Human aspect: Creutzfeldt-Jakob disease situation in EU

Joint Workshop of the European Reference Laboratories for Transmissible Spongiform Encephalopathies and Animal Proteins Rome Italy – May 13-15, 2024

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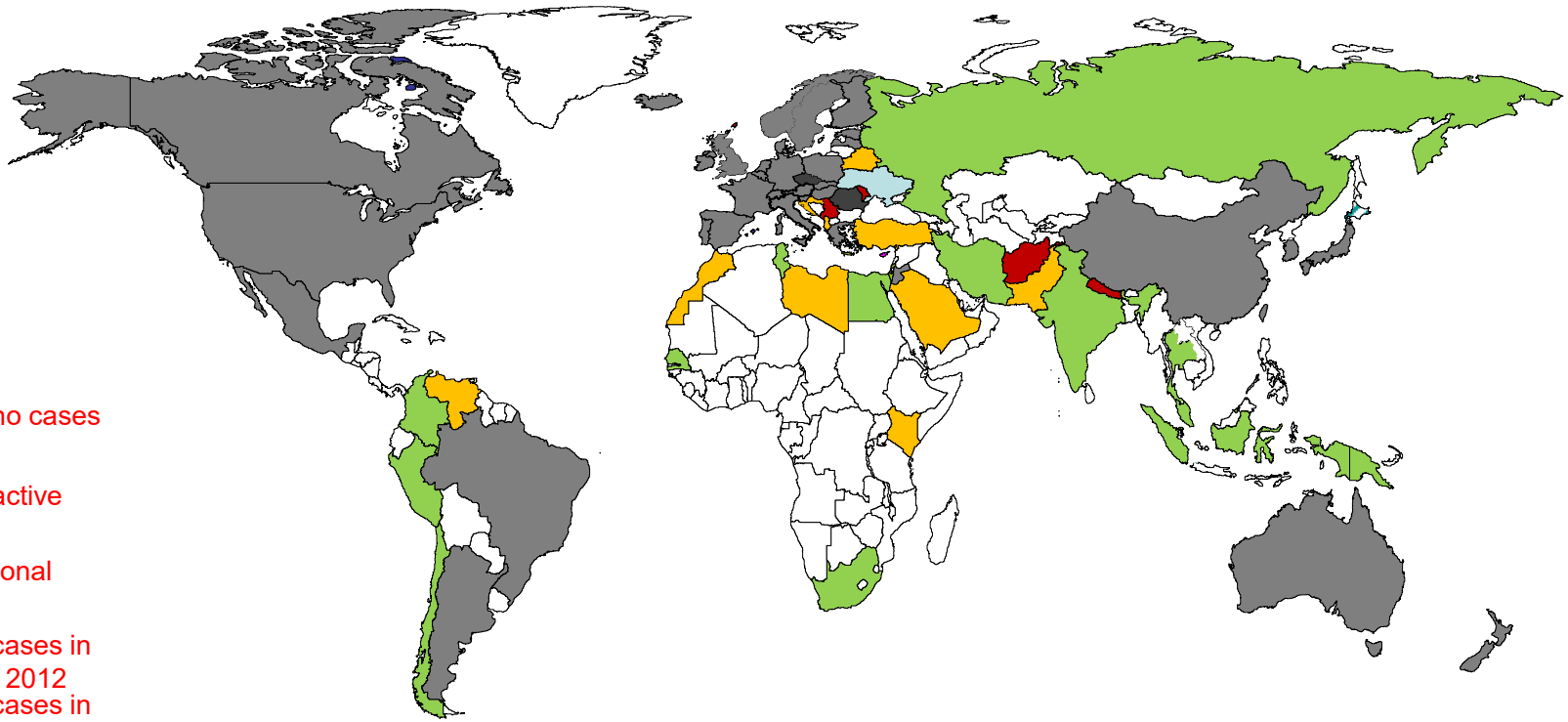
HUMAN PRION DISEASES

Sporadic Creutzfeldt-Jakob disease (CJD)	**- Unknown**
Genetic TSE (genetic CJD, GSS, FFI)	**- Linked to insert/point mutation in the PrP gene (*PRNP*)**
Iatrogenic CJD	**- Linked to medical procedures**
Variant CJD	**- Linked to BSE agent** **- Human-to-human transmission**

Countries reporting CJD

- **Rare disease (1-2 cases per million per year)**
- **Worldwide distribution**
- **Transmissible, however, the majority of cases are sporadic forms**



