

21 YEARS OF CREUTZFELDT-JAKOB'S DISEASE SURVEILLANCE IN BELGIUM, 1998 - 2018.

C. FASTL • A. LITZROTH

WHO WE ARE

SCIENSANO can count on more than 700 staff members who commit themselves, day after day, to achieving our motto: Healthy all life long. As our name suggests, science and health are central to our mission. Sciensano's strength and uniqueness lie within the holistic and multidisciplinary approach to health. More particularly we focus on the close and indissoluble interconnection between human and animal health and their environment (the "One health" concept). By combining different research perspectives within this framework, Sciensano contributes in a unique way to everybody's health.

For this, Sciensano builds on the more than 100 years of scientific expertise of the former Veterinary and Agrochemical Research Centre (CODA-CERVA) and the ex-Scientific Institute of Public Health (WIV-ISP).

Sciensano

Epidemiology and public health – Epidemiology of infectious diseases

November 2019 • Brussels • Belgium
Internal reference number: D/2019/14,440/91
Approved by: Dr. Sophie Quoilin

—

C. Fastl¹

•

A. Litzroth¹

¹ Sciensano, Scientific direction of Epidemiology and public health, Service of Epidemiology of infectious diseases, Brussels

Contactperson: Amber Litzroth • T+32 2 6425020 • amber.litzroth@sciensano.be

Please cite as: C. Fastl, A. Litzroth. 21 years of Creutzfeldt-Jakob's Disease surveillance in Belgium, 1998 - 2018. Brussels, Belgium: Sciensano; 2019 22p. Report number: D/2019/14,440/91. Available from: <https://epidemiology.wiv-isp.be/ID/Pages/Publications.aspx>

EXECUTIVE SUMMARY

Creutzfeldt-Jakob's disease (CJD) is a rare and fatal neurodegenerative disorder that belongs to the family of prion diseases or transmissible spongiform encephalopathies (TSE). It occurs mainly sporadically (sporadic CJD) but can be connected to inherited mutations (genetic CJD) or be transferred from one organism to another (iatrogenic or variant CJD). Variant CJD has first been found in 1996 in the United Kingdom (UK), where its occurrence reached an epidemic extent in the years after. It is linked to the consumption of meat infected with bovine spongiform encephalopathies (BSE) during the BSE outbreak in cattle in the 1980s in the UK.

Belgium introduced a CJD surveillance system in 1998 with two main objectives: (1) to detect any cases of variant CJD in the country and (2) to monitor potential changes in the overall incidence of CJD. The system records definite cases of CJD, that have been confirmed by an autopsy, and probable cases, where no autopsy was performed but clinical and laboratory evidence suggest CJD.

This report summarizes the CJD surveillance data in Belgium between 1998 and 2018.

No case of variant CJD has been reported in Belgium up to date. Of the 275 reported probable or confirmed CJD cases between 1998 and 2018, the vast majority (96.7%) was sporadic, 2.9% were genetic and 0.4% iatrogenic CJD. The mean annual CJD mortality was 1.23 cases per million persons. Most deaths occurred within the first six months after diagnosis and in persons older than 60 years. The sex distribution was fairly equal.

Our results match the previous observations from other countries of CJD being a rare but severe disease. As there are still unknown factors surrounding prion diseases, and newly emerging types or new transmission modes cannot be excluded, the need for a sound surveillance remains.

TABLE OF CONTENTS

EXECUTIVE SUMMARY	4
ABBREVIATIONS	6
INTRODUCTION	7
METHODS	8
Diagnosis and case definition.....	8
Functioning of the Belgian surveillance system	8
Data analysis	9
RESULTS	10
Autopsies and biopsies	10
Performance of RT-QuIC	10
Number and type of CJD cases and estimated incidence	10
Age and sex distribution	11
Disease duration	12
DISCUSSION AND CONCLUSION	13
REFERENCES	14
ANNEX 1: VARIANT CJD CASES WORLDWIDE	15
ANNEX 2: INCLUSION CRITERIA FOR CJD REGISTER IN BELGIUM	16
NATIONAL REFERENCE CENTRES	18
1. Support for diagnosis and confirmation by autopsy	18
2. Support for diagnosis	18
3. RT-QuIC assay.....	19
ACKNOWLEDGEMENTS	20

ABBREVIATIONS

CJD	Creutzfeldt-Jakob's Disease
TSE	Transmissible Spongiform Encephalopathies
BSE	Bovine Spongiform Encephalopathies
PrP^C	Cellular Prion Protein
PrP^{Sc}	Misfolded Prion Protein
PRNP	Gene coding for the prion protein
EEG	Electroencephalography
MRI	Magnetic resonance imaging
RT-QuIC	Real-Time Quaking-Induced Conversion
UK	United Kingdom

INTRODUCTION

Creutzfeldt-Jakob's disease (CJD) is a prion disease that manifests itself as progressive degeneration of the brain. Prion diseases or transmissible spongiform encephalopathies (TSE) are rare, inevitably fatal disorders that are caused by the accumulation of post-translationally misfolded prion proteins in the brain. The misfolded prion protein (PrP^{Sc}) is able to induce the conversion of normally folded cellular prion proteins (PrP^C) into PrP^{Sc}. There are four known types of CJD: sporadic CJD, genetic (or familial) CJD, iatrogenic CJD and variant CJD (1, 2). The overall annual CJD mortality is around 1 to 1.5 per million people (3, 4).

