Author's response to reviews

Title: Evaluation indicates that the Belgian Creutzfeldt-Jakob disease surveillance meets its objectives but can be optimized

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Version: 2 Date: 9 July 2015

Author's response to reviews: see over
Dear Editor,

On behalf of all co-authors, I have the pleasure to submit the revised version of the manuscript entitled “Evaluation indicates that the Belgian Creutzfeldt-Jakob disease surveillance meets its objectives but can be optimized” for publication in BMC Neurology.

Please find the point-by-point responses to the concerns raised by the reviewers at the end of this letter.

We sincerely hope that this revised manuscript will be accepted for publication in BMC Neurology.

Yours sincerely,

Amber Litzroth, Patrick Cras, Bart De Vil, Sophie Quoilin
Point-by-point responses to the concerns raised by the reviewers:

Reviewer: André Karch

Major compulsory revisions

1. The text lacks focus as it on the one hand tries to stress the study objectives (although they cannot be formally evaluated) and on the other hand wants to report the results obtained during the surveillance period and the results of the survey. I think that the manuscript would benefit from shifting the focus a bit more to reporting the results of the surveillance period (including annual incidence rates, maybe even together with rates standardized for an international standard population).

Line 121-123: Added: “and the age-standardized yearly incidence of probable and confirmed CJD cases according to the age distribution in the World Health Organization (WHO) World standard population [18].”

Line 174-175: Added: “and age-standardized incidence ranged from 0.2 to 1.4 cases per million inhabitants per year (average 0.8) (Figure 1).”

Figure 1: added incidence and standardized incidence

2. More information on surveillance data is necessary (incidence rates, description of the Belgian population in these years, standardized incidence rates). This should also be reported in a separate table and/or figure

See answer to remark 1.

3. The same is true for the reports of data quality. More information would be nice on which variables showed which level of data completeness and on what kind of information became worse over time. In this case I’m not sure on how the test for linear trend was performed (summed up over all variables?)

Line 129-132: “We calculated the annual completeness per variable, the annual completeness over all variables and the total completeness per variable over the period 1998-2012. For the years 1998-2012, we looked for trends in annual completeness per variable and in annual completeness over all variables.”

Line 182-192. “The variables with lowest total completeness over this period were MRI result (49%) and PrP gene analysis result (33%). The variables with highest total completeness over this period were sex (100%), date of birth (97%), date of death (96%) and postcode (91%). Total completeness over this period of the other variables ranged between 60 and 80%. For 1998-2012, a significant downward trend in annual completeness was observed in the following variables: symptoms at onset (p=0.004), EEG result (p=0.023) and familial history of CJD (p=0.004). For 1998-2012, a significant upward trend in annual completeness was observed in the following variables: date of birth (p=0.034), date of death (p=0.028) and familial history of CJD (p=0.004). For the other variables we observed no trend in annual completeness over
the period 1998-2012. The annual completeness over all variables decreased significantly from 1998 to 2012 (p=0.024).”

4. **Capture-recapture methodology should be used to estimate the true number of CJD cases. One focus of the study is the use of two data separate data sources which provide differing information. These conditions are a perfect prerequisite for a capture recapture analysis; the value of the manuscript would be improved considerably.**

In this situation a capture-recapture analysis is unfortunately not possible. Although patients in the hospital discharge data are diagnosed with CJD according to the code attributed, we do not know what this diagnosis is based on, and it cannot be a definite (confirmed) diagnosis, since this requires autopsy, which happens after hospital discharge (and all autopsies are recorded in the surveillance system) and is recorded in the surveillance system. The diagnosis attributed in the hospital is based on clinical suspicion (and only a fraction of these would get confirmed by autopsy), therefore performing capture recapture analysis in this situation would highly overestimate the total number of CJD cases. Ideally, all patients dying with a true clinical suspicion of CJD at the moment of death, should be referred to a reference centre for autopsy, therefore we decided to look at the proportion that actually undergoes autopsy and the proportion that is captured (either by autopsy or as a probable case).