Countries with no cases

Countries with active surveillance

Ladogana, personal communication

Countries with cases in Ladogana et al. 2012

Countries with cases in Masters et al. 1979

Pubmed search, update 2023

History of Surveillance of CJD in Europe

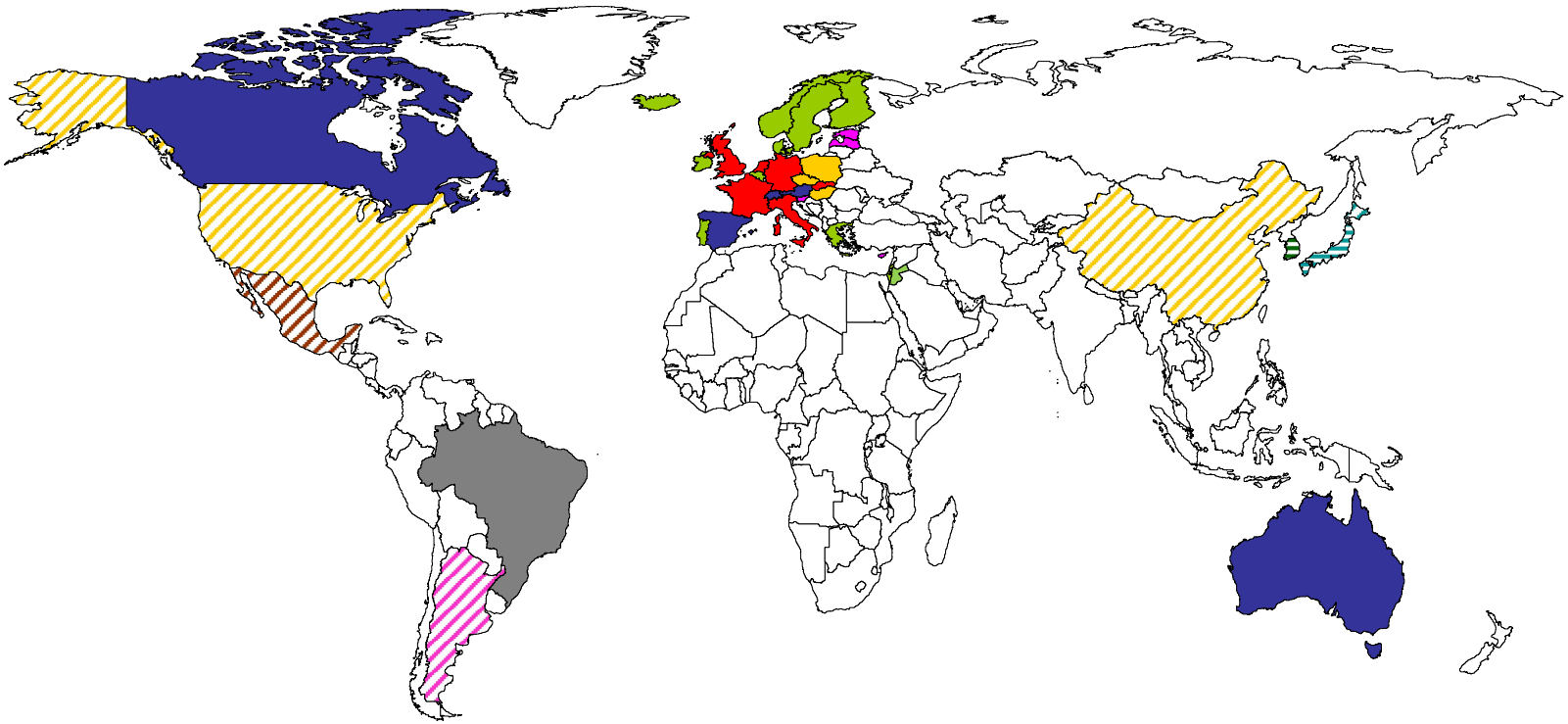
- A collaborative study of CJD in the European Union was funded by the European Commission through the BIOMED1 and 2 programme in 1993-2003: The European and Allied Countries Collaborative Study Group of CJD (EUROCJD) plus the Extended European Collaborative Study Group of CJD (NEUROCJD)

- DG SANCO (2004-2007) : The European and Associated Countries CJD surveillance network

- ECDC from 2007 to 2021: outsourced to UK Unit as Creutzfeldt-Jakob Disease international surveillance network

The CJD International Surveillance Network in the World

1993	6
1997	11
1998	21
2002	24/26
2004	28/31
2005	28/32
2006	28/33
2009	28/34



Surveillance of CJD in Europe in 2024

- Funding for Creutzfeldt-Jakob Disease international surveillance network ended in April 2021
- Mandatory notification of Variant CJD to ECDC is still in place (EU countries have mandatory notifications of all forms of Prion Diseases)
- EU countries supported the notion of surveillance of all TSE entities as a requirement for proper clinical identification of vCJD cases.
- EuroCJD Coordination Committee (CC) has been formally appointed by ECDC's Director, Andrea Ammon, on 29 January 2024
- The term of the CC is for January 2024 – December 2026
- The composition of the Disease Network CC is the following: JP Bradel, P Cras, A. Ladogana, S Papacostas, i. Zerr, however other experts can be invited on specific topic of interest.

Common Diagnostic Criteria for CJD Surveillance in EU
History of diagnostic criteria for sporadic CJD

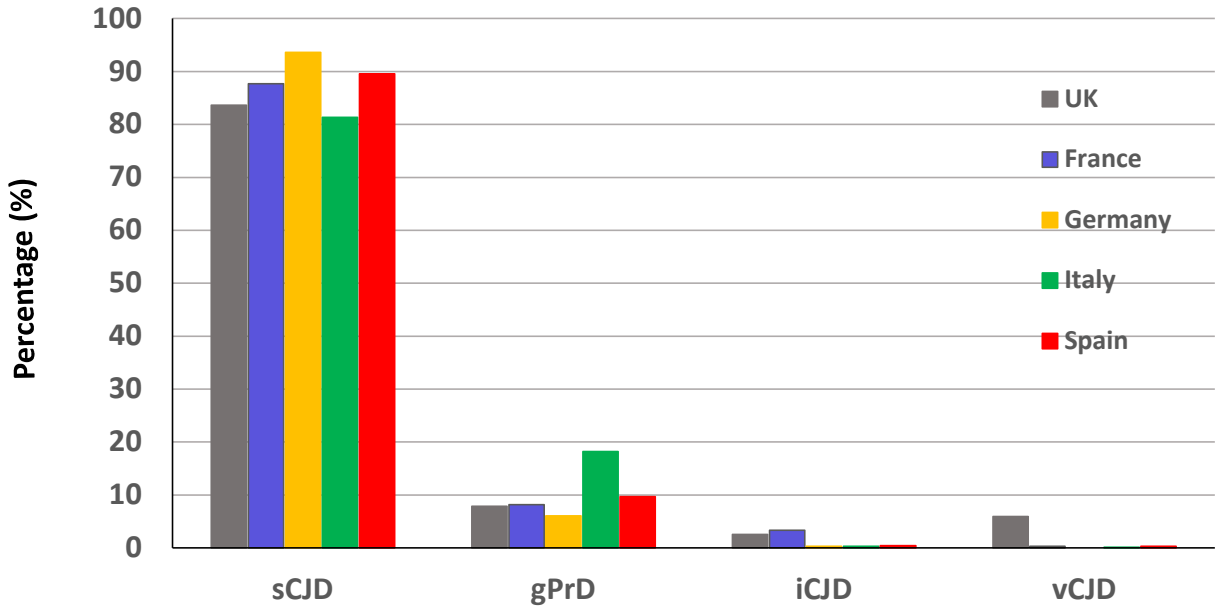
Clinical, diagnostic and instrumental data	Master 1979	EuroCJD 1993	EuroCJD 1998	EuroCJD 2010	EuroCJD 2017
Clinical signs*	+*	+	+	+	+°
Generalized triphasic periodic complexes on EEG	+	+	+	+	+
14-3-3 proteins in the CSF and disease duration < 24 m°			+	+	+
High signal in caudate/putamen on MRI brain scan				+	
High signal in caudate/putamen on MRI brain scan or at least in two cortical regions (temporal, parietal, occipital) in DW o FLAIR					+
RT-QuIC°° in CSF or other body tissues/fluids					+

