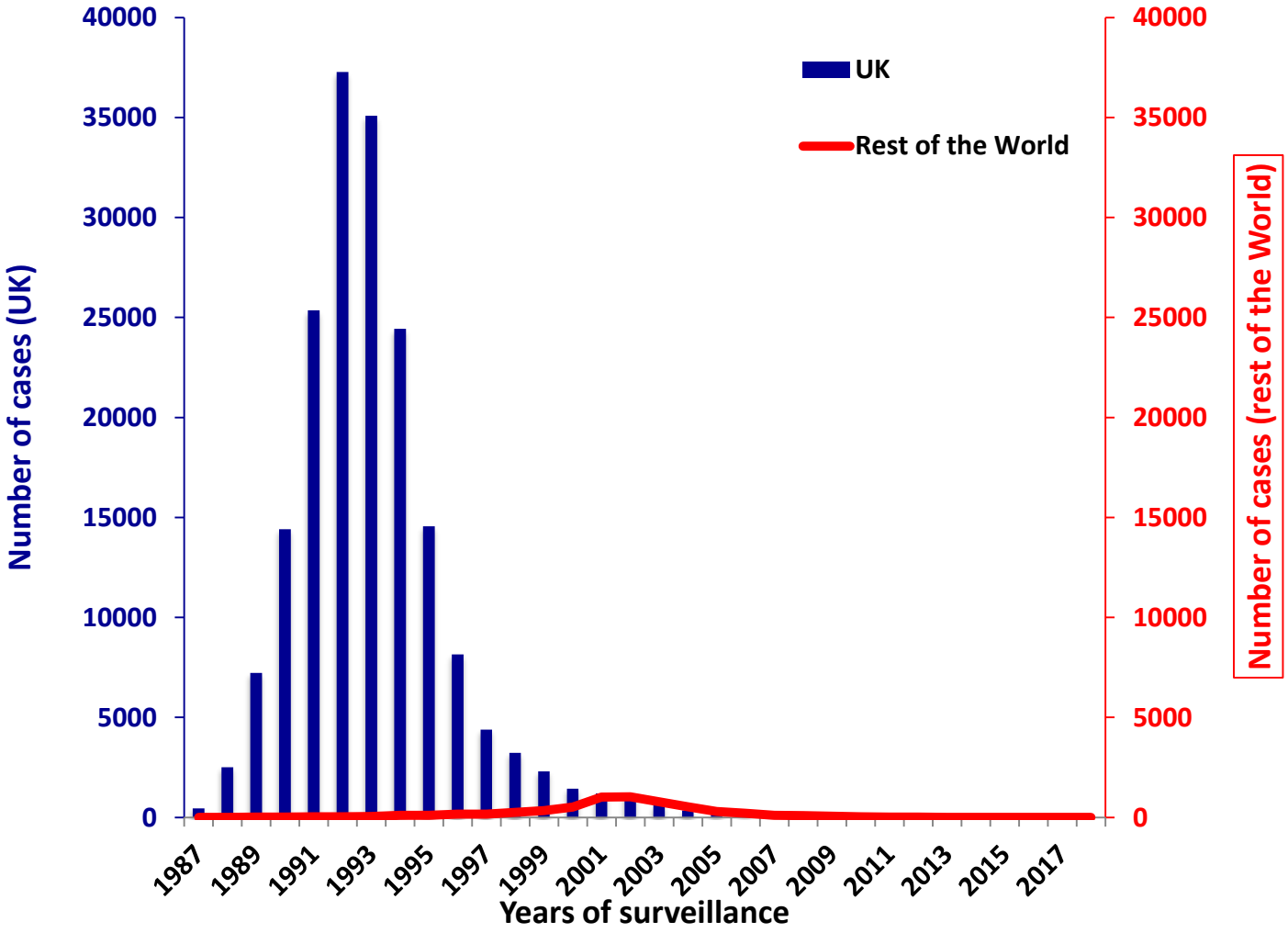
The Veterinary Record, October 31 1987

A novel progressive spongiform encephalopathy in cattle

G. A. H. Wells, A. C. Scott, C. T. Johnson,
R. F. Gunning, R. D. Hancock, M. Jeffrey,
M. Dawson, R. Bradley

Veterinary Record (1987) **121**, 419-420

BSE IN THE UK AND IN THE REST OF THE WORLD



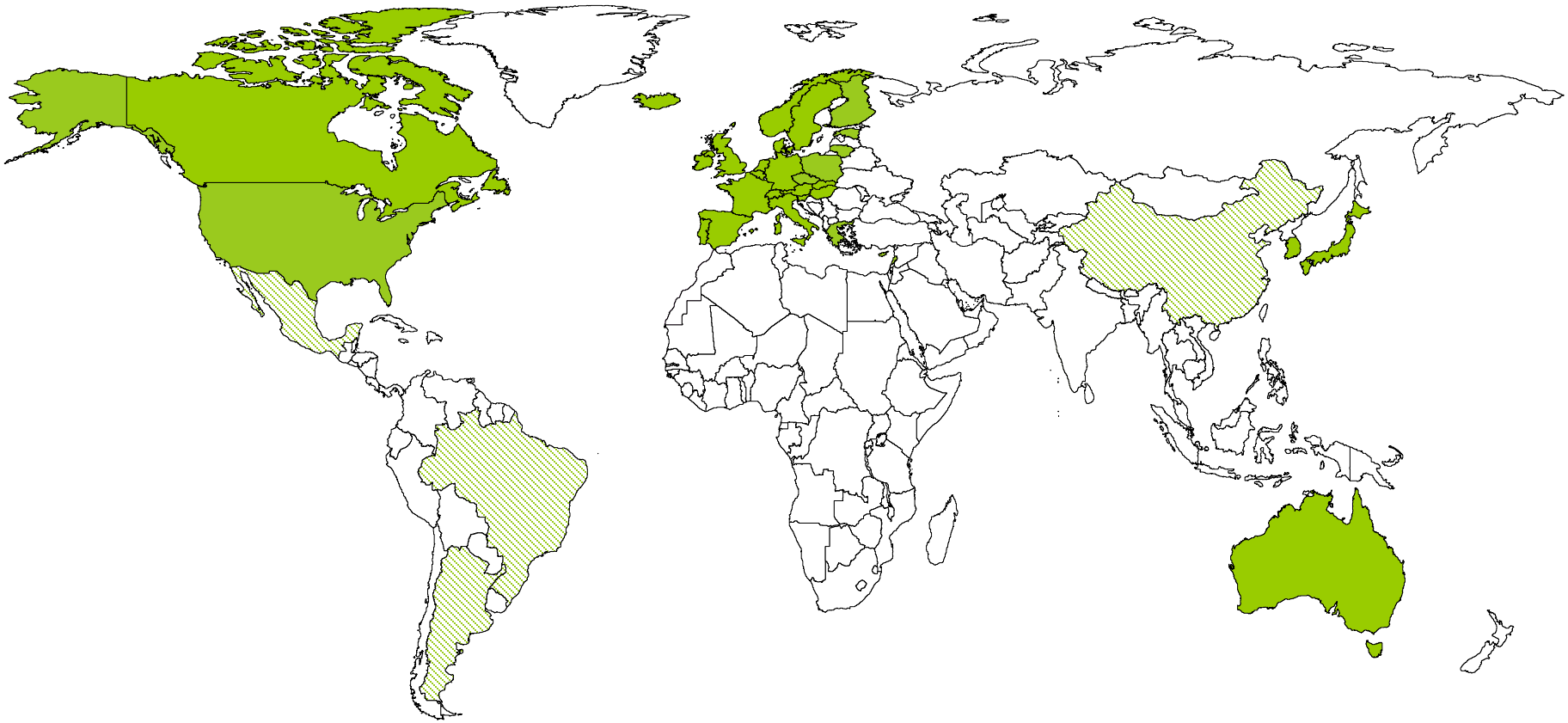
Data from OIE, update 2019

- **A collaborative study of CJD in the European Union was funded by the European Commission in 1993.**

- **The principal goal was to determine whether the incidence of CJD was similar throughout the EU, and if there was any major difference between putative risk factors in various countries.**

