Risk of variant Creutzfeldt–Jakob disease in France

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Background France has the second highest number of variant Creutzfeldt–Jakob disease (vCJD) cases worldwide. Imports of bovine carcasses from the UK probably constituted the main source of exposure of the French population to the bovine spongiform encephalopathy (BSE) agent. Meat products consumed whilst visiting the UK have also been considered as a possible source of exposure.

Methods We estimated the number of future vCJD cases in France using a simulation approach. Both the distribution of the vCJD incubation period and the age-dependent susceptibility to the BSE agent were estimated from UK data. The French epidemic was simulated by gender and birth-cohort from data on the infectivity of UK bovine tissues and simulations of the French consumption of infected beef products. We also used data on travel to the UK between 1980 and 1995.

Results We predicted 33 future cases of vCJD: 12 in the 1940–69 birth-cohort and 21 in the post-1969 birth-cohort. No case was predicted in the pre-1940 cohort. Based on our model, simulated vCJD cases occurred later in the older (1940–69) than in the younger cohort (post-1969). Age at onset was stable in the post-1969 cohort and increased in the older cohort. The model predicted a small excess of male patients. No case was attributed to travels in the UK.

Conclusions This modelling confirms that a large vCJD epidemic in France is very unlikely. Since France (where 60% of the total British exports of bovine carcasses were exported) has been highly exposed to the BSE agent, our results are reassuring for most countries worldwide.

Keywords Epidemiology, vCJD, France, predictions, simulation, exposure to BSE agent, birth-cohort

The data available indicate that the French population has been highly exposed to the bovine spongiform encephalopathy (BSE) agent from the early 1980s to the embargo on British beef, in 1996. France has the second highest incidence of variant Creutzfeldt–Jakob disease (vCJD) worldwide. The number of vCJD cases are, however, much lower in France than in the UK: 6 and 146, respectively at the time of this study (since, two new cases occurred in France and five in the UK). Several predictions of the vCJD epidemics in the UK have already been published. While early studies predicted very large epidemics, most recent studies predict that the number of future vCJD cases in the UK should not be greater than a few hundreds.\textsuperscript{1–6} To date, models that were used to estimate the risk of vCJD in the UK have not been applied to French data. Fitting models on only 6 cases, key parameters such as the incubation period distribution and the susceptibility to vCJD cannot be accurately estimated. But recent studies on the epidemics in the UK provided consistent estimates for these parameters.\textsuperscript{1–3} They can be used to assess the risk of vCJD in France, assuming factors that modulate these parameters to be similar in France and the UK.

vCJD cases have two remarkable characteristics. First, they all are homozygous for methionine at the codon 129 of the prion protein (\textit{PRNP}) gene.\textsuperscript{3,4} Therefore, predictions of vCJD incidence only apply to this genotype which accounts for 40% of both French and British populations. Second, about two-thirds of the vCJD cases are aged between 15 and 35 years; only 3 cases were older than 60 years. This age distribution raises the issue of an age-dependant pattern in exposure, susceptibility and/or incubation period. Modelling approaches require those relations to be assessed and defined.
Dietary exposure to the BSE agent is the most likely cause of vCJD. Products containing beef as mechanically recovered meat (MRM) (burgers, sausages, etc.) are generally considered as the major source of exposure as they could have been contaminated with infectious nervous tissues. There were three potential sources of BSE exposure in the French population: (i) the consumption of contaminated French meat, (ii) the consumption of contaminated British meat imported to France and (iii) the consumption of contaminated British meat in the UK whilst French travellers visited the UK. Previous studies indicated that the exposure due to indigenous BSE was low.\textsuperscript{7–10}

The aim of this study is to forecast the number of vCJD cases in France based on exposure to BSE through British infected meat and meat products which were imported to France or consumed by French travellers during stays in the UK. Assessment of the exposure of the French population to BSE was based on previous studies by our group and others. We had already estimated the French consumption of beef MRM contained in burgers and other beef products. To investigate the observed age-dependent risk of vCJD, consumptions were computed by birth-cohorts (pre-1940, 1940–69, post-1969) and gender.\textsuperscript{11} The present analysis also required estimates of the infectivity in UK beef MRM by calendar year, which were provided by Cooper and Bird.\textsuperscript{12}