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

° Rapid progressive dementia modified in '**Cognitive decline rapidly progressive'.**

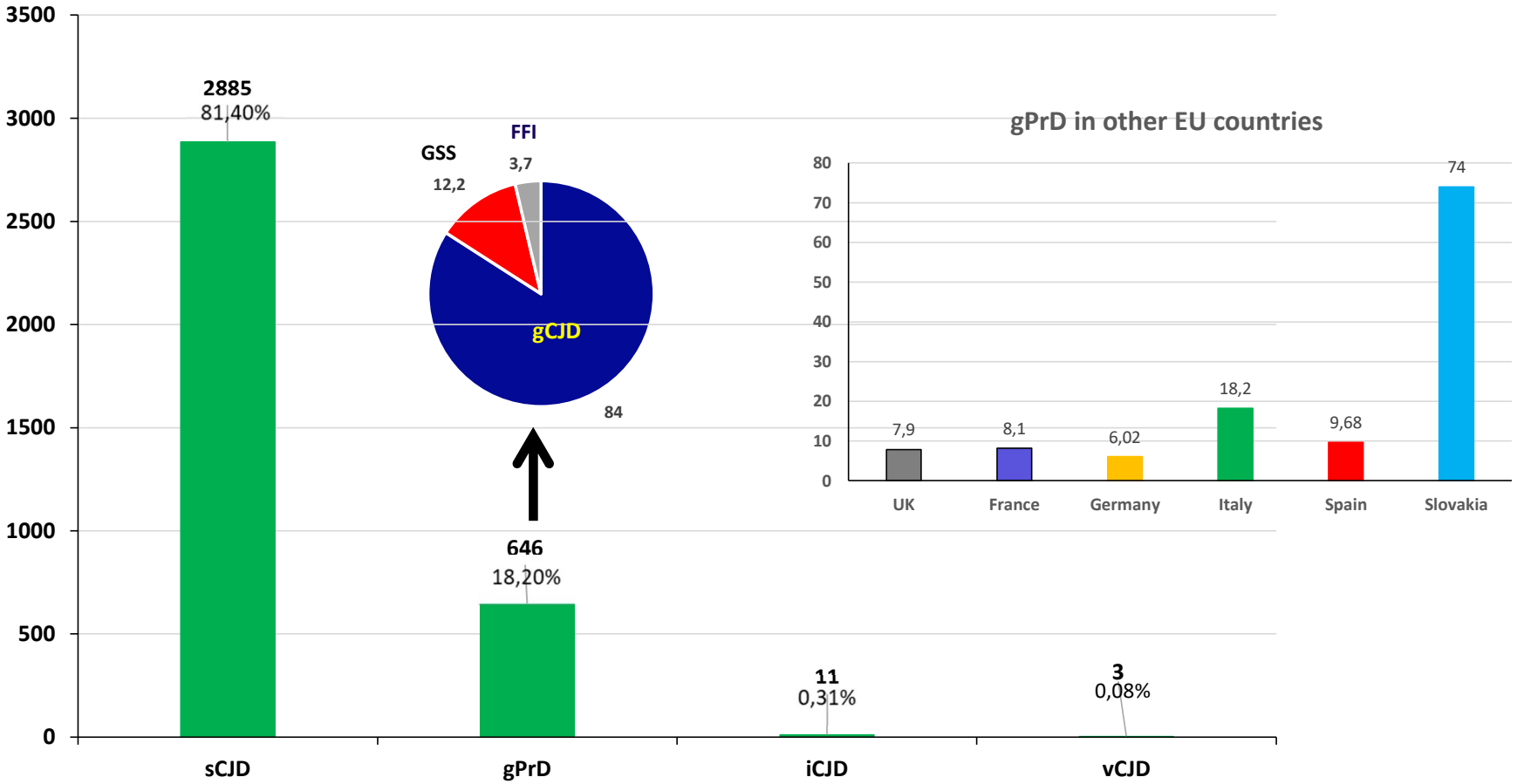
°°If RT-QuIC positive, clinical sign is 'Progressive neurologicas syndrome'.