EUROCJD SURVEILLANCE

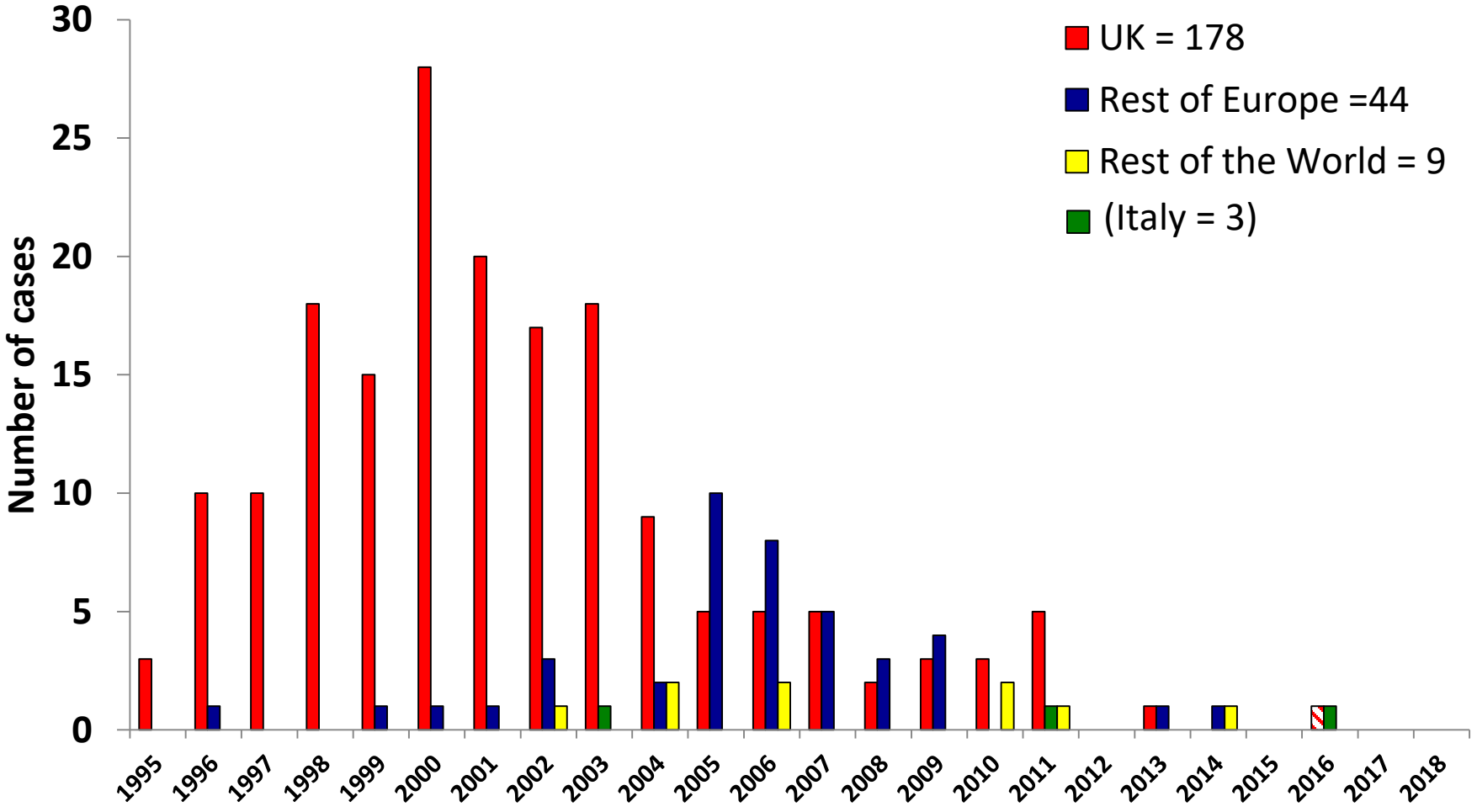
LAUNCHED IN 1993



VARIANT CREUTZFELDT-JAKOB DISEASE (n=231)

- Distribution by year and geographic areas –

All Met/Met at codon 129 but 1 Met/Val



EuroCJD Surveillance 2019, n=231

CJD Epidemiology and Research

80s-90s

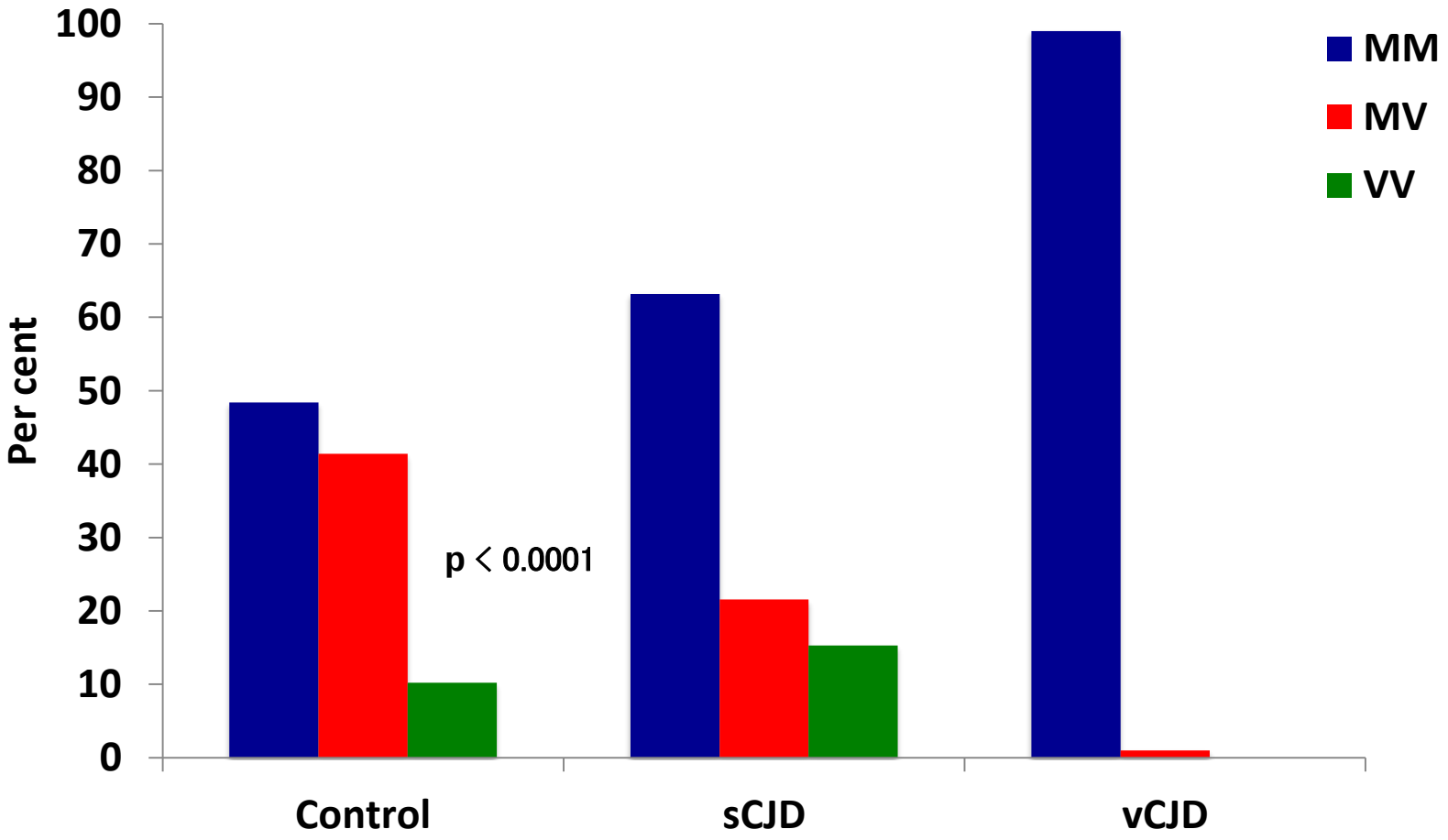
Stanley Prusiner

Novel Proteinaceous Infectious Particles Cause Scrapie

Stanley B. Prusiner

- Pathological prion protein PrP^{TSE}
- Sequence of the prion protein gene (*PRNP*)
- The codon 129 polymorphism
- Pathogenic mutations of the *PRNP* gene
- Different conformations of PrP^{TSE}

CODON 129 DISTRIBUTION



Control, from Mercier et al., 2008 (only Italian people)
sCJD, from the Italian CJD Surveillance Unit
vCJD, from