In sporadic CJD, the misfolding of the prion protein happens sporadically, without a known cause. It is the most common type of CJD and accounts for 87% of all CJD cases in Europe. In genetic CJD, the process of misfolding is initiated by mutations in the gene coding for the PrP^C. It is the second most common type of the disease, accounting for 8% of cases in Europe (3, 4). Iatrogenic CJD is caused by the transmission of PrP^{Sc} from another organism to the affected person and has mainly been documented in recipients of contaminated human growth hormone or dura mater, but has also been associated with other sources, such as contaminated neurosurgical instruments. Due to the improvement of case detection methods and disinfection practices, it occurs only scarcely nowadays, but in the past it accounted for about 5% of cases in Europe (4, 5).

Variant CJD has first been observed in 1996 in the United Kingdom (UK), where its occurrence reached an epidemic extent in the years after. There is strong evidence linking it to the consumption of meat infected with bovine spongiform encephalopathies (BSE) during the BSE outbreak in cattle in the 1980s in the UK. Patients present with a characteristic neuropathological picture and are usually younger than persons affected by other types of CJD. They typically express behavioral changes and other psychiatric symptoms in early stages of the disease. Painful sensory symptoms are also common (6-8).

In reaction to the BSE outbreak and its subsequent linkage to variant CJD, the Creutzfeldt-Jakob Disease International Surveillance Network (formerly EuroCJD) was initiated by seven European countries in 1993 to monitor the epidemiology of CJD. Nowadays, it is under the responsibility of the ECDC (European Center for Disease Control) and receives notifications on probable and definite CJD cases from 28 European and nine non-European countries, including Belgium. As of October 2019, 232 deaths due to variant CJD have been reported in 12 countries worldwide, the majority of which (77%) occurred in the UK around the turn of the millennium, the peak years of the epidemic. The incidence has drastically declined since; only three definite cases have been reported globally over the past five years (see Annex 1). Most cases outside of the UK have been linked to either imported beef from the UK or a stay in the country during the years of the BSE outbreak (9-11).

Belgium introduced its CJD surveillance system in 1998. The initial aim was to detect variant CJD cases in the country to enable source identification and the prevention of secondary infections, for example via blood transfusions. Based on the possibility of newly emerging prion diseases or new transmission modes, its second objective was to monitor any changes in the overall CJD incidence. A study published in 2015 showed, that this objective is successfully fulfilled by the surveillance system (12). Up to date, no case of variant CJD has been reported in Belgium.

METHODS

Diagnosis and case definition

The diagnosis of CJD is performed in accordance with the updated 1998 Rotterdam classification criteria and the 2000 UK criteria for diagnosing variant CJD (Annex 2).

A definite diagnosis of CJD requires neuropathological confirmation of the presence of PrP^{Sc} in the brain tissue of the affected person, which is usually obtained post-mortem. If the clinical signs indicate CJD but no autopsy was performed and no additional test results are available, a case is considered a possible CJD. If additional evidence in form of an EEG, an MRI or suggestive laboratory results or positive tonsil biopsy (for variant CJD) is available, a case is classified as probable (12).

Although neuropathological confirmation by autopsy remains the gold standard for CJD diagnoses, the Real-Time Quaking-Induced Conversion (RT-QuIC) assay, performed on cerebrospinal fluid, presents the first promising *in vitro* diagnostic tool for sporadic CJD. First evaluations show that RT-QuIC is not only highly sensitive (92%) but also highly specific (100%), allowing for a differentiation between sporadic CJD and similar neurological conditions. The available evidence indicates a comparable utility of RT-QuIC for genetic CJD cases and also shows some effectiveness for detecting iatrogenic CJD, although data on the latter is very scarce. RT-QuIC can, however, not be used to identify variant CJD infections (13, 14). The test has been in use in Belgium since 2014. Because of the high number of differential diagnoses of CJD in Belgium and the scarcity and costliness of the reagents necessary to perform the RT-QuIC assay, its application is restricted to CSF samples from patients who meet the minimal criteria of a possible diagnosis of sporadic or familial CJD (Annex 2) or have $\geq 1100\text{pg/ml}^1$ total tau protein with low to moderate P-tau_{181P} levels in their CSF in addition to (rapidly) progressive neurodegeneration.

Functioning of the Belgian surveillance system

In Belgium, neurologists can refer suspect cases to one of seven reference centers in Belgium, four of which perform autopsies. Autopsies are reimbursed by the surveillance system and results of all autopsies in suspect cases are reported to the Belgian Institute for Health, Sciensano, regardless of the final diagnose. The reported data include demographic and personal information, the name of the physician in charge, symptoms, diagnostic findings and risk factors.