Distribution of Prion Diseases in EU Countries (1993-2022#)



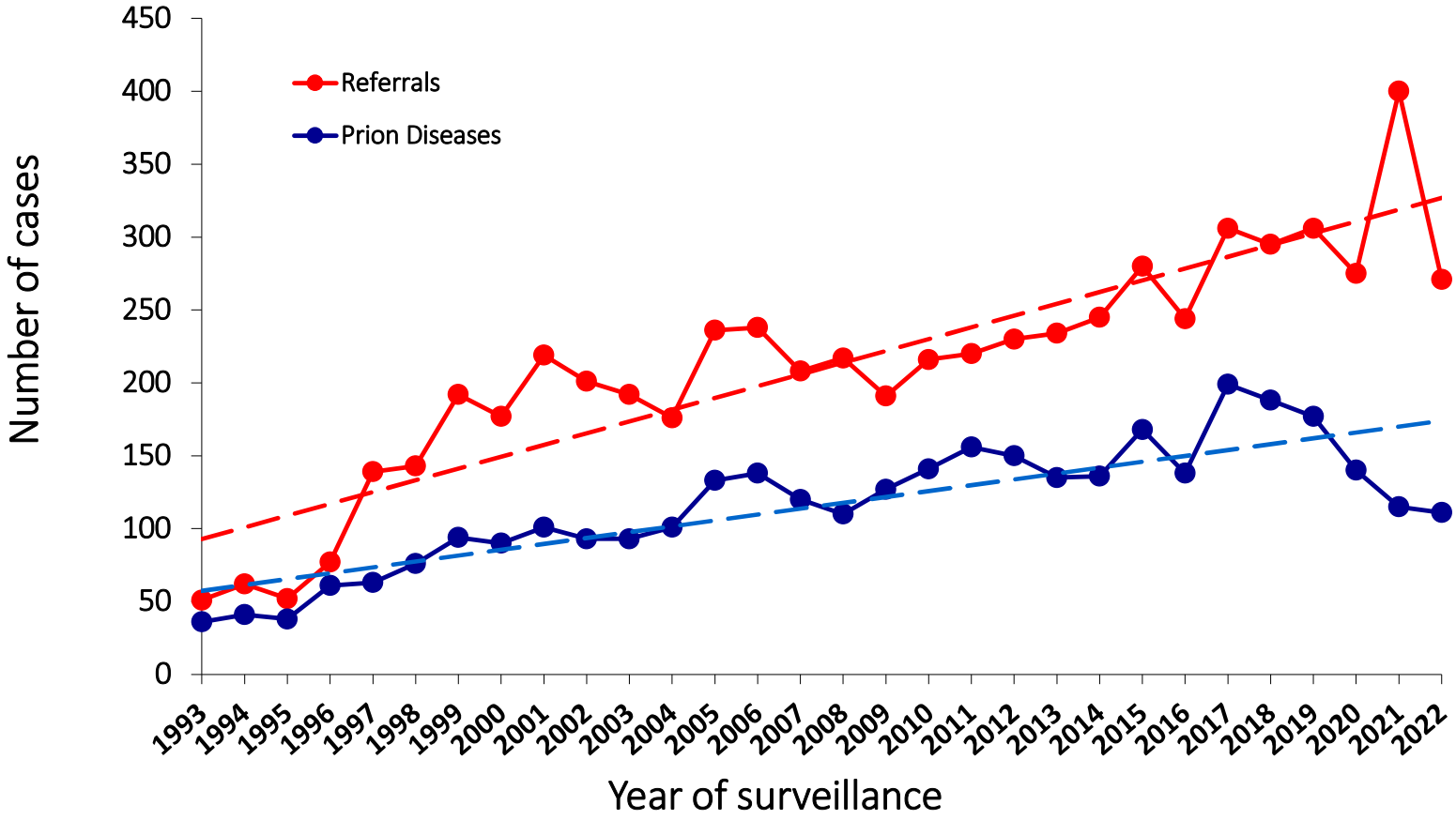
Data from countries web sites, accessed in April, 2024
#Data from Spain updated at 2021

Different forms of Prion Diseases in Italy (ISS data, 1993-2022)