Molecular Basis of Creutzfeldt-Jakob disease

- Clinical and pathological phenotypes -

Sporadic CJD

***PRNP* Genotype**

Met Met | Met Val | Val Val

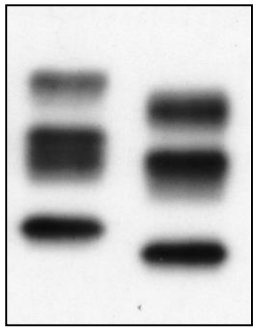
Polymorphism at Codon 129

MM-1
MM-2A
MV-1
MV-2
VV-1
VV-2

PrP^{TSE}

PrP^{TSE} Type 1 — 21 kDa

PrP^{TSE} Type 2 — 19 kDa



Variant CJD

***PRNP* Genotype**

Met Met

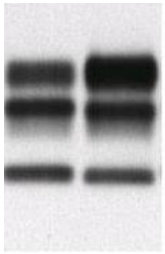
Polymorphism at Codon 129

MM-2B

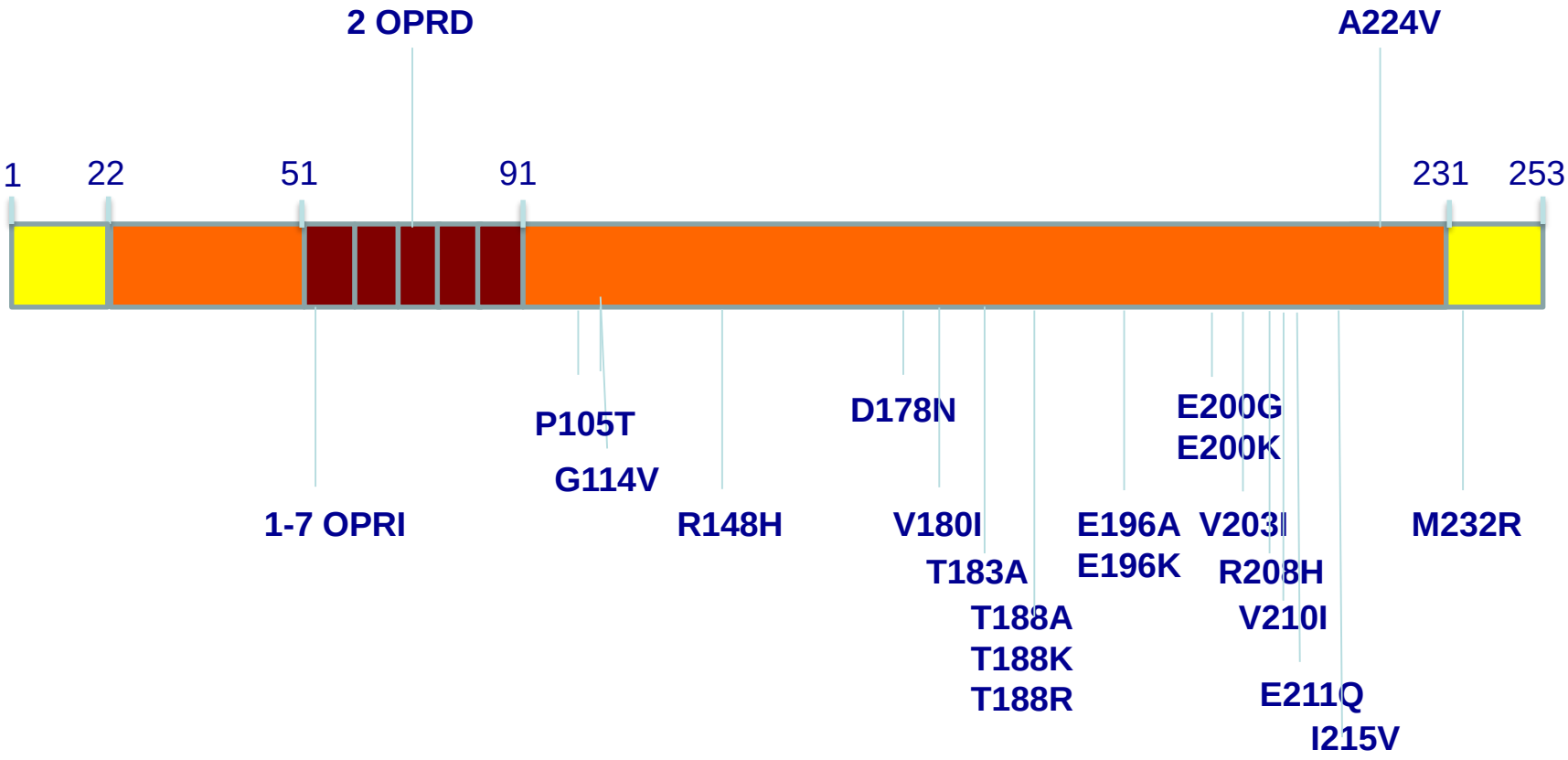
PrP^{TSE}

PrP^{TSE} Type 2A

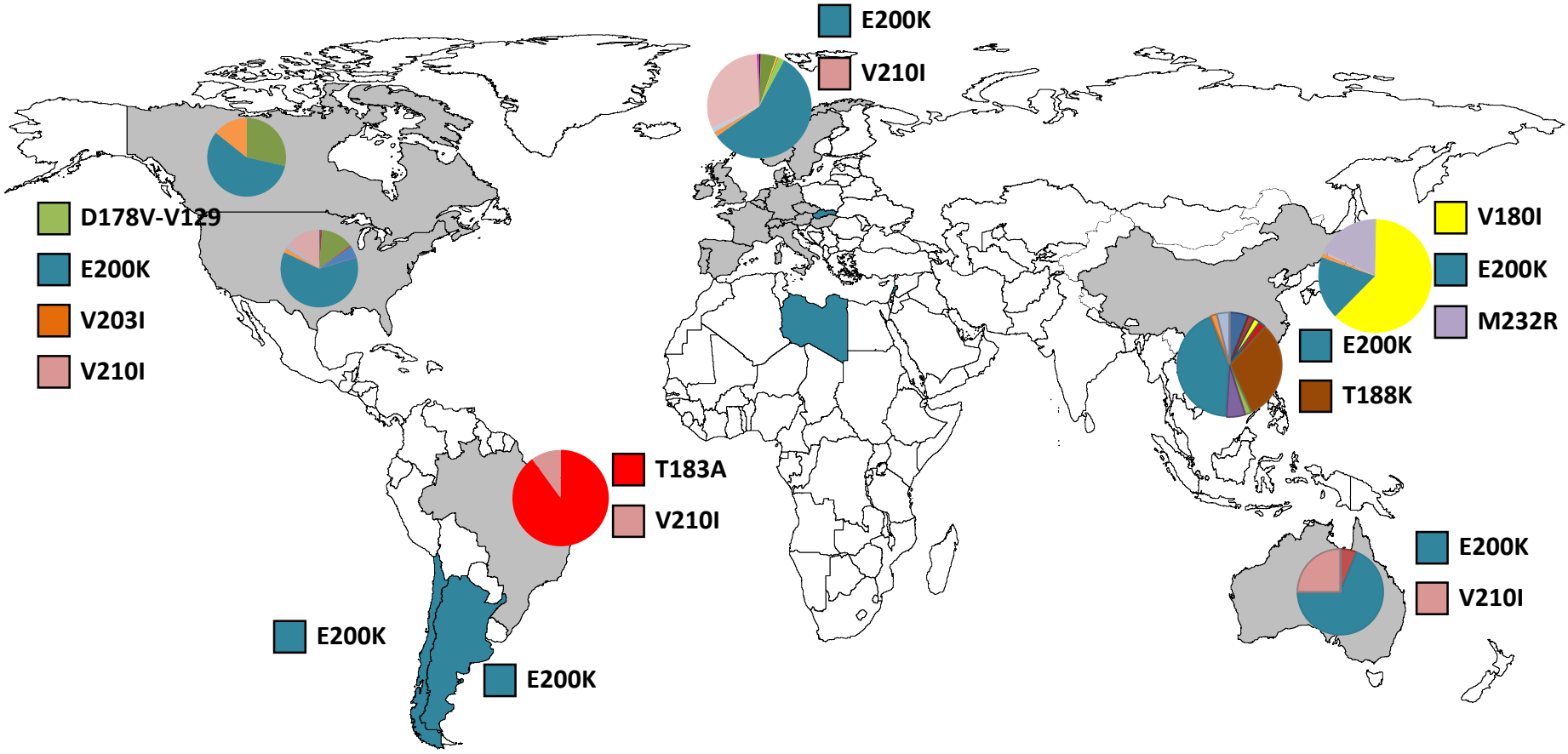
PrP^{TSE} Type 2B



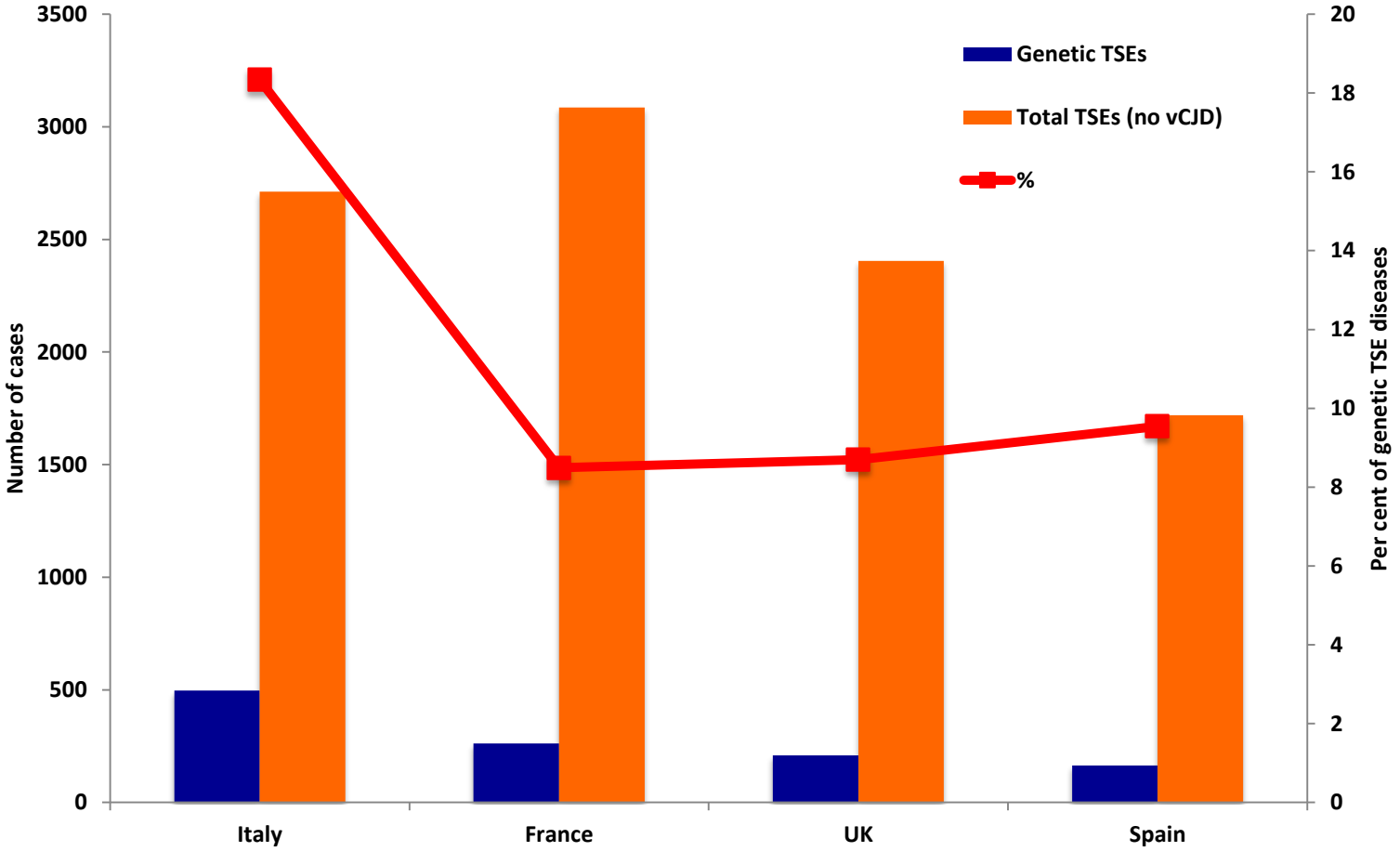