If no autopsy is performed and the patient fits the case definition for a probable case, the case can also be reported to the surveillance system. Possible cases are not being reported. Up until 2019, reporting was done by a paper form, but a web based reporting system has been developed and is planned to be implemented in 2020.

¹ Experience of the Neurological Laboratory at the University of Antwerpen; the threshold may be higher in other laboratories depending on the used protocol to determine the concentration of total tau protein.

Data analysis

This report summarizes the data gathered by the Belgian CJD surveillance system on patients who died or who underwent brain biopsy between February 27th, 1998 and December 31st, 2018. The database contains information on probable and definite cases of CJD and on all biopsies and autopsies performed on suspect CJD cases.

To calculate the incidence per million, the population size of Belgium at the 1st of January of each included year was used (15). Comparisons of disease durations between men and women and between disease types were done with the Mann-Whitney test. The level of significance was defined as 0.05.

RESULTS

Autopsies and biopsies

During the observational period, 347 autopsies were conducted on persons with suspected CJD, 231 of which confirmed a CJD diagnosis (66.6%). Only six biopsies with the purpose of investigating potential CJD were carried out in Belgium during the observational period, of which all but one were negative. The positive biopsy result was later confirmed by autopsy.

Performance of RT-QuIC

46 RT-QuIC assays were performed in addition to an autopsy, leading to 14 negative, 32 positive or weak positive and four inconclusive results. 97.8% (95% CI: 88.47-99.9%) of the conclusive results were in line with the autopsy diagnosis (45 out of 46). The available data on conclusive results thus showed a sensitivity of 97.0% (95% CI: 84.2-99.9%) and a specificity of 100% (95% CI: 75.29-100%) for RT-QuIC compared to autopsy, the gold standard for CJD diagnosis. If inconclusive outcomes are considered as negative results, the specificity stays 100% (95%CI: 76.84-100%), but the sensitivity drops to 88.89% (95%CI: 73.94%-96.89%).

Two of the correct positive and none of the false negative RT-QuIC results were identified to be genetic CJD cases, all others were classified as sporadic CJD.

In the above calculations, we excluded the five negative RT-QuIC results from cases where only a biopsy but no autopsy was performed, as a negative biopsy result cannot not reliably rule out CJD.

Number and type of CJD cases and estimated incidence

Between 1998 and 2018, 275 cases of definite or probable CJD were reported in Belgium. 96.7% were classified as sporadic CJD (224 confirmed and 42 probable cases), 2.9% were categorized as genetic CJD (six confirmed and two probable) and 0.4% were found to be iatrogenic CJD (one confirmed case) (Fig. 1).

Overall, the majority of diagnoses was confirmed by autopsy; only 16% of total diagnoses were categorized as probable CJD, spanning from 45% in 2004 to 0% in 2008, 2009 and all years after 2012. The mean annual number of total CJD associated deaths was 13, varying from six to 22 cases per year. With an average population size of 10.72 million people over the 21 years of observation period, this corresponds to a mean mortality of 1.23 cases per million inhabitants (95% confidence interval (CI): 1.02-1.44), ranging from 0.54 per million in 2013 to 2.12 per million in 2002 (Fig. 1).

RESULTS

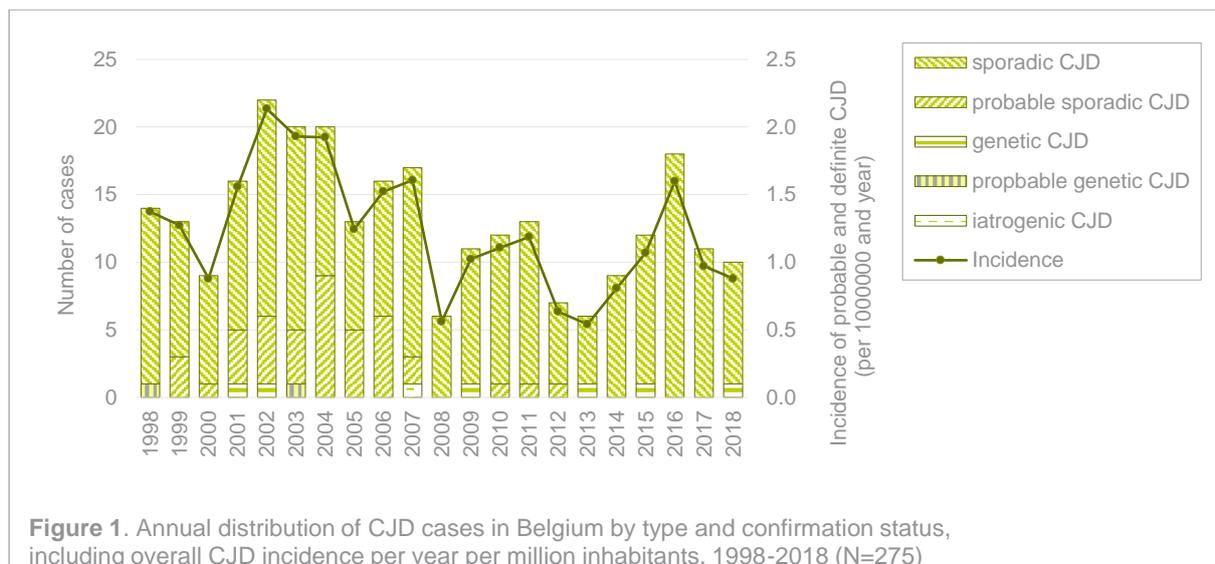


Figure 1. Annual distribution of CJD cases in Belgium by type and confirmation status, including overall CJD incidence per year per million inhabitants, 1998-2018 (N=275)