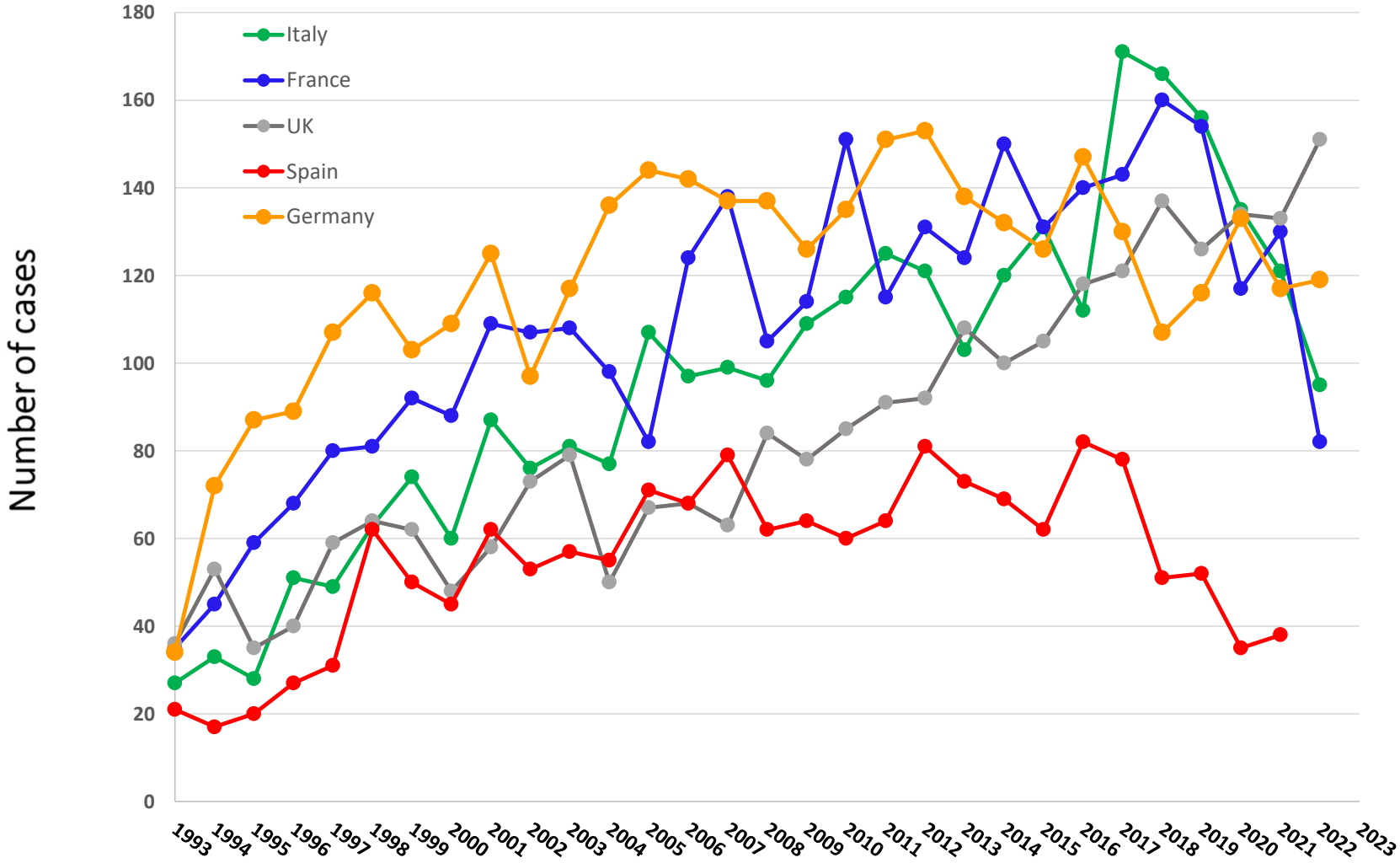


°to 31th December 2022; updated at 31th March 2024sCJD, sporadic Creutzfeldt-Jakob disease; gPD, genetic Prion Disease; iCJD, iatrogenic CJD; vCJD, variant CJD; gCJD, genetic CJD; GSS, syndrome of Gerstmann-Sträussler-Scheinker; FFI, Fatal familial Insomnia

Number of referrals and Prion Disease cases in Italy (ISS data, 1993-2022)



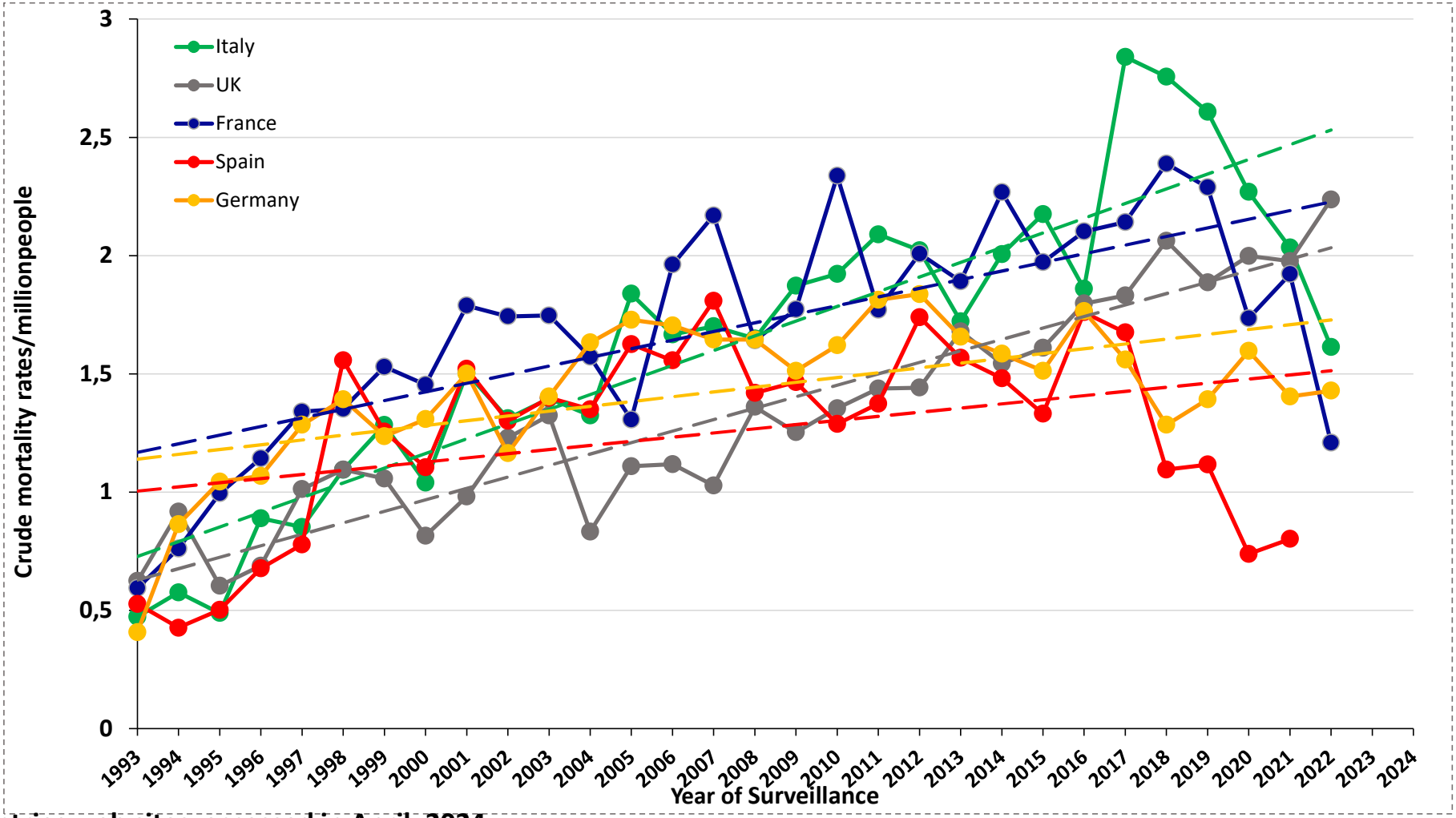
Number of deaths from sporadic CJD in European countries (1993-2022 #)