PATHOGENIC MUTATIONS



DISTRIBUTION OF GENETIC TSE



THE IMPACT OF GENETIC TSE DISEASES



SPONTANEOUS *VERSUS* ACQUIRED TSE DISEASES

ACQUIRED TSE DISEASES

Human

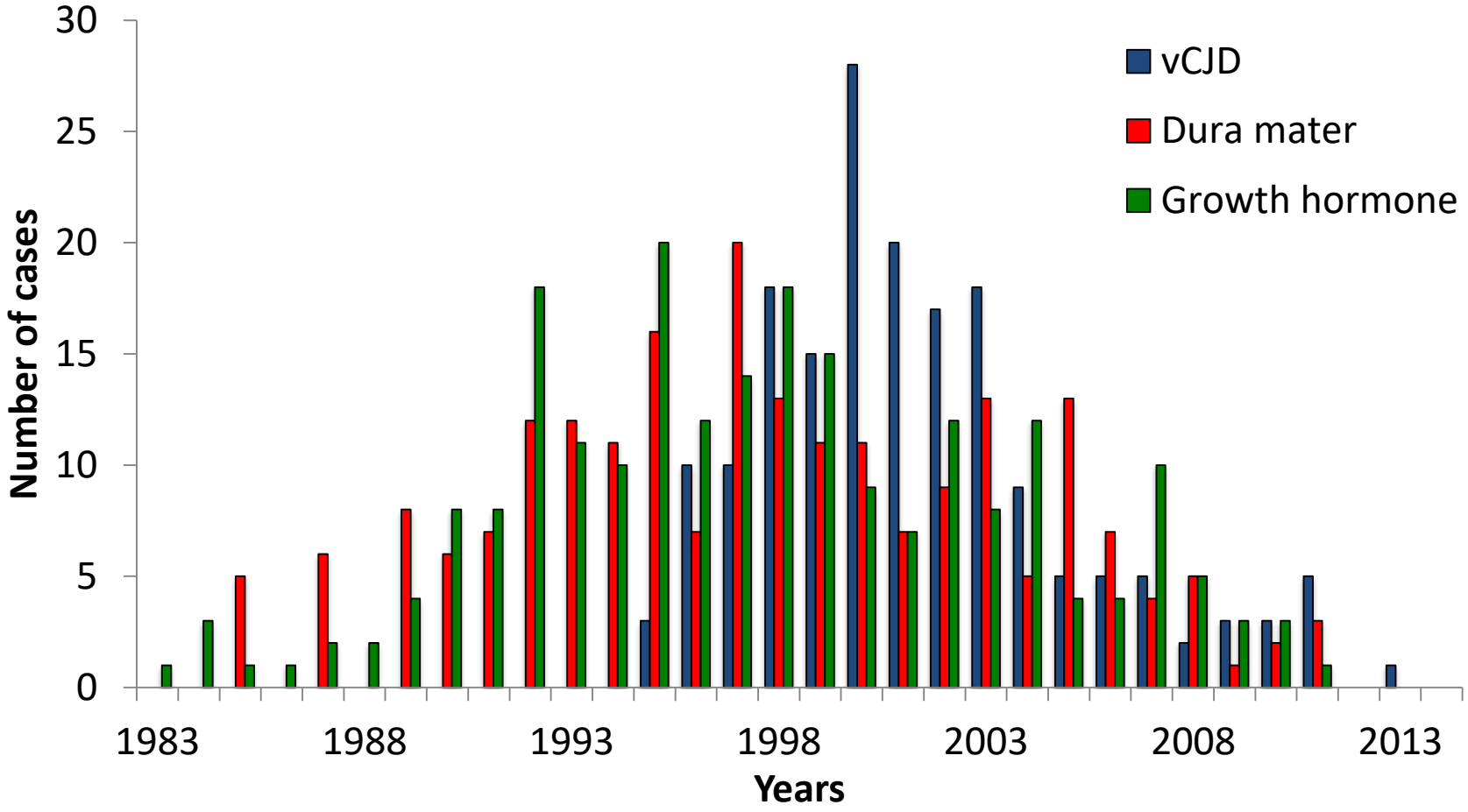
- **Medical procedures (iatrogenic CJD)**
- **Food (variant CJD)**
  - BSE, food
  - Possibly scrapie, CWD

Animals

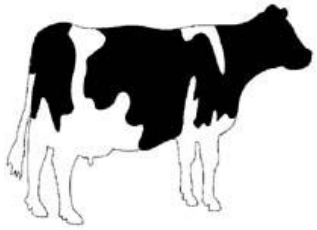
- **Medical procedures**
  - Scrapie
- **Oral transmission (or other possible routes)**
  - Transmissible mink encephalopathy
  - Classical BSE
  - Feline spongiform encephalopathy
  - Scrapie
  - Chronic Wasting disease (CWD)