5. **Rotterdam criteria are no longer up to date for sCJD; usually criteria proposed by Zerr et al. (2011) are used as they include typical MRI abnormalities. Please comment on why you chose these criteria for your manuscript. If the Belgian surveillance system still uses these criteria, please discuss it critically**

This was a mistake in the text. A modification to the case definition was indeed proposed in 2009, and included in 2010.

Line 95-97 “The 1998 Rotterdam criteria, with a 2010 modification, classify sporadic, familial and iatrogenic CJD [14-16] (Table 1). A possible case requires clinical evidence. Probable cases require additional electroencephalogram (EEG), magnetic resonance imaging (MRI) or laboratory suggestive evidence.”

Table 1 was modified.

6. **The description of the analysis strategy and the tests used is not clear enough. Did the authors test for a linear trend only? How was the test for spatial heterogeneity performed? Did you ignore spatial dependencies defining provinces as different levels of the same categorical variable?**

*Did the authors test for a linear trend only?*

As stated in line 161, we tested for trends using the Cuzick non-parametric test for trends. This test uses ranks and therefore it is not restricted to linear trends.

*How was the test for spatial heterogeneity performed? Did you ignore spatial dependencies defining provinces as different levels of the same categorical variable?*
The difference of the proportion of suspect cases undergoing autopsy (or the proportion of suspect cases that were referred either for autopsy either as a probable case) between the provinces was assessed with a chi-square test (see line 160-161: “We compared proportions using the chi-square test”). Province was indeed considered a categorical variable and spatial dependencies were not looked into. However, we do not consider this necessary in this approach and with the current results (no differences between the provinces observed).

Additional changes done:
Based on this comment and comments raised by other reviewers, we decided to look at all the available factors possibly impacting the referral for autopsy. Previously, we had only looked at the effect of province and year (trend over time), now we included age, gender and whether CJD was a primary or secondary diagnosis. We performed univariate analysis and multivariable logistic regression.

Moreover, we decided to repeat these analyses for total referral (for autopsy and reporting as a probable case) instead of for probable cases, as we did previously. Total referral is a more relevant factor than being reported as a probable case and it gives a better idea of the total performance of the surveillance system. Paragraphs “Estimation of suspect cases captured by the surveillance system” and “Statistical analysis” in methods and “Estimation of suspect cases captured by the surveillance system” in the results were therefore rewritten and the results were taken into account in the discussion and the conclusion.

Line 136-144: “We calculated the annual proportion of suspect cases that died in hospitals with CJD as primary or secondary diagnosis (ICD 9 code: 046.1) for which autopsy was performed in a reference centre. We assessed differences in the proportion of autopsies performed between the year of death, the province, gender and those with CJD as primary or as secondary diagnosis. We assessed the effect of age of the patient on the performance of an autopsy. For 1999-2010, we looked for a trend in the proportion of suspect cases that underwent autopsy.
We repeated these procedures for suspect cases that died in hospitals with CJD as primary or secondary diagnosis that were captured by the surveillance system either through an autopsy either as a probable case.”

Line 161-167: “The effect of age on the performance of an autopsy and on total capture by the surveillance system was assessed by calculating odds ratios (OR) in a logistic regression model. Variables associated with autopsy with a p-value of <0.2 in the univariate analysis were included in a backward stepwise multivariable logistic regression model. A similar model was built for variables associated with total capture by the surveillance system. We considered a p-value <0.05 significant.”