Data from countries web sites, accessed in April, 2024

#Data from Spain updated at 2021

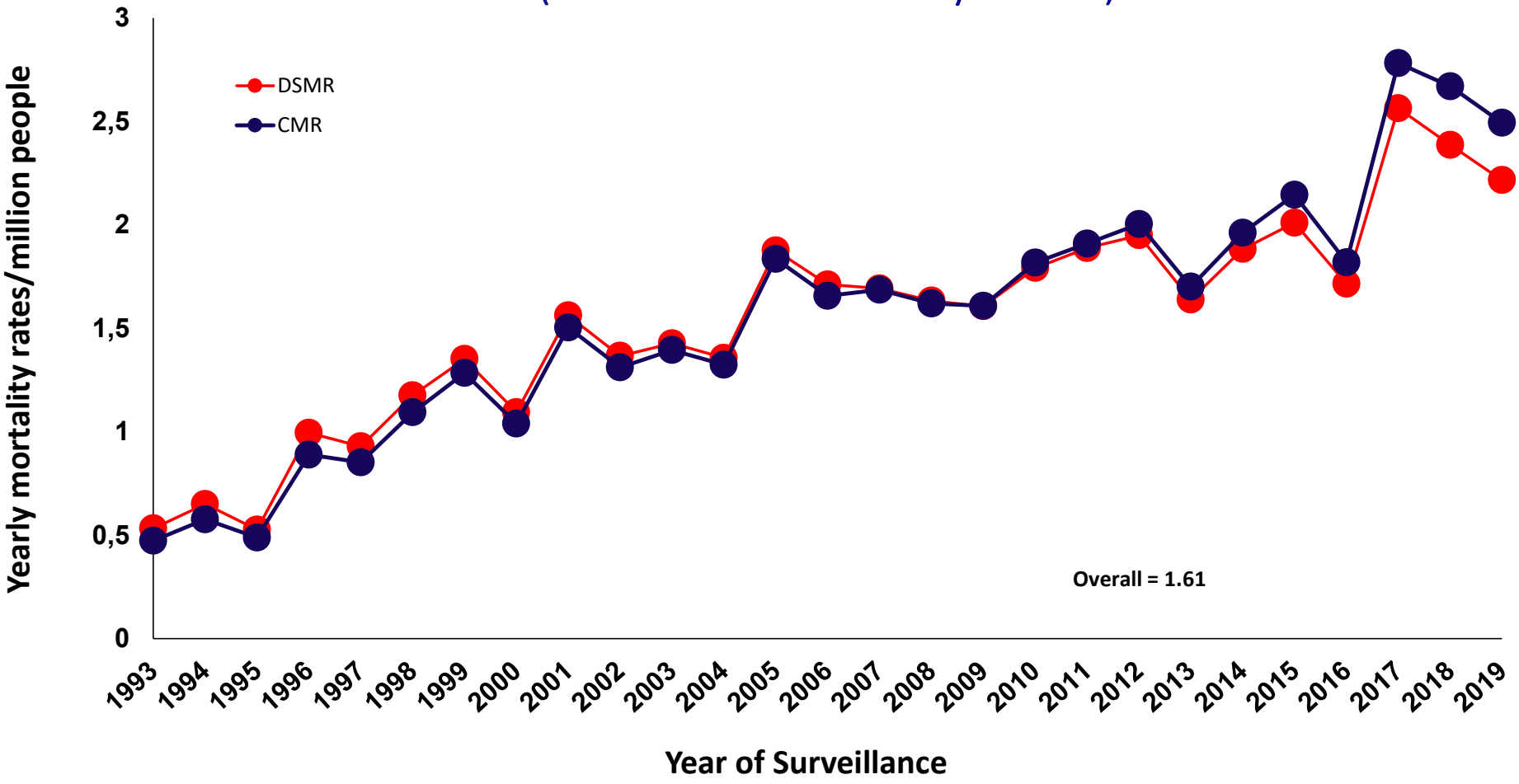
Crude mortality rates from sporadic CJD in European countries (1993-2022 #)