Methods

Exposure to the BSE agent through consumption of UK beef MRM

Dietary exposure intensities to the BSE agent were expressed as bovine oral ID\textsubscript{50} (Bo-ID\textsubscript{50}), the oral dose required to cause an infection in 50% of an exposed bovine population. Two infectivity options were considered.\textsuperscript{12} Assuming an exponential increase in infectivity in the last year of incubation with a doubling time of 6 months (optimistic option), infected bovines slaughtered <12 months before their onset were approximately half (54%) as infectious as bovines with clinical signs. The pessimistic option assumed that pre-clinical and clinical bovines were equally infectious. The Monte Carlo simulation process providing estimates of the infectivity titre per tonne of UK beef MRM, for each calendar year from 1980 to 1995, has been detailed by Cooper and Bird.\textsuperscript{12} Their study showed that the infectivity titre of UK beef MRM increased exponentially between 1980 and 1992, and then fell; in 1995, MRM infectivity was approximately at the 1987–1988 level. In 1989, a sharp but transitory drop in MRM infectivity was observed when specified bovine offal (SBO) legislation was introduced in the UK. These measures prevented potentially infectious products from entering the human food chain.

Exposure to BSE agent through bovine carcasses imported from the UK

In a previous study, we estimated by calendar year the total quantity of beef MRM produced for human consumption in France and the proportion of MRM produced from imported bovine carcasses.\textsuperscript{11} To estimate the annual number of Bo-ID\textsubscript{50} consumed due to imports, we simulated the infectivity titre distribution in French MRM due to British imported bovines, using the methodology developed by Cooper and Bird.\textsuperscript{12} Combining estimated individual consumption of products containing MRM by age group and gender with the simulated infectivity titre of French MRM, we first got the simulated distribution of the individual exposure and then the total population exposure to BSE by birth-cohort, calendar year and gender.

Exposure to BSE whilst visiting the UK

This part of our study is detailed elsewhere.\textsuperscript{13} Briefly, to know the proportion of blood donors who had travelled to the UK from 1980 to 1996, the French Blood Transfusion Service conducted a nationwide survey in 1999. Donors (n = 16 191) answered questions about dates and durations of their visits to the UK during the critical years. About one-third of the French donors had spent at least one day in the UK during the surveyed period. Only 1.2% had spent more than six months in the UK. Data from blood donors were extrapolated to the general population, with adjustments which were necessary to take into account the specific age and gender characteristics of the donors. Based on these data, we simulated the distribution of the number of weeks spent in the UK by French travellers and we estimated exposure to BSE during those trips by birth-cohort and gender.

Estimation of the vCJD incidence in France

The approach we used is derived from the one described by Cooper and Bird.\textsuperscript{3} The evolution of the health status of each infected individual was simulated. Individuals were all attributed a calendar year of infection and an incubation period. Consequently, the size and the temporal pattern of French vCJD epidemic could be described. To get distributions, 5000 independent epidemics were simulated.

The required number of infected individuals was not fixed but set along the simulation runs. A run stopped once as many cases as really observed in each birth-cohort by the end of 2003 were simulated. The year in which infection took place (y) was randomly attributed according to the probability of being infected at year y. That probability was assumed to be proportional to the density of the exposure that year. Exposure itself depended on gender g, birth-cohort c and on how the individual was exposed (during trips to the UK or not): the source of exposure s. Therefore, y was sampled simultaneously with the three other parameters from their joint distribution (\( P_{y=g,c,s} \)). Let (\( E_{y=g,c,s} \)) denote the exposure intensity simulated for iteration i, for given y, g, c and s, and (\( P_{y=g,c,s} \)) the corresponding probability of getting infected. (\( P_{y=g,c,s} \)) was estimated for given y, g, c, s with the exposure density:

\[
\left( P_{y=g,c,s} \right) = \frac{\left( E_{y=g,c,s} \right)^{i}}{\sum_{g,c,s} \left( E_{y=g,c,s} \right)^{i}}
\]