Line 194-208: “In 1999-2010, the hospital discharge database contained 241 suspect cases. Of these, 122 (51%) underwent an autopsy in a reference centre. The annual proportion ranged from 35% in 2010 to 65% in 2002 (Table 2), with no trend (p=0.14). In univariate analysis we did not detect a significant difference in proportion referred for autopsy between years (p=0.65, \( \chi^2 \)-test), province (p=0.11, \( \chi^2 \)-test), gender (p=0.74, \( \chi^2 \)-test) and those with CJD as
primary or as secondary diagnosis (p=0.22, \chi^2\text{-test}). The odds of undergoing an autopsy significantly decreased with age (OR 0.97, p=0.01). Only the effect of age remained significant in the multivariable analysis (OR 0.97, p=0.01). Out of 241 patients that died in hospital with CJD as a primary or secondary diagnosis, 144 (60\%) were captured by the surveillance system (autopsy or probable case). The annual proportion varied between 35\% in 2010 and 80\% in 2002. This proportion showed a downward trend (p=0.004). In univariate analysis we did not detect a significant difference in this proportion between years (p=0.1, \chi^2\text{-test}), gender (p=0.66, \chi^2\text{-test}) and between groups with CJD as primary or as secondary diagnosis (p=0.15, \chi^2\text{-test}). We detected a significant difference between the provinces (p=0.023) and the odds of capture significantly decreased with age (OR 0.95, p=0.001). Only the effect of age remained significant in the multivariable analysis (OR 0.95, p=0.001).”

7. The discussion needs to include all of the points above and should in general be a bit more critical, especially about the survey results.

The discussion was changed, we elaborated more on the survey results in particular: Line 291-303: “An important limitation of this evaluation lies in the unknown representativeness of survey respondents. Those with a special interest in CJD may have been more likely to respond. The impact of this on our evaluation cannot be estimated, and therefore the results of the survey should be interpreted with caution and verified where possible. An example of the responder bias might be represented in the difference between measured referral of suspect cases and self-reported referral. Sixty-eight percent of respondents said they referred suspect CJD cases for autopsy. However, when linking the hospital discharge data with the cases referred for autopsy, only 50\% of cases were referred. However, a possible alternative explanation for the difference between the estimated referral and the self-reported referral may lie in a reporting error on hospital level or an autopsy refusal of the family. Checking death records of suspect CJD cases that did not undergo an autopsy in a reference centre would provide us with more insight into referral practices and would perhaps allow us to estimate the Belgian incidence more precisely. Moreover, it could clarify the decrease in capture by the surveillance system with increasing age.”

Minor Essential Revisions
8. The color code of the figures is not suitable for b&w printers. Please try to improve this.

Figure 1 and 2 were improved.

9. There is a typo in lines 210-214 (results, acceptability): a at the moment vCJD is reported twice and sCJD not at all – one should be sCJD

Corrected

Reviewer: Eiji Nakatani

Major compulsory revisions
1. Result should be separated into following four sections, 1. difference of numbers of CJD patients between CJD surveillance data and hospital based data, 2. variable completeness as data quality, 3. survey for referral behavior of neurologists, 4. survey for importance and collecting method of CJD and vCJD surveillance in neurologists, reference centers and public health officials.

We took this remark as much as possible into account by creating the following sections in the results:

- Belgian CJD surveillance 1998-2012
- Data quality
- Estimation of suspect cases captured by the surveillance system
- Survey response
- Survey results on referral behaviour of neurologists
- Survey results on acceptability and simplicity of the surveillance system

These sections do not exactly meet the reviewer’s demand, however we feel that “Belgian CJD surveillance 1998-2012” and “Estimation of suspect cases captured by the surveillance system” are two distinct sections of the results. The first describes the results of surveillance from 1998-2012 (a section that has been given more focus as requested by the previous reviewer), the second one elaborates on the results of the linking a part of this database (1999-2010) with hospital discharge data. We would like to keep these sections separated for clarity and because of the 2 distinct ideas behind them.

We also kept the section of survey response because it refers to both sections below.

2. Particularly, to compare CJD surveillance data with hospital-based data, you should make a crossed table with “underwent autopsy”, “reported as probable”, “reported as suspected” and “not reported” as category, stratified by a suitable category of years. I recommend to refer to number and characteristics for cases that did not reported as surveillance data.

Table 2: The requested table was added (figure 2, showing this information in a graph, was deleted and replaced by table 2).

We also investigated any difference between the suspect cases that had autopsy and those that did not and between those that were captured by the surveillance system and those that were not.