Age and sex distribution

Between 1998 and 2018, the sex distribution among the total number of CJD cases was fairly even, with 51% female and 48% male (in 1% there was no information on sex available). Among the cases of genetic CJD, women were affected more often, accounting for seven out of eight total cases. The only reported case of iatrogenic CJD was male (Fig. 2).

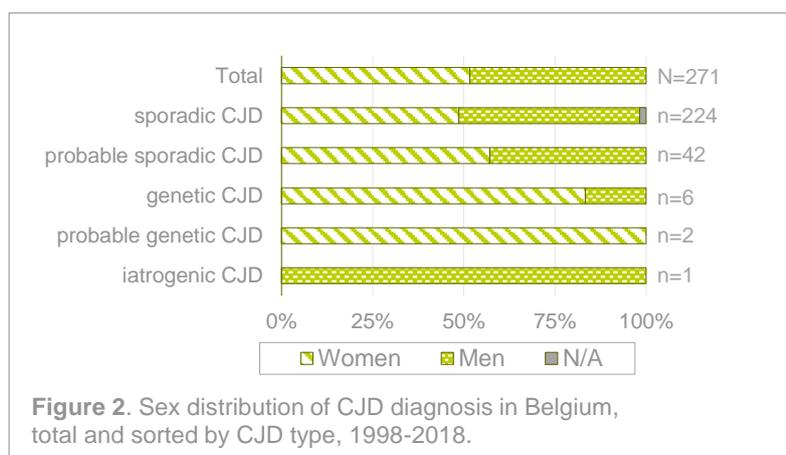


Figure 2. Sex distribution of CJD diagnosis in Belgium, total and sorted by CJD type, 1998-2018.

Between 1998 and 2018, age at death ranged from 31 to 88 years, with an average of 66.4 years (95% CI: 65.2-67.6). As displayed in Figure 3, the biggest proportion of CJD related deaths occurred in the age groups 60 to 69 and 70 to 79 years (35.9% and 33.7%, respectively). Genetic CJD related deaths occurred most often among the 50 to 59 year olds (50% of all genetic CJD deaths).

Figure 4 displays the distribution of age at death by sex for all CJD cases. Overall, age at death was similarly distributed in both sexes, however, it peaked in the 60 to 69 year age group among women and in the 70 to 79 year age group among men.

RESULTS

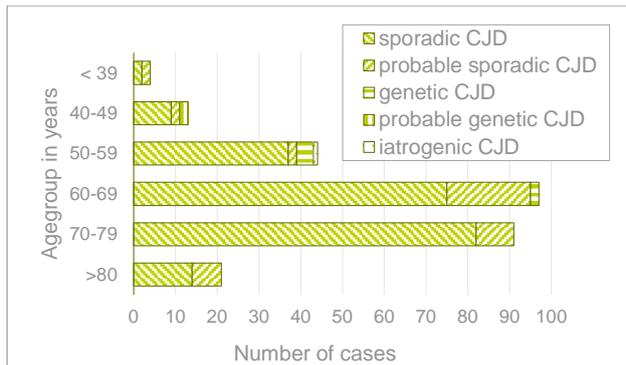


Figure 3. Age at death distribution of CJD cases in Belgium by CJD type and confirmation status, 1998-2018 (N=270)

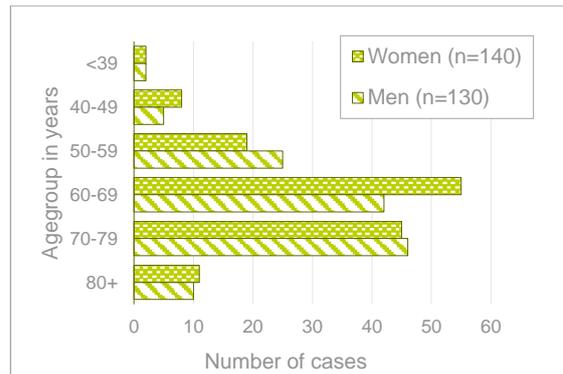


Figure 4. Age at death distribution of CJD cases in Belgium by sex, 1998-2018 (N=270)

Disease duration

Information on the disease duration was available for 210 persons (76.4%). Disease onset was defined as the timepoint where the first symptoms were reported and, as CJD always ends fatal, the end was marked by the death of the affected person.

The median disease duration was four months and ranged from one to 48 months. Most persons died within the first three months and over 75% did not survive longer than six months. Only 1% (three cases) had a disease duration of more than 25 months after onset of symptoms (Fig. 6).