Each infected individual was then randomly attributed a combination of modalities for those four variables describing how and when their infection occurred. Incubation periods were sampled from a log-normal distribution whose parameters were dependent on the birth-cohort c.\textsuperscript{3} Values were the ones which provided the best fitting epidemic in the UK according to a \( \chi^2 \) criterion, namely a mean of 11 years (SD 1.5) for the youngest cohort, and a mean of 26 years (SD 16.5) for the two older cohorts. Finally, to know whether each onset was observed or censored, the year of death from other reasons than vCJD cases in France based on exposure to BSE through British infected meat and meat products which were imported to France or consumed by French travellers during stays in the UK. Assessment of the exposure of the French population to BSE was based on previous studies by our group and others. We had already estimated the French consumption of beef MRM contained in burgers and other beef products. To investigate the observed age-dependent risk of vCJD, consumptions were computed by birth-cohorts (pre-1940, 1940–69, post-1969) and gender.\textsuperscript{11} The present analysis also required estimates of the infectivity in UK beef MRM by calendar year, which were provided by Cooper and Bird.\textsuperscript{12}
vCJD was simulated according to French mortality rate by age, gender, and calendar year (http://www.ined.fr). Simulated individuals were only considered if (i) their onset led to an epidemic which was compatible with observations and (ii) they were susceptible, according to an age-related susceptibility function \( s(a) \). We considered individuals aged <15 years old to be totally susceptible \( s(a) = 1 \); thereafter, the susceptibility exponentially decreased, with 6% decrease per year of age.\(^2\)

**Results**

**French exposure to BSE through imports and travels to the UK**

Figure 1 shows the total exposure of the French population by birth-cohort and calendar year, assuming that pre-clinical bovines were 54% as infectious as clinical BSE bovines (optimistic option). In all cohorts, exposure peaked in 1993. The pre-1940 birth-cohort was far less exposed than the two younger cohorts. The exposure patterns of the 1940–69 and post-1969 cohorts were similar, the 1940–69 cohort being, however, more exposed. A direct interpretation of these figures can be misleading because sizes of the cohorts were very different and varied differently with time: while the population in the oldest cohort decreased, it increased in the post-1969 cohort. In order to get size-independent results, exposure was simulated for virtual birth-cohorts whose size was fixed to \( 10^6 \) individuals. That simulation indicated that individuals born before 1940 had been as exposed to BSE as the younger ones (Figure 2). Under the optimistic infectivity option, the French population was exposed to 36 142 Bo-ID\(_{50} \) (Table 1).

During the same period, the exposure of the UK population was equal to 710 350 Bo-ID\(_{50} \)\(^{12,13} \) (ratio UK/France: 20). As expected, the exposure was roughly multiplied by two under the pessimistic option, but the UK/France ratio remained unchanged.

Travels to the UK accounted for only 2% of the French total exposure to BSE.

**Number of future vCJD cases in France**

Under the optimistic infectivity option (Table 2), a total of 33 vCJD cases are expected:12 cases in the 1940–69 cohort and 21 cases in the post-1969 cohort. Only three cases were expected to occur after 2020. No case was predicted in the pre-1940 cohort. Almost all simulated onsets, except three in the 1940–69 cohort, occurred in individuals infected between 1990 and 1995. The temporal distribution of onsets differed between the two cohorts: while all expected vCJD onsets occurred before 2010 in the youngest cohort, 7 out of 12 onsets in the 1940–69 cohort were predicted to occur after 2010. We also found that no onset was censored in the youngest cohort whereas three onsets were censored in the 1940–69 cohort. According to our simulation, the age at onset of the simulated vCJD cases in the post-1969 cohort remained stable along time, whereas it increased in the 1940–69 cohort. As a consequence of gender differences in exposure to BSE, we predicted an excess of male patients in both cohorts (around 60%). That proportion was constant over time and consistent with French and British data, which did not suggest any gender-related susceptibility function. Simulations did not predict any case that could be attributed to travels in the UK.