Acquired prion diseases

A vanishing epidemic



Definite and Theoretical Prion Zoonosis



Definite

Variant CJD

Scrapie

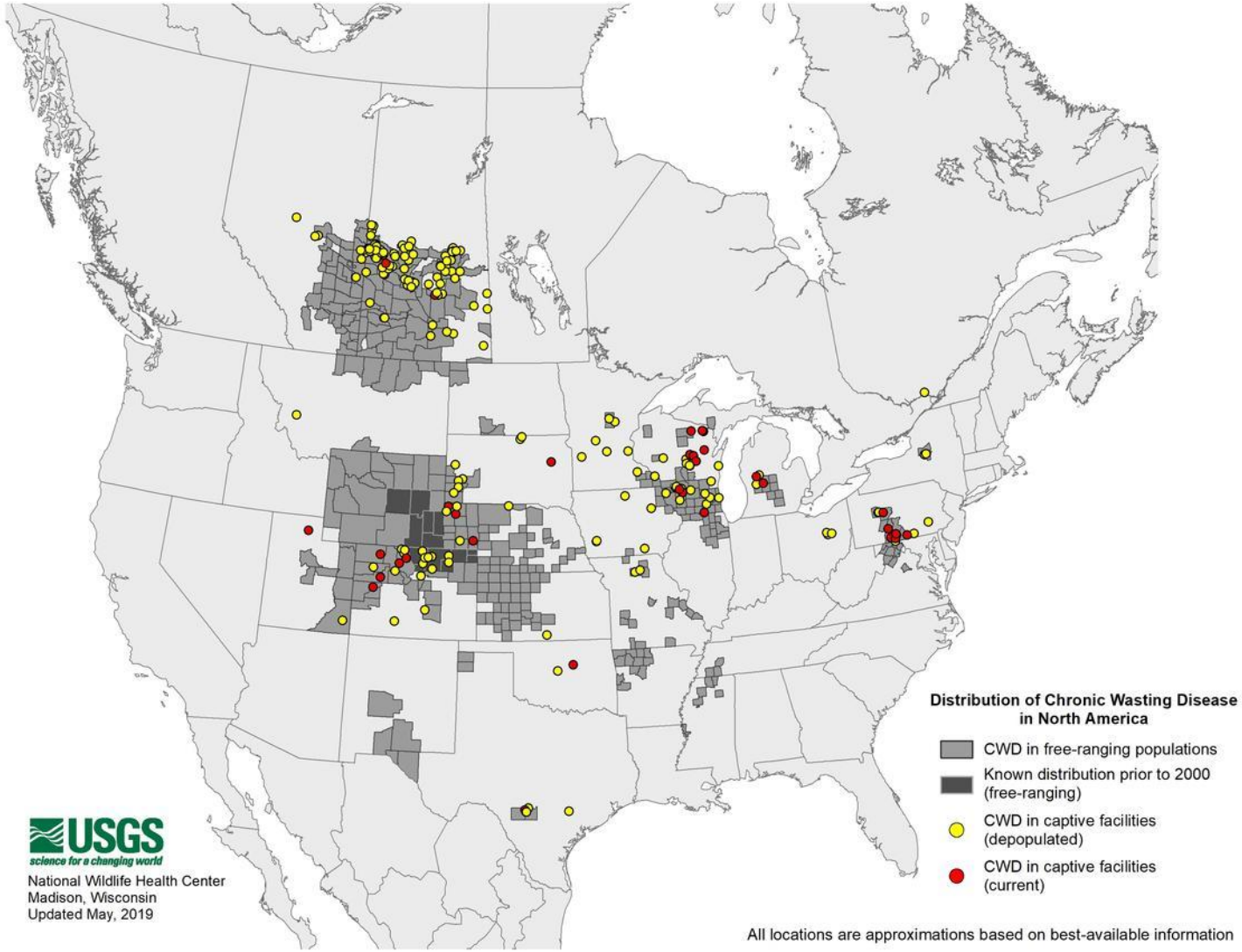
Theoretical

CWD

Which phenotype?

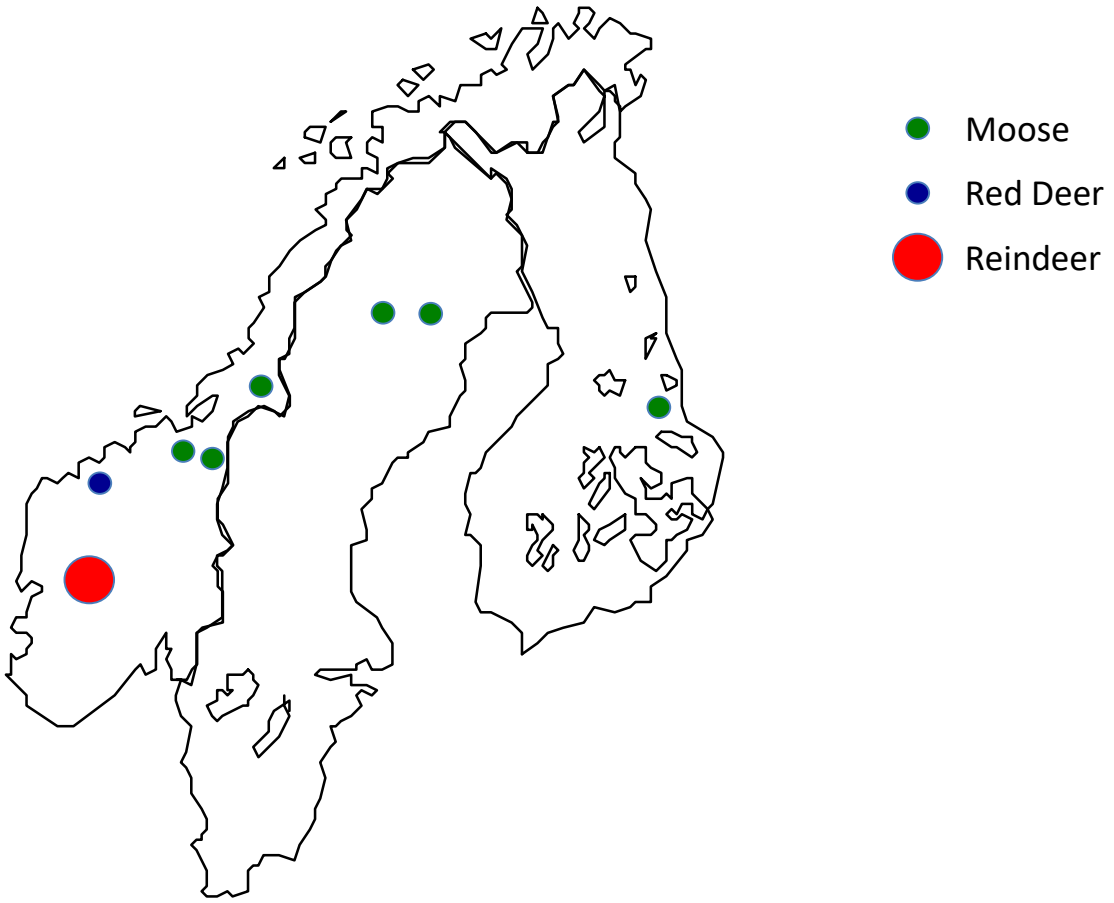
Chronic Wasting Disease in North America

(reported in 1980, but presents in Colorado and Wyoming for about 40 years)



Chronic Wasting Disease in Europe

(First reported in Norway in 2016)



Updated, May 2019

SPONTANEOUS TSE DISEASES

Human

- Sporadic CJD
- **Genetic TSE diseases**

Animal

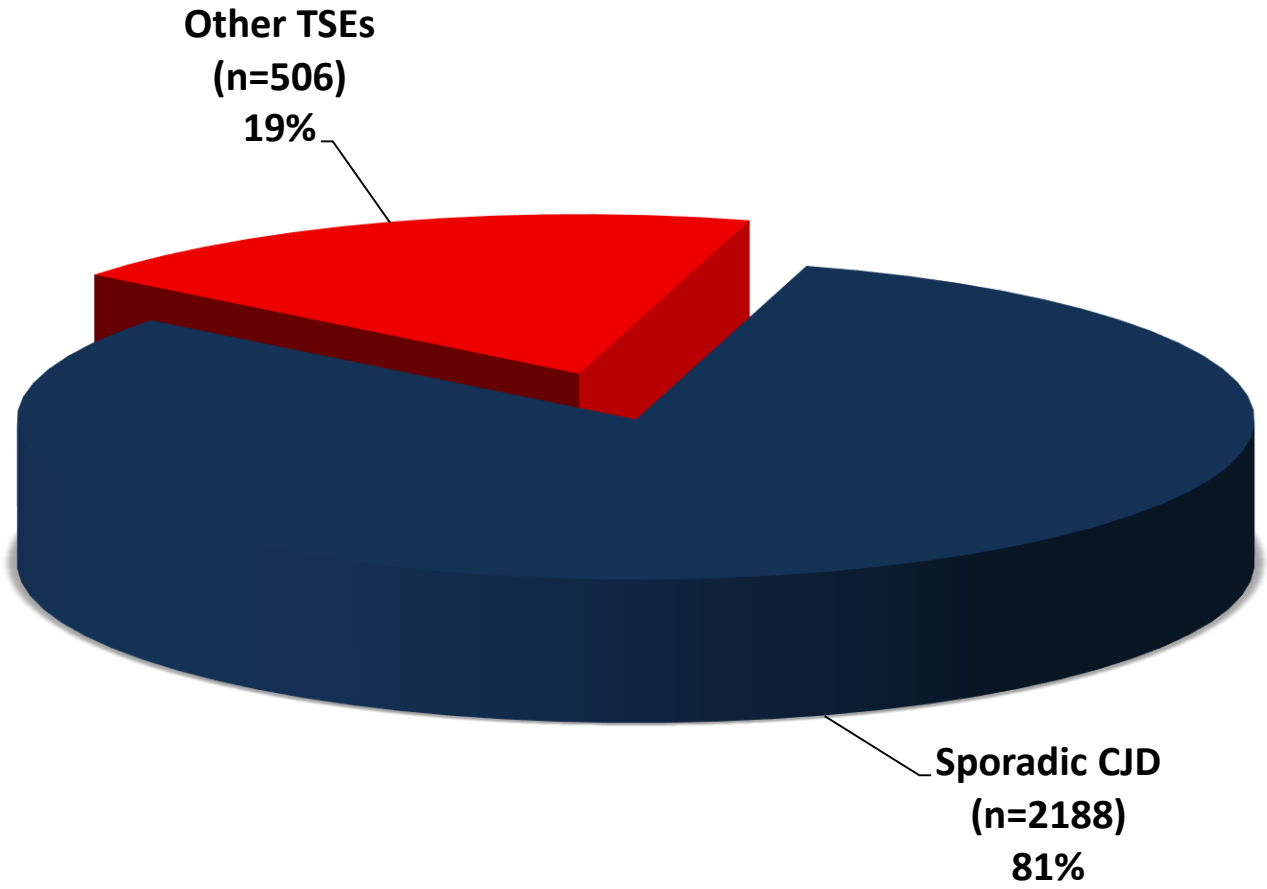
- Atypical BSEs
  - L-type, H-type
- Atypical scrapie
  - Nor98