Minor Essential Revisions

3. The sentence: “Confirmed cases require neuropathological confirmation” is duplicated.

It refers to CJD the first time and to vCJD the second time.

4. In method, How did you evaluate “completeness for all variables”?

Methods was changed
Line 129-132: “We calculated the annual completeness per variable, the annual completeness over all variables and the total completeness per variable over the period 1998-2012. For the years 1998-2012, we looked for trends in annual completeness per variable and in annual completeness over all variables.

5. “We could not calculate response proportions, because we did not have access to the email distribution lists of the organization.” and “We could therefore not calculate response proportions.” are not necessary in Method, these belong to Result.

This has been corrected.

Reviewer: Masahito Yamada

1. Other pathological diagnoses than CJD in patients who died with suspected CJD.

The authors described that 167 (55%) of 304 autopsied cases had the pathological diagnosis of CJD (lines 179-180). It is important to describe pathological diagnoses in 45% of the autopsied cases without CJD.

We added this.

Line 123-124: “We described the final diagnosis for autopsies on patients that were found negative for CJD in the autopsy.”

Line 176-179: “Among the 137 (45%) autopsies that were found negative for CJD, 31 (23%) were cases of Alzheimer’s dementia, 18 (13%) of dementia (not further specified), 16 (12%) of Lewy body dementia, 8 (6%) of encephalitis, 24 (18%) had no final diagnoses and 40 (29%) had various other diagnoses.”

What was the level of clinical diagnosis (probable/possible CJD) for these cases in which the diagnosis of CJD was suspected clinically and denied pathologically?

We have tried to apply the case definition to those cases that were not autopsy diagnosed as non-CJD. However, due to the high proportion of missing data for some of the key criteria, it was not possible to get a reliable estimate of the proportion of probable/possible cases among this group.

2. Capture of the 245 patients who died in hospital with CJD diagnosis by the surveillance system.

According to the descriptions in lines 189-191, the reviewer understands that 127 (52%) of the 245 cases did not undergo autopsy, but 23 (9.8%) were captured by the surveillance system as probable cases. Was registration by the surveillance system
rejected by the families in the remaining cases? Or, did some of them have other levels of CJD diagnosis such as “possible” after the surveillance?

Unfortunately we do not have this information since these cases come from a different dataset (hospital discharge data) that holds limited information. However, we do agree that this information could be very useful and therefore we recommend in line 321-322: “exploring the reasons for not undergoing autopsy, for example by performing a validation study on the CJD suspected deaths in hospital that do not undergo autopsy.”

3. Response rate to the survey (line 199)
The response rate to the survey was 72 (14%) of 533 neurologists in Belgium. As the response rate is low, the reviewer wonders if the survey data represent the thought of Belgian neurologists.

The discussion was changed, we elaborated more on the survey results in particular: Line 291-303: “An important limitation of this evaluation lies in the unknown representativeness of survey respondents. Those with a special interest in CJD may have been more likely to respond. The impact of this on our evaluation cannot be estimated, and therefore the results of the survey should be interpreted with caution and verified where possible. An example of the responder bias might be represented in the difference between measured referral of suspect cases and self-reported referral. Sixty-eight percent of respondents said they referred suspect CJD cases for autopsy. However, when linking the hospital discharge data with the cases referred for autopsy, only 50% of cases were referred. However, a possible alternative explanation for the difference between the estimated referral and the self-reported referral may lie in a reporting error on hospital level or an autopsy refusal of the family. Checking death records of suspect CJD cases that did not undergo autopsy in a reference centre would provide us with more insight into referral practices and would perhaps allow us to estimate the Belgian incidence more precisely. Moreover, it could clarify the decrease in capture by the surveillance system with increasing age.”

4. The conclusion (lines 278-281)
The reviewer feels that more reasons are necessary to conclude that vCJD cases are likely to be captured by the surveillance system.

In discussion we added
Line 275-277: “Moreover, the younger age of vCJD patients, the longer disease duration and its rareness make it highly unlikely that vCJD cases will remain undetected by the surveillance system, even if the neurologist does not contact the reference centre immediately.”