We also computed a crude estimate of the bovine-to-human transmission barrier (T-barrier) in the genetically susceptible population. As a consequence of the assumed age-dependent susceptibility, an individual in the 1940–69 birth-cohort required more \((\times 1.5)\) infectious units to be infected than an individual from the post-1969 cohort. Indeed, the mean estimated number of infectious units required to cause one infection was around 280 for the youngest cohort and 420 for the 1940–69 cohort. Confidence intervals were very large: [167–1382] and [106–972] for the 1940–69 and post-1969 cohorts respectively. Under the pessimistic infectivity option, the mean T-barrier roughly doubled.

**Comments**

Our model predicted a low vCJD incidence in the French genetically susceptible population (methionine homozygous), with a median estimate of 33 future clinical cases between 2004 and 2020. We found that two-thirds of the simulated vCJD cases were expected in the post-1969 birth-cohort and the remaining one-third in the 1940–69 cohort.

As six cases were not sufficient enough to get reliable estimates for the key parameters of our model, their values were fixed to the ones obtained by the modelling of the vCJD epidemics in the UK. First, the incubation period was sampled from an age-dependent log-normal distribution whose parameters best fitted Cooper’s model.\(^3\) Second, as proposed by others,\(^1,2\) we used an age-dependent susceptibility function exponentially decreasing after the age of 15 years. Previous modelling studies showed that these assumptions and parameters were accurate enough to predict the vCJD epidemics in the UK. As incubation period and susceptibility are mainly related to biological mechanisms, UK estimates are valid in other populations as well. However, a sensitivity analysis (results not shown) indicated that our conclusions remained stable while considering alternative values.

Assuming that vCJD was a consequence of eating BSE-infected beef, we estimated dietary exposure intensities to BSE by combining two categories of data: estimated distributions of the French consumption of products containing beef MRM, by birth-cohort and gender, and infectivity titre in MRM produced from British bovines, expressed as number of units of Bo-ID\(_{50} \). This methodology had been proposed to predict vCJD incidence in the UK.\(^3\) Others used estimates of the number of BSE-infected animals entering the human food chain to quantify human exposure to BSE.\(^1,2,4,5\) Both approaches resulted in comparable predictions. The advantage of the latter methodology is that it required neither any assumption about which types of beef products are infective nor any data on the consumption of meat products which induced serious uncertainties that have already been discussed.\(^11,15\) On the other hand, our methodology, derived from Cooper and Bird’s study, facilitates the discussion about age-dependent exposure and/or incubation period.

To get an estimate of the French exposure to BSE during stays in the UK, we extrapolated data from blood donors to the general population. We adjusted for age distribution and sex ratio differences between donors and the general population. It is established that, on the average, French blood donors have lower socioeconomic level than the general population. Since the proportion of travellers increases with the
socioeconomic level, this could have resulted in underestimating the proportion of travellers in the general population. Consequently, the number of vCJD cases due to infections whilst travelling in the UK may be slightly higher than expected in our analysis. But probably, no more than one French vCJD case might be due to infections contracted in the UK.

Based on a previous analysis, the exposure due to BSE-infected cattle in France was neglected in our model. This major
Table 1  Total infectivity (in Bo-ID<sub>50</sub> units) consumed in France and in the UK between 1980 and 1995, by birth-cohorts. Figures are based on 5000 simulation runs. Median values are reported.

<table>
<thead>
<tr>
<th>Birth-cohorts</th>
<th>Optimistic infectivity option</th>
<th>Pessimistic infectivity option</th>
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<tbody>
<tr>
<td></td>
<td>French exposure</td>
<td>British exposure</td>
</tr>
<tr>
<td>Pre-1940</td>
<td>5379</td>
<td>86 500</td>
</tr>
<tr>
<td>Post-1970</td>
<td>14 351</td>
<td>271 350</td>
</tr>
<tr>
<td>Total</td>
<td>36 142</td>
<td>710 350</td>
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</tbody>
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Table 2  Estimated incidence of vCJD linked to the importation of British bovines in France by birth-cohort. Figures are based on 5000 simulation runs, under the optimistic infectivity option. Mean values, (bold), median values, and [5th, 95th] percentiles are presented.