PREVENTION IN GENETIC TSE DISEASES

- Predictive tests in unaffected individuals
  - future life planning
    - no curative treatment to offer them if they test positive
    - preventive treatment (?)
  - reproductive planning
    - possibilities of prenatal genetic testing
    - preimplantation diagnosis
- Preventive treatment
  - ongoing in FFI

DISTRIBUTION OF PRION DISEASES IN ITALY

1993-2018



SPONTANEOUS TSE DISEASES

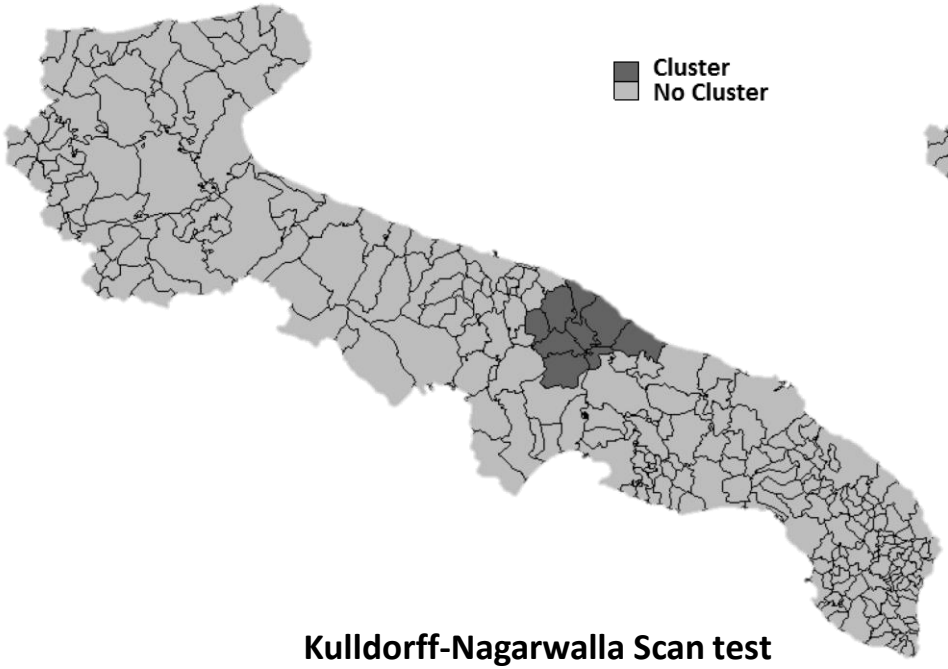
Sporadic CJD

One possible mechanism to explain sporadic prion diseases involves precursor proteins becoming transformed into disease-causing prions through a stochastic process, which most of the time probably represents a dead-end route in which small numbers of prions are cleared via protein degradation pathways.

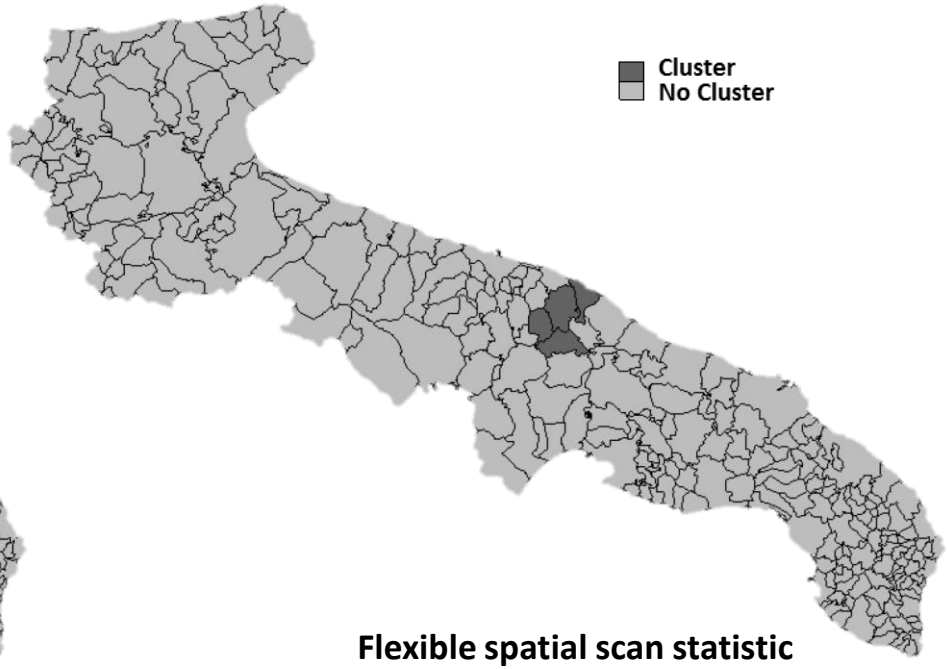
Stanley Prusiner

Is it really so?