While a bigger proportion of female cases died within the first three months of disease (53% compared to 39% of male cases) (Fig. 5), the sex difference in disease duration was not statistically significant ($p=0.055$, Mann-Whitney).

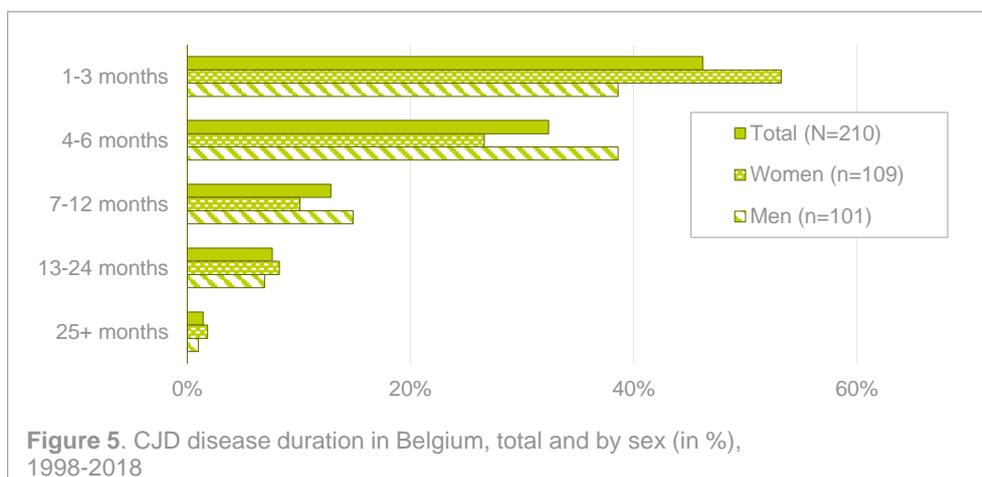


Figure 5. CJD disease duration in Belgium, total and by sex (in %), 1998-2018

DISCUSSION AND CONCLUSION

The incidence and demographic distribution of CJD in Belgium between 1998 and 2018 match previously reported observations from other countries (3, 4). The mean total mortality per year was 1.23 cases per million persons and most deaths occurred among persons aged above 60 and below 80 years. On average, CJD progressed quickly, with a median duration of four months. Women and men were similarly affected by the disease. Due to the high probability of reporting bias (familial predisposition might, for example, lead to an earlier diagnosis) and the low case number, we only investigated differences in disease duration between the sexes, but not between age groups or type of CJD. In line with previous findings, our data indicates a high sensitivity and perfect specificity of the RT-QuIC assay when compared to autopsy. However, as false negative results may occur, the technique cannot be used to rule out CJD as differential diagnosis. Furthermore, while positive RT-QuIC results are useful for supporting a suspected CJD diagnosis, autopsies should still be performed to validate the test. The absence of probable cases in recent years most likely does not reflect a change in diagnosis practices but can rather be explained by a lack of reporting.

The results of this report show that CJD is a very rare disease in Belgium. However, a potential future rise in public health relevance of CJD or other prion diseases cannot be completely excluded for several reasons.

Firstly, in the UK, three cases of secondary infections with variant CJD via blood transfusions and one asymptomatic infection after plasma donation from a donor who later developed variant CJD have been identified (7). These findings raised concerns regarding the potential transferability of other types of CJD via blood, which could, if proven, also be of relevance in Belgium. Studies investigating this possibility indicate, however, that the risk of sporadic CJD transfer via blood transfusions is, if existing, negligibly small (16).

Secondly, based on the discrepancy between the estimated expectable prevalence of variant CJD in the UK following the BSE epidemic in the 1980s and the actual observed number of cases, the existence of variant CJD “carriers” or cases with far longer incubation periods than previously observed has been suggested (17, 18). A proposed explanation for this hypothesis is a single-nucleotide polymorphism in the gene coding for the prion protein (PRNP). It has been established that most reported cases of variant CJD are methionine homozygous at codon 129 of the PRNP gene (19). In fact, of the 178 reported cases of variant CJD in the UK, only the last reported case, who died in 2016, was confirmed to be methionine valine heterozygous at this codon. This could indicate that the heterozygous genotype is not less susceptible to developing variant CJD, but is associated with a longer incubation period, which would imply the possibility of a second wave of variant CJD in the UK (20). However, no case of variant CJD has been reported in the UK since (see Annex 1), hence, the currently available evidence may not support this theory at this stage.