Data from countries web sites, accessed in April, 2024

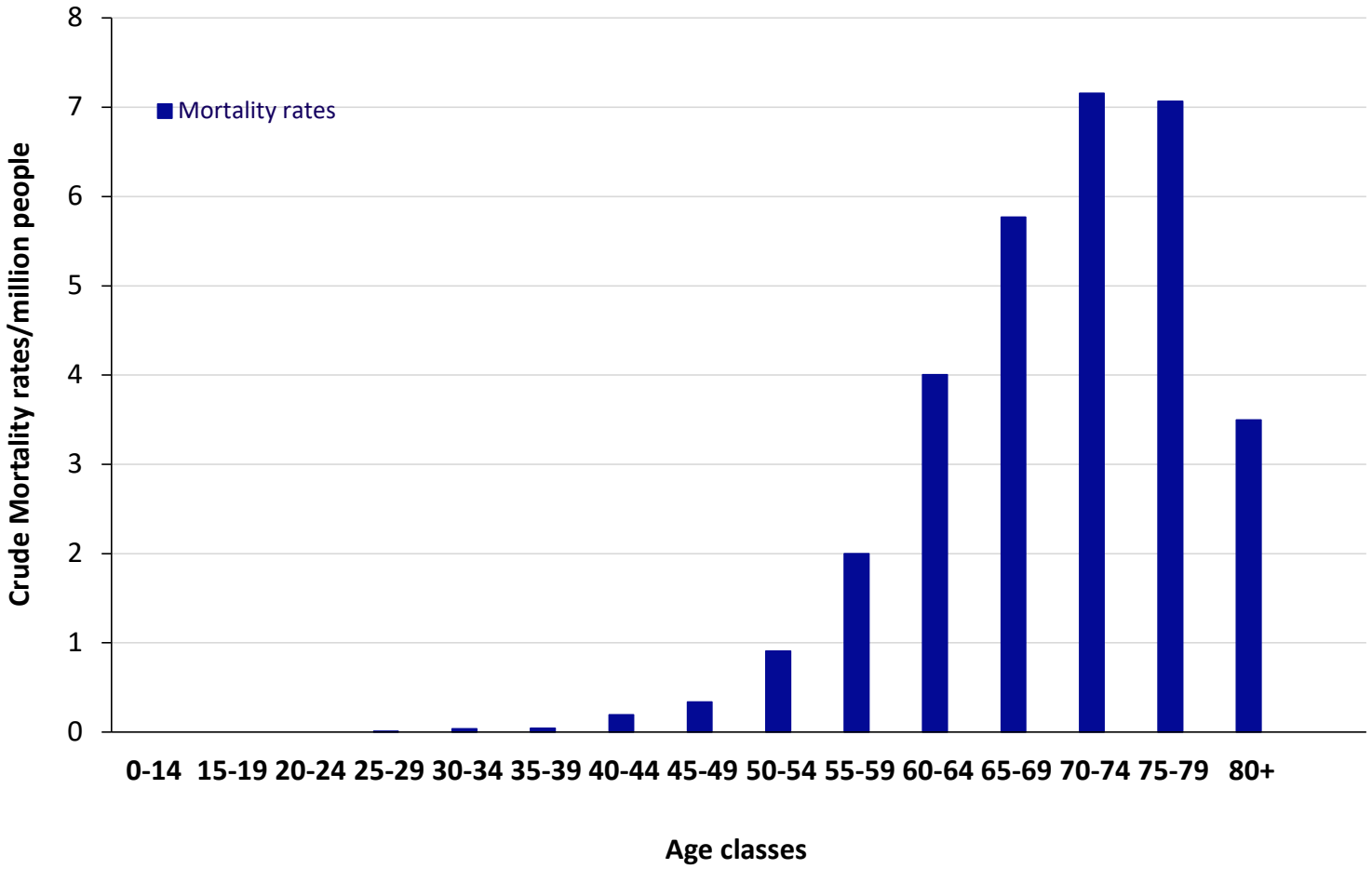
#Data from Spain updated at 2021

Epidemiological trends of sporadic CJD 1993-2019 (Standardized Mortality Rates*)



*Direct standardization, using 2013 European Reference Population, EUROSAT,

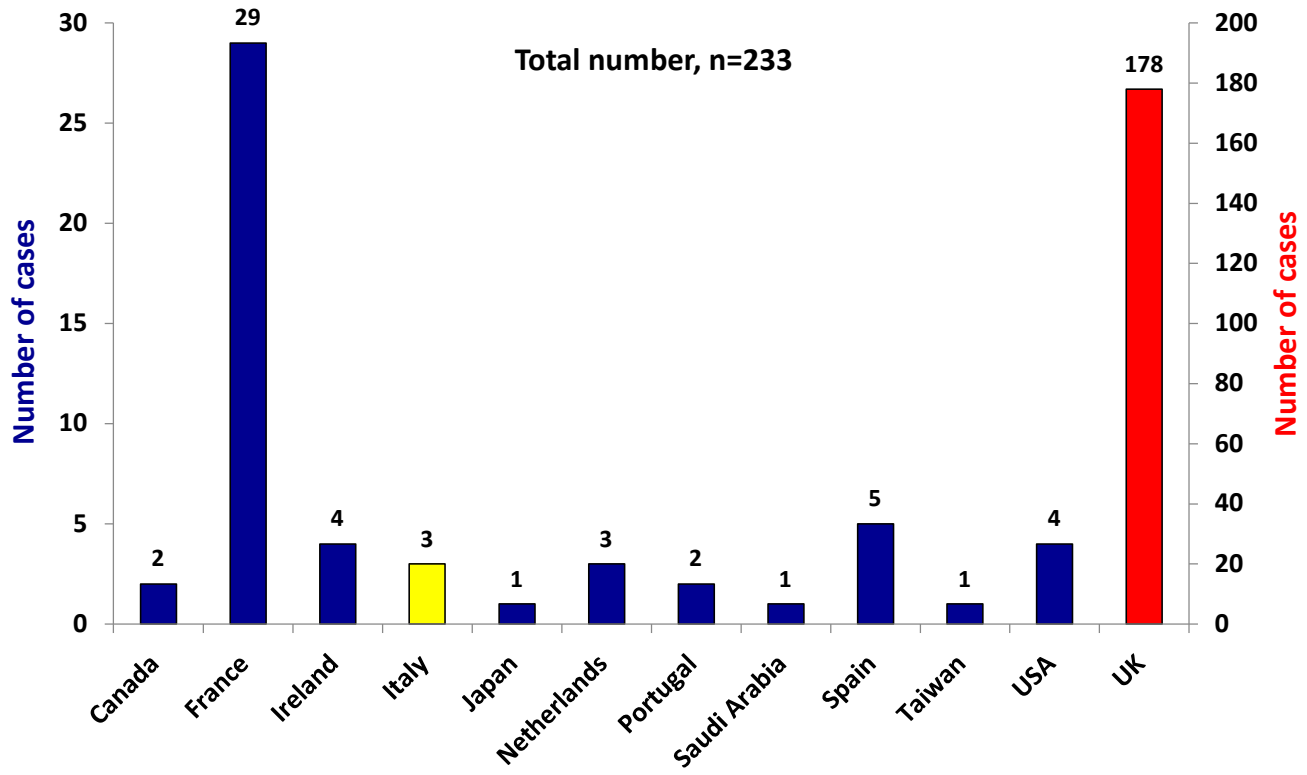
MORTALITY RATES FROM SPORADIC CJD BY AGE GROUPS IN ITALY(1993-2019)