POSSIBLE CLUSTER OF SPORADIC CJD IN APULIA



Kulldorff-Nagarwalla Scan test

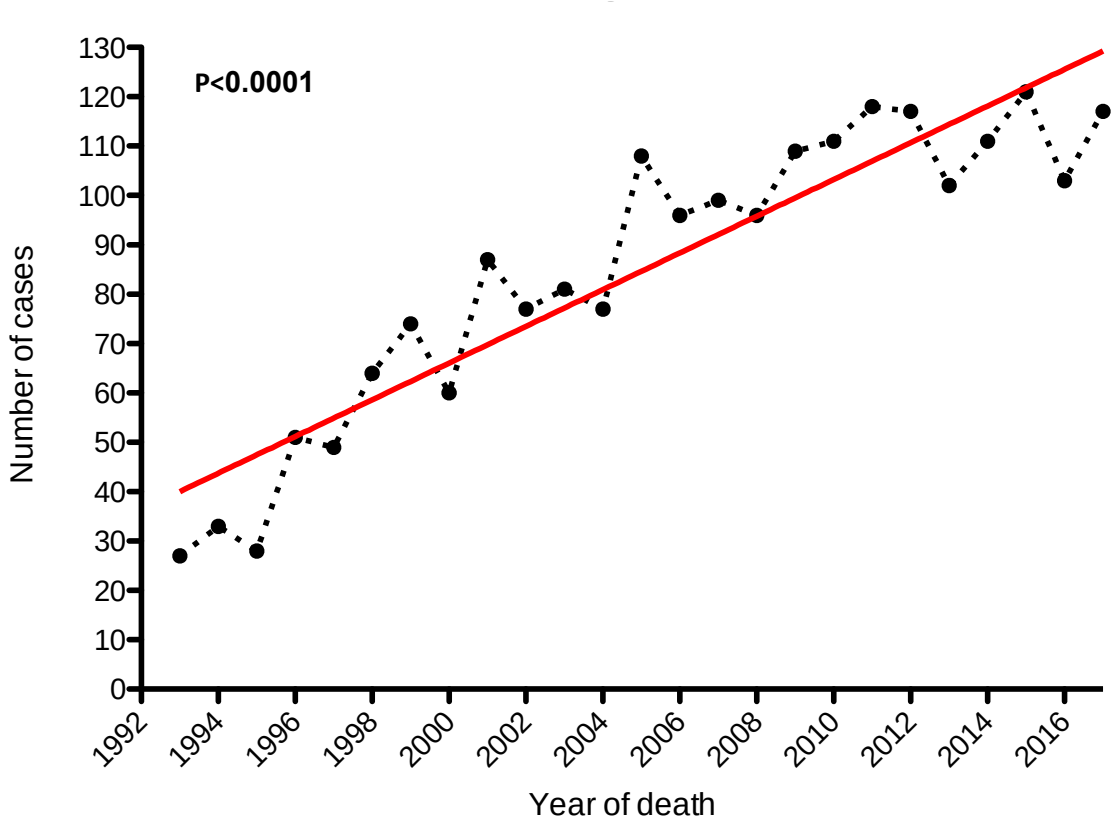


Flexible spatial scan statistic

Puopolo et al., unpublished data

SPORADIC CJD IN ITALY

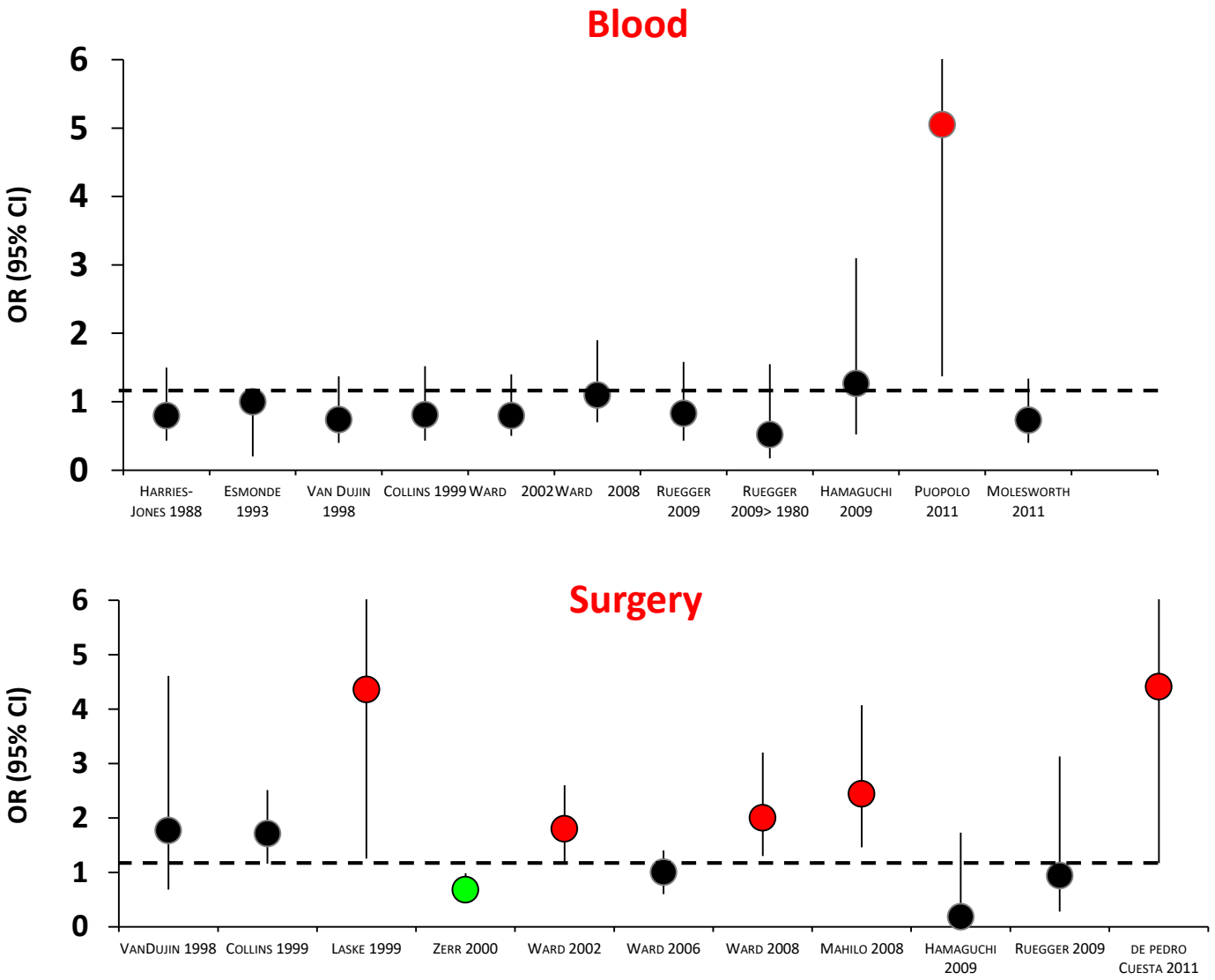
(MORTALITY DATA)



Updated, May 2019

CASE-CONTROL STUDIES

MEDICAL PROCEDURES AND RISK OF ACQUIRING SPORADIC CJD



INCREASED NUMBER OF SPORADIC CJD CASES

- **Ascertainment bias**
  - Referrals
  - Diagnostic criteria
- **True increase. Possible risk factors**
  - Medical/surgical procedures
  - Zoonoses
  - Environment

HISTORY OF CLINICAL DIAGNOSTIC CRITERIA FOR SPORADIC CJD

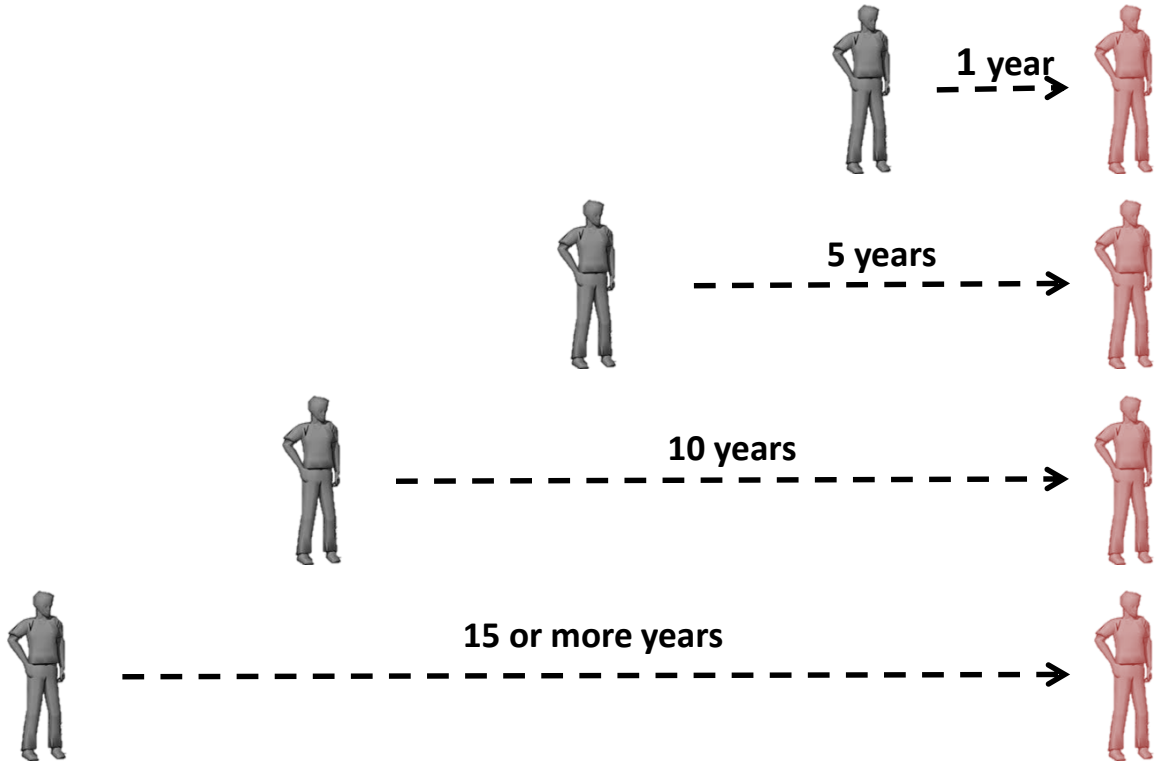
Clinical, diagnostic and instrumental data	Master et al, 1979	EuroCJD, 1993	EuroCJD, 1998	EuroCJD, 2010	EuroCJD, 2010
Clinical signs	+	+°	+°	+°	+°
Generalized triphasic periodic complexes on EEG	+	+	+	+	+
14-3-3 proteins in the CSF and disease duration < 24m			+	+	+
High signal in caudate/putamen on MRI brain scan				+	
High signal in caudate/putamen on MRI brain scan or at least two cortical regions (temporal, parietal, occipital) either on DWI or FLAIR					+
RT-QuIC					+

*Rapid progressive dementia + 2 (1 in Master's) of the following signs: myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal, and akinetic mutism features.