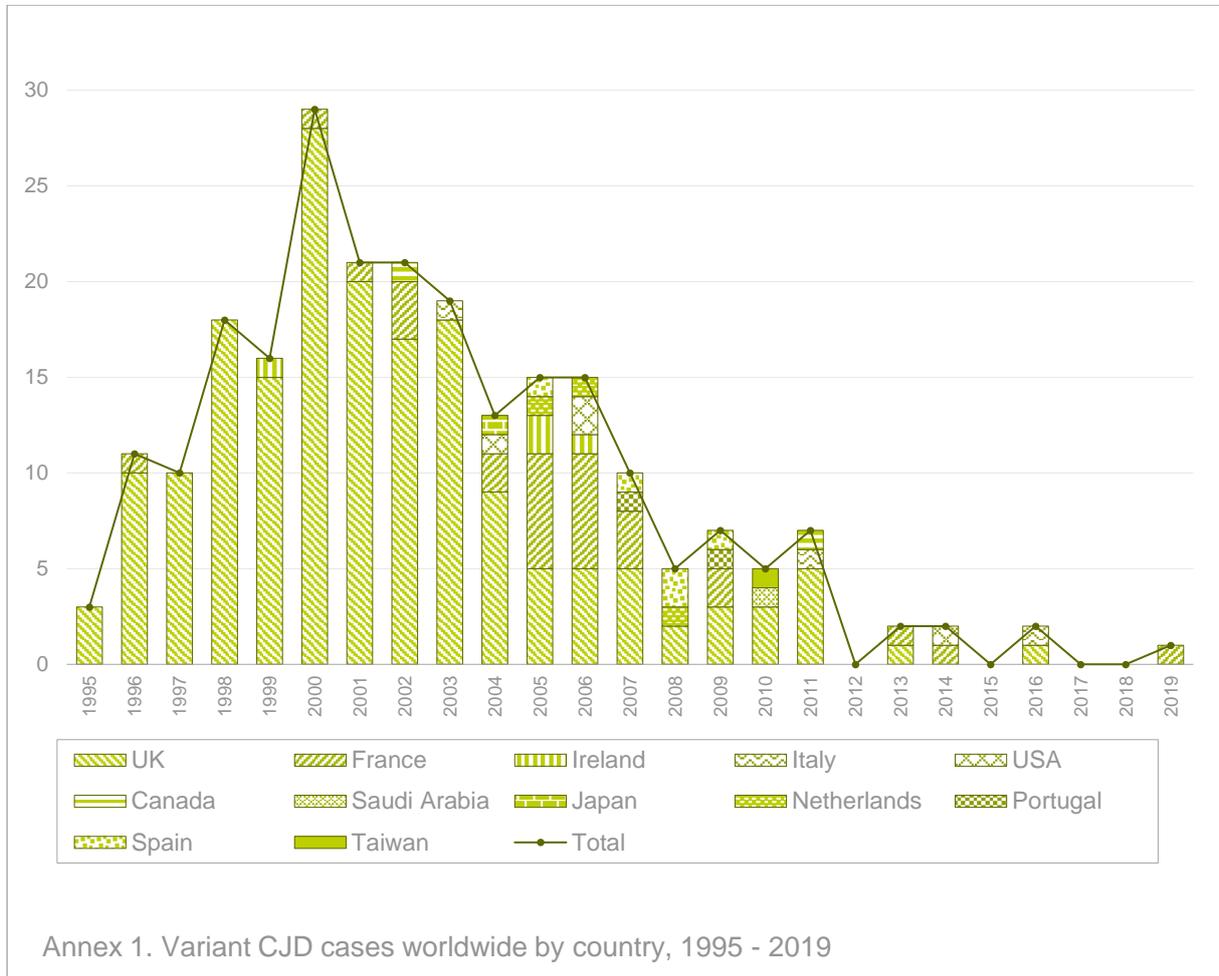
Thirdly and most importantly, the epidemic of variant CJD originated from a species crossing of BSE from cattle to humans. While BSE is hardly relevant in Belgium, where no cases have been reported since 2007 and the BSE risk has officially been determined to be “negligible”, the inability of other known animal TSE to cross the species border to humans has not yet been proven (21, 22).

These reasons underpin the need of sound surveillance of both animal and human prion diseases, as the presence of a functioning national CJD surveillance system can be crucial in the early detection of future events.