<table>
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<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Simulated</td>
<td>Simulated</td>
<td>Simulated</td>
<td>Simulated</td>
</tr>
<tr>
<td>Pre-1940</td>
<td>0</td>
<td>0.00</td>
<td>[0,0]</td>
<td>0.05</td>
<td>0.09</td>
</tr>
<tr>
<td>1940–69</td>
<td>3</td>
<td>3.00</td>
<td>[3,3]</td>
<td>1.17</td>
<td>3.08</td>
</tr>
<tr>
<td>Post-1969</td>
<td>3</td>
<td>3.00</td>
<td>[3,3]</td>
<td>12.57</td>
<td>8.82</td>
</tr>
</tbody>
</table>

assumption must be carefully discussed. Although available estimates of the BSE epidemics in France were not perfectly consistent, they indicated that exposure due to infected French meat had probably been small.7–9 For the period 1987–2000/2001, estimates of the number of infected animals varied from 7000 to 70 000 according to the assumptions considered. The number of infected animals entering the food chain comprised between 100 and 7600 in France, compared with 3.3 million in the UK during the same period of time. On the other hand, the data indicated that exports of British bovine carcasses to France represented about 10% of the beef meat consumption in the UK. Based on these figures, French infected bovines could have been responsible for a very small percentage of the total BSE exposure of the French population between 1987 and the early 2000s. A study suggested that the number of BSE infections in France could have been much higher before 1987 than after.9 If confirmed, this result could lead to revisiting some models of the BSE and vCJD epidemics. Another argument which supports our assumption is the comparison between estimated exposure and observed vCJD incidence: the ratio between the exposure in the UK computed by Cooper and Bird and that provided by our model (20:1) is consistent with the current vCJD incidence ratio (21:1) between these countries.

However, if it was necessary to consider indigenous French exposure to BSE in modelling, the temporal and age-sex distributions of the predicted vCJD cases might be affected, but not (or only very slightly) the predicted number of vCJD cases.
the observed numbers of cases, estimates of the French exposure are only involved in the description by gender, age, and calendar year of simulated vCJD cases.

We set the end of the exposure period in 1995 as the embargo on British beef was ordered at the beginning of 1996. Afterwards, indigenous BSE constituted the unique source of infection of the French population. A total of 1500 French bovine carcasses were estimated to have entered the human food chain after 1995.9 If all those carcasses had been used to produce MRM, French exposure between 1996 and 2001 would have represented less than 2% of the French total exposure.

Other limitations of these predictive models have been already pointed out. Other genotypes at the PRNP gene codon 129 could be susceptible to the BSE agent with longer incubation period. Indeed, in both iatrogenic CJD due to human growth hormone treatment17 and Kuru,18,19 individuals with the methionine-valine heterozygous genotype, which represents about 50% of the French population, have longer incubation periods than the methionine-methionine homozygotes. As heterozygotes also have a lower susceptibility to prion diseases, they should not contribute much to the vCJD epidemics. Moreover, possible transmission of vCJD by blood transfusion was suggested by recent case reports in the UK20,21 and iatrogenic transmission of vCJD through medical or surgical procedures cannot be excluded. But, a series of effective measures to reduce the risk of transmission of vCJD by infected material and blood products were taken in France. In addition, transfused individuals were banned from blood donation.

Predictions of the vCJD epidemics in the UK, France, and the Republic of Ireland6 are consistent and reassuring. To date, the best estimates of the number of future clinical cases were between 200 and 400 cases in the UK, approximately 30 in France and between one and two in the Republic of Ireland. The Republic of Ireland had the second highest incidence of BSE worldwide. Harney et al. estimated that exposure due to the BSE epidemic in Ireland and exposure due to Irish imports from the UK were equivalent.9 Our study suggests that, in France, imports from the UK have represented the main source of infection by the BSE agent and that exposure due to BSE in French cattle plays a negligible role in the vCJD epidemic.