Increase in figures for sporadic CJD

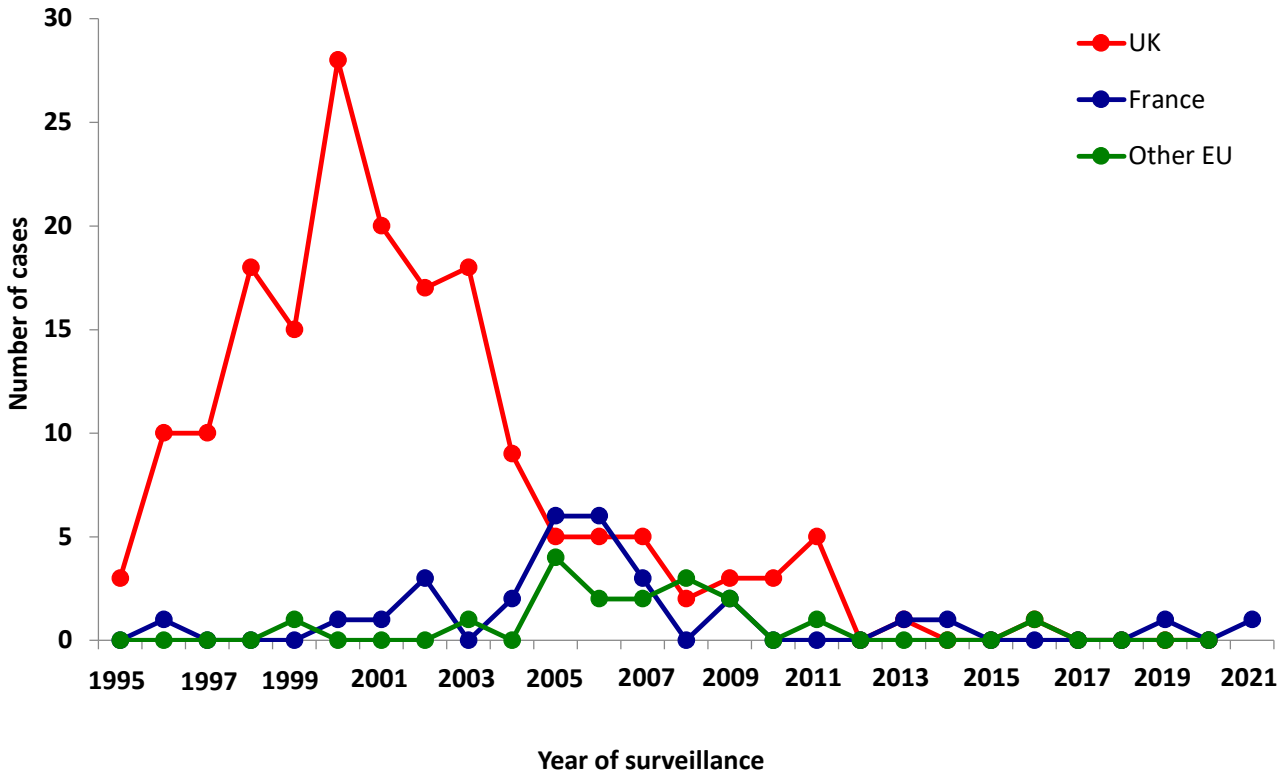
- **Numbers of referrals (Clinical suspicion)**
- **Sensitivity of diagnostic test (RT-QuIC)**
- **Age classes**

VARIANT **CREUTZFELDT-JAKOB IN THE WORLD**



All tested patients were M/M but one, who was heterpzigous, M/V (UK)

VARIANT CJD IN UK, FRANCE AND IN OTHER EU COUNTRIES



UK, n=178; France, n=29; Other EU (Ireland, Italy, Netherlands, Portugal, Spain), n=17

VARIANT CJD

INFECTION NOT LINKED TO BSE-INFECTED MEAT CONSUMPTION

Risk factors	Numbers	Year
Transfusion with red cells w/o leucodepletion	3 + 1 (no clinical disease)	2003-2005 (2004)
Therapy with VIII factor concentrated	1 (no clinical disease)	2008
Working in Prion Laboratories	3	2016, 2019, 2021

Acknowledgements

- **CJD and related Disorder Registry, Istituto Superiore di Sanità, Rome:**
    - **Dorina Tiple, clinical consultant**
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    - **Marco Sbriccoli Biochemistry**
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- **Neuroscience Departement**
    - **Maria Puopolo statistic**
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    - **Milano, Giorgio Giaccone**
    - **Torino, Daniele Imperiale**
    - **Verona, Gianluigi Zanusso**
    - **Cagliari, Sara Vascellari, laboratory tests**
    - **Napoli, Gianfranco Puoti**
- **Neurologists, neuroradiologists, neuropatologists at hospital and University**
- **Patient families**

Surveillance of CJD in Italy

Patient with cognitive decline rapidly progressive

NEUROLOGY Unit
- Neurological examinationn
- Cerebral MRI
- CSF analyses

Suspect PrD

Yes/No PrD

Surveillance Network (Bologna, Milano, Roma, Torino, Verona, Cagliari)
- Cerebral MRI view
- RT-QuIC on CSF and other tissues samples
- *PRNP* sequencing
- Possible Risk factors

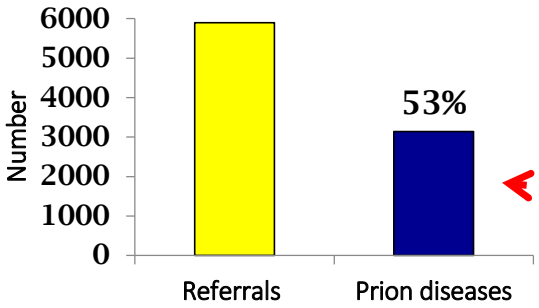
Diagnostic Classification

PrD definite* PrD probable

PrD possible No PrD

Official statistics

Not included in the statistics



*Progressive neurological syndrome **AND** Neuropathologically **or** immunocytochemically **or** biochemically confirmed