REFERENCES

1. Prusiner S. Molecular biology of prion diseases. *Science*. 1991;252(5012):1515-22.
2. Prusiner SB, Scott MR, DeArmond SJ, Cohen FE. Prion Protein Biology. *Cell*. 1998;93(3):337-48.
3. Ladogana A, Puopolo M, Croes EA, Budka H, Jarius C, Collins S, et al. Mortality from Creutzfeldt–Jakob disease and related disorders in Europe, Australia, and Canada. *Neurology*. 2005;64(9):1586-91.
4. Will RG, Alperovitch A, Poser S, Pocchiari M, Hofman A, Mitrova E, et al. Descriptive epidemiology of Creutzfeldt-Jakob disease in six european countries, 1993–1995. *Annals of Neurology*. 1998;43(6):763-7.
5. Brown P, Brandel J-P, Sato T, Nakamura Y, MacKenzie J, Will RG, et al. Iatrogenic Creutzfeldt-Jakob disease, final assessment. *Emerging infectious diseases*. 2012;18(6):901-7.
6. Will RG, Ironside JW, Zeidler M, Estibeiro K, Cousens SN, Smith PG, et al. A new variant of Creutzfeldt-Jakob disease in the UK. *The Lancet*. 1996;347(9006):921-5.
7. Ironside JW. Review article Variant Creutzfeldt-Jakob disease: an update. *Folia Neuropathologica*. 2012;50(1):50-6.
8. Zerr I, Poser S. Clinical diagnosis and differential diagnosis of CJD and vCJD. *APMIS*. 2002;110(1):88-98.
9. CJD International Surveillance Network. CJD Surveillance Data 1993-2018. Edinburgh: University of Edinburgh. 2018 [cited 2019 Nov 25]. Available from: <http://www.eurocjd.ed.ac.uk/surveillance%20data%201.html#vcjd-cases>.
10. European Centre for Disease Prevention and Control. European Creutzfeldt-Jakob Disease Surveillance Network (EuroCJD). [cited 2019 Nov 25]. Available from: <https://www.ecdc.europa.eu/en/about-uspartnerships-and-networksdisease-and-laboratory-networks/european-creutzfeldt-jakob-disease>.
11. Chen C, Dong X-P. Epidemiological characteristics of human prion diseases. *Infectious Diseases of Poverty*. 2016;5(1):47.
12. Litzroth A, Cras P, De Vil B, Quoilin S. Overview and evaluation of 15 years of Creutzfeldt-Jakob disease surveillance in Belgium, 1998-2012. *BMC neurology*. 2015;15:250-.
13. Franceschini A, Baiardi S, Hughson AG, McKenzie N, Moda F, Rossi M, et al. High diagnostic value of second generation CSF RT-QuIC across the wide spectrum of CJD prions. *Scientific Reports*. 2017;7(1):10655.
14. Green AJE. RT-QuIC: a new test for sporadic CJD. *Practical Neurology*. 2019;19(1):49-55.
15. STATBEL. Population by place of residence, nationality (Belgian/ non-Belgian), marital status, age and gender Brussels: Statistics Belgium. 2019 [cited 2019 Nov 25]. Available from: <https://bestat.statbel.fgov.be/bestat/crosstable.xhtml?view=fc14c1ce-7361-4d42-a892-fce8e81a1b79>.
16. Seed CR, Hewitt PE, Dodd RY, Houston F, Cervenakova L. Creutzfeldt-Jakob disease and blood transfusion safety. *Vox Sanguinis*. 2018;113(3):220-31.
17. Gill ON, Spencer Y, Richard-Loendt A, Kelly C, Dabaghian R, Boyes L, et al. Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey. *BMJ : British Medical Journal*. 2013;347:f5675.
18. Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Ritchie D, et al. Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *The Journal of Pathology*. 2004;203(3):733-9.
19. Saba R, Booth SA. The Genetics of Susceptibility to Variant Creutzfeldt-Jakob Disease. *Public Health Genomics*. 2013;16(1-2):17-24.
20. Diack AB, Will RG, Manson JC. Public health risks from subclinical variant CJD. *PLOS Pathogens*. 2017;13(11):e1006642.
21. Houston F, Andréoletti O. The zoonotic potential of animal prion diseases. 1532018. p. 447-62.
22. Litzroth A, Quoilin S. Surveillance network for Creutzfeldt-Jakob Disease in Belgium 2011 [Réseau de surveillance de la maladie de Creutzfeldt-Jakob en Belgique 2011]. Brussels: Scientific Institute of Public Health (WIV-ISP), population Iditg; 2012. Report No.: D/2013/2505/08.

ANNEX 1: VARIANT CJD CASES WORLDWIDE



Reference:

CJD International Surveillance Network. CJD Surveillance Data 1993-2018. Edinburgh: University of Edinburgh. 2018 [cited 2019 Nov 25]. Available from: <http://www.eurocjd.ed.ac.uk/surveillance%20data%201.html#vcjd-cases>.

ANNEX 2: INCLUSION CRITERIA FOR CJD REGISTER IN BELGIUM

All CJD related biopsies and autopsies will be registered in the surveillance system, regardless of the result of the biopsy/autopsy.

All probable cases (see case definitions below) of all forms of CJD will also be registered in the project (if no autopsy has been performed).

CASE DEFINITION SPORADIC CDJ									
Criteria to be used for classification									
I	Rapidly progressive cognitive impairment								
II	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 5%; text-align: center;">A</td> <td>Myoclonus</td> </tr> <tr> <td style="text-align: center;">B</td> <td>Visual or cerebellar problems</td> </tr> <tr> <td style="text-align: center;">C</td> <td>Pyramidal or extrapyramidal features</td> </tr> <tr> <td style="text-align: center;">D</td> <td>Akinetic mutism</td> </tr> </table>	A	Myoclonus	B	Visual or cerebellar problems	C	Pyramidal or extrapyramidal features	D	Akinetic mutism
A	Myoclonus								
B	Visual or cerebellar problems								
C	Pyramidal or extrapyramidal features								
D	Akinetic mutism								
Classification (using the criteria mentioned above)									
Confirmed sporadic CJD	Progressive neurological syndrome + neuropathologically or immunohistochemically or biochemically confirmed								
Probable sporadic CJD	<ul style="list-style-type: none"> • I + 2 of II + CJD-typical generalized periodic complexes in EEG <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • I + 2 of II + high signal in caudate/putamen on MRI brain scan or at least two cortical regions (temporal, parietal, occipital) either on DWI or FLAIR <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • I + 2 of II + positive CSF 14-3-3 <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • Progressive neurological syndrome + positive RT-QuIC in CSF or other tissues 								
Possible sporadic CJD	I + 2 of II + duration < 2 years								
IATROGENIC CJD									
Progressive cerebellar syndrome in a pituitary hormone recipient <i>OR</i> sporadic CJD with a recognised exposure risk, e.g. dura mater transplant									
FAMILIAL CJD									
Confirmed or probable CJD plus confirmed or probable CJD in a first-degree relative <i>OR</i> neuropsychiatric disorder plus disease-specific PRNP mutation									