Data from Customs and Excise in the UK indicated that, over the period 1980–1995, about 60% of the total exports of UK bovine carcasses to the European Community (EC) countries (about 2 million tonnes equivalent of carcasses) were exported to France. Therefore, very few vCJD cases due to the past BSE epidemics are expected in other EC countries, and worldwide. Nevertheless, as long as BSE and other forms of animal transmissible spongiform encephalopathies are not eliminated, surveillance of human prion diseases at both the national and international levels remains necessary.

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KEY MESSAGES

• The French population may have been mainly exposed to the BSE agent through the consumption of BSE-infected bovines which were imported from the UK.
• Thirty-three future vCJD cases are expected in the French population, with the upper bound at lower than 100 cases.
• Expected cases of vCJD are young: two-thirds of the simulated vCJD cases are expected in the post-1969 birth-cohort and the remaining one-third in the 1940–69 cohort. Cases in people born before 1939 are very unlikely to occur.
• No gender-related susceptibility to the BSE agent can be outlined.

References

†The possibility of life-long infection without the development of disease

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Alperovitch assesses these potential risks in France and the risk period 1980–1996. The paper by Chadeau-Hyam and from the UK, or exposure to BSE during travel to the UK in import of infected animals, animal feed, and food products other than the UK may be due to exposure to indigenous BSE, developing this condition is likely to be proportional to the extent of human exposure to BSE, presumptively through spongiform encephalopathy (BSE) and the population risk of hypothesis that vCJD is caused by human infection with bovine Disease (vCJD) in the UK is currently on a decline. 1


Commentary: The risk of variant Creutzfeldt–Jakob Disease: reassurance and uncertainty

RG Will

The annual number of deaths from variant Creutzfeldt–Jakob Disease (vCJD) in the UK is currently on a decline. Epidemiological and laboratory evidence strongly supports the hypothesis that vCJD is caused by human infection with bovine spongiform encephalopathy (BSE) and the population risk of developing this condition is likely to be proportional to the extent of human exposure to BSE, presumptively through contaminated meat products. The risk of vCJD in countries other than the UK may be due to exposure to indigenous BSE, import of infected animals, animal feed, and food products from the UK, or exposure to BSE during travel to the UK in the risk period 1980–1996. The paper by Chadeau-Hyam and Alperovitch assesses these potential risks in France and concludes that overall there may be a limited number of future vCJD cases in the French population (33 cases from 2004–2020) and that the main risk was through consumption of infected bovines from the UK. Travel to the UK was assessed to account for only 2% of BSE exposure and exposure to French cases of BSE was not considered because this was judged to represent a low risk. This paper and a similar study in Ireland suggest that the number of future cases of vCJD may be very limited outside the UK. There are, however, a number of important caveats. To date all clinical cases of vCJD in which the prion protein gene (PRNP) has been examined have been methionine homozygotes, with no identified cases in the 68% of the Caucasian population with the alternative valine homozygotes or heterozygous genotypes. All predictive studies of vCJD to date have overtly assumed that only methionine homozygotes, with no identified cases in the 68% of the Caucasian population with the alternative valine homozygotes or heterozygous genotypes. All predictive studies of vCJD to date have overtly assumed that only methionine homozygotes will be affected, but the possibility that infection with BSE can occur in the other genetic backgrounds has been supported by the recent publication of a presumed preclinical case of vCJD in a PRNP heterozygous blood transfusion recipient. If heterozygotes can be infected with BSE it would be surprising if valine homozygotes could not also be infected, although Chadeau-Hyam and Alperovitch suggest that heterozygotes (and presumably valine homozygotes) may have a lower susceptibility to infection and may not add significantly to the vCJD epidemic. Cattle are uniformly methionine homozygotes and homology of prion protein types is thought to lead to