°Visual and akinetic mutism were added in the European criteria

The Difficulties of Searching for risk factors in sporadic CJD

Lag Time between infection and disease



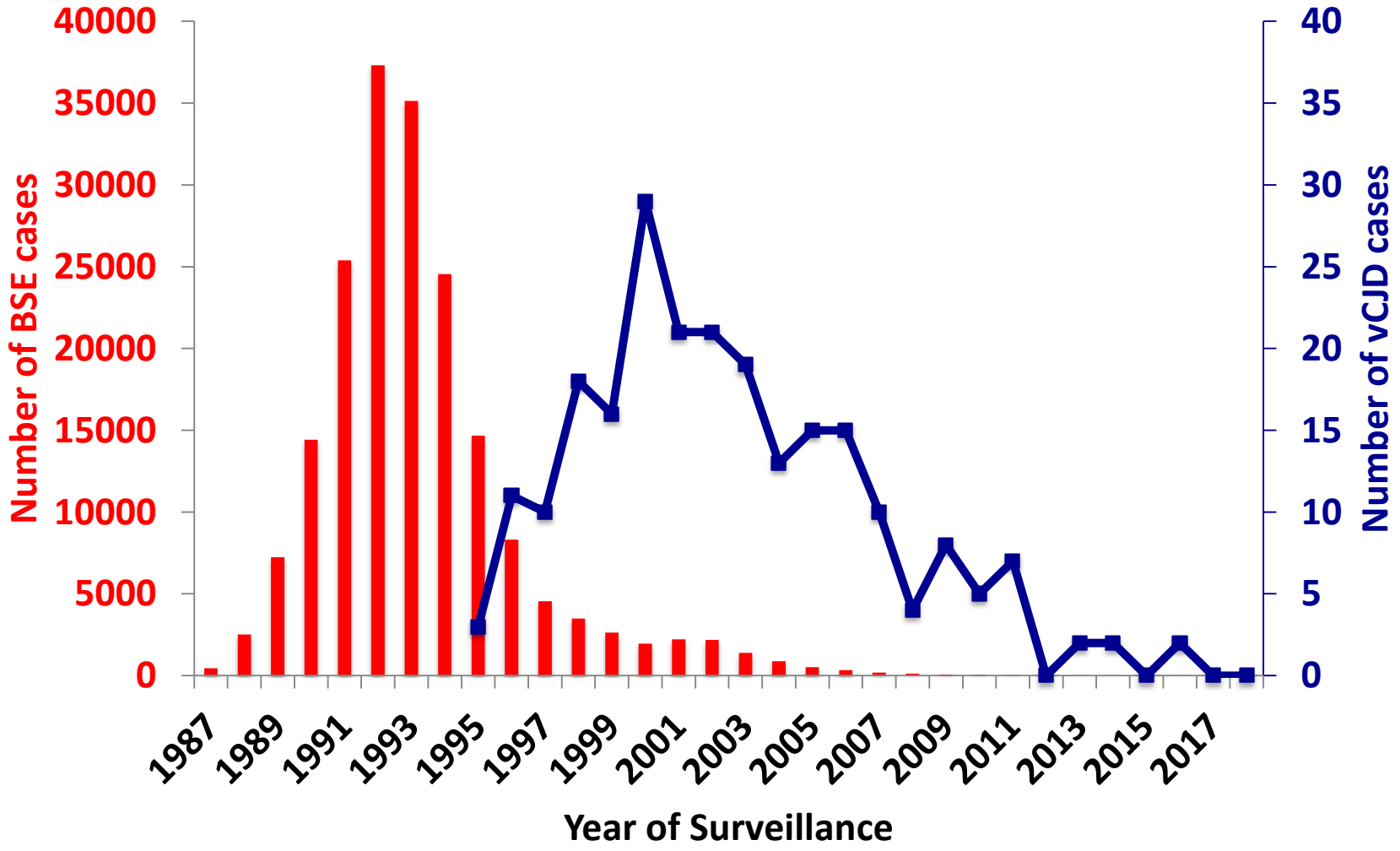
Place of residence

Route of infection

Source of infection (titre)

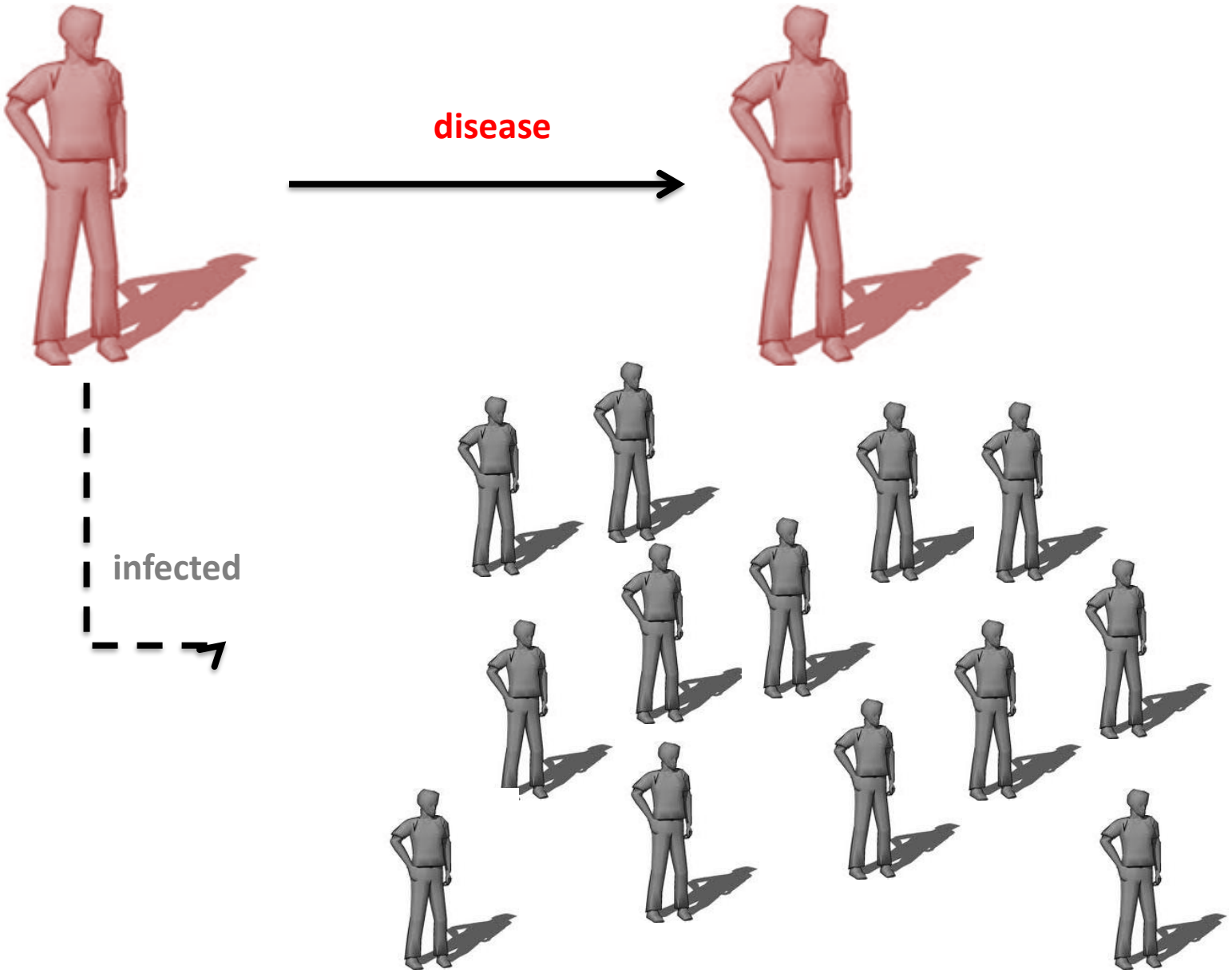
Prion strain

BSE AND vCJD EPIDEMIC IN THE WORLD



Data updated 2019

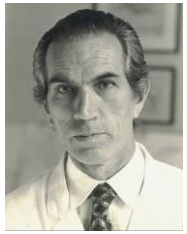
INFECTIOUS *VERSUS* DISEASE



EPIDEMIOLOGICAL STUDIES IN THE FUTURE

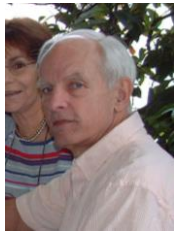
- Full molecular epidemiology of sporadic CJD
  - Correct classification of sporadic CJD by subtypes (129 polymorphism and PrP^{CJD} typing)
    - Improve the identification of PrP^{CJD} conformers in easily accessible tissues
- Screening of prion-exposed people
  - Family members, medical and paramedical personnel
    - Improve the detection of PrP^{CJD} (PMCA, RT-QuIC, others) in easily accessible tissues in pre-clinical or sub-clinical infected people
- Search for genes, other than *PRNP,* that modulate the pathogenesis of prion diseases and influence disease onset

PRIONS REMAIN A FASCINATING FIELD OF DISCOVERY


Giovanni Alemà


Bryan Matthews


Colin Masters


Paul Brown


Françoise Cathala


Eva Mitrova


Richard Knight


Bob Will

Half of what scientists told you will turn out to be wrong, but they don't know which half

From Larry Peiperl, Chief Editor, Plos Medicine, 2017