CASE DEFINITION VARIANT CDJ	
Criteria to be used for classification	
I	<p>A Progressive neuropsychiatric disorder</p> <p>B Duration of illness > 6 months</p> <p>C Routine investigations do not suggest an alternative diagnosis</p> <p>D No history of potential iatrogenic exposure</p> <p>E No evidence of a familial form of TSE</p>
II	<p>A Early psychiatric features*</p> <p>B Persistent painful sensory symptoms‡</p> <p>C Ataxia</p> <p>D Myoclonus or chorea or dystonia</p> <p>E Dementia</p>
III	<p>A EEG does not show the typical appearance of sporadic CJD in the early stages of illness¶</p> <p>B Bilateral pulvinar high signal on MRI scan</p>
IV	A Positive tonsil biopsy
Classification (using the criteria mentioned above)	
Confirmed variant CJD	IA + neuropathological confirmation of vCJD§
Probable variant CJD	<ul style="list-style-type: none"> • I + 4/5 of II + IIIA + IIIB <p>OR</p> <ul style="list-style-type: none"> • 1 + IVA
Possible variant CJD	I + 4/5 of II + IIIA
<p>* Depression, anxiety, apathy, withdrawal, delusions</p> <p>‡ Including both frank pain and/or dysaesthesia</p> <p>¶ Generalised triphasic periodic complexes at approximately one per second</p> <p>§ Spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum</p>	

NATIONAL REFERENCE CENTRES

1. Support for diagnosis and confirmation by autopsy

Universitaire Ziekenhuis **Antwerpen**
Pr Dr P. Cras
Departement Neurologie
T +32 3 821 34 23
patrick.cras@uantwerpen.be

Universitaire Ziekenhuis **Leuven**
Pr Dr Th. Tousseyn
Pathology
T +32 16 33 65 82
thomas.tousseyn@uzleuven.be

Centre hospitalier universitaire **Liège**
Dr E. Bianchi
Service de neuropathologie
T +32 4 366 24 10
ebianchi@chuliege.be

2. Support for diagnosis

Universitair Ziekenhuis **Brussel**
Pr Dr A. Michotte
Dienst Neurologie en Pathologie
T +32 2 477 60 12 (neurologie) ou +32 2 477 50 80 (pathologie)
alex.michotte@uzbrussel.be

Cliniques Universitaires Saint-Luc **Bruxelles**
Pr Dr A. Ivanoiu
Neurologie
T +32 2 764 17 79
Adrian.Ivanoiu@uclouvain.be

Hôpital Erasme - Cliniques universitaires de **Bruxelles**
Pr Dr N. Gaspard
Service de Neurologie
T +32 2 555 33 57
Nicolas.Gaspard@erasme.ulb.ac.be

Universitair Ziekenhuis **Gent**
Pr Dr P. Santens
Neurologie
T +32 9 240 21 11
Patrick.Santens@UGent.be

3. RT-QuIC assay

Eng. Bart De Vil MSc.

Laboratory of Neurology - Born-Bunge Institute, non-profit association

Campus Drie Eiken - Room D.T.634

Universiteitsplein 1 - 2610 Antwerp - Belgium

T +32 3 265 26 05

bart.devil@uantwerp.be

ACKNOWLEDGEMENTS

We would like to thank the seven CJD reference centres contributing to the surveillance system, namely Universitair Ziekenhuis Antwerpen, Universitair Ziekenhuis Brussel, Universitair Ziekenhuis Gent, Cliniques Universitaires St-Luc, Centre Hospitalier Universitaire de Liège – Sart Tilman, Universitair Ziekenhuis Leuven and Cliniques Universitaires de Bruxelles – Hôpital Erasme and the Laboratory of Neurology, Translational Neurosciences of the University of Antwerp and the Born Bunge Institute, non-profit association, for supporting the surveillance activities and providing their expertise on the usage of RT-QuIC assays in Belgium.

CONTACT

Amber Litzroth • T+32 2 6425020 • amber.litzroth@sciensano.be

MORE INFORMATION

—
Visit our website
>www.sciensano.be or
contact us at
>info@sciensano.be

Sciensano • Rue Juliette Wytsmanstraat 14 • Brussels • Belgium • T + 32 2 642 51 11 • T press + 32 2 642 54 20 •
info@sciensano.be • www.sciensano.be

Responsible editor: Dr. Pierre Kerkhofs, Managing director • Rue Juliette Wytsmanstraat 14 • Brussels • Belgium • >D/xxxx/xxxx/xx