Encéphalopathies spongiformes transmissibles/Transmissible spongiform encephalopathy

Predicting the size of the vCJD epidemic in France

Annick Alpérovitch[a]*, Robert G. Will[b]

[a] *Institut national de la santé et de la recherche médicale, unité 360, hôpital de la Salpêtrière, 75651 Paris cedex 13, France*
[b] *National CJD Surveillance Unit, Western General Hospital, Edinburgh, UK*

Presented by Jean Rosa

Abstract – More than 5 years after the description of the first cases of variant Creutzfeldt-Jakob disease (vCJD), there is still great uncertainty about the size of the vCJD epidemic in the United Kingdom (UK), although the most recent predictions based on statistical modelling are more optimistic than the previous ones. The number of vCJD cases in France is far too small to attempt any direct modelling of the vCJD epidemic in the French population. Comparative assessment of the level of exposure to the bovine spongiform encephalopathy (BSE) agent in the UK and France could help to estimate the size of the vCJD epidemic in France. Data on imports of beef products from the UK between 1985 and 1996, BSE epidemic in French cattle, and travel of French people to the UK suggest that the French population was much less exposed to the BSE agent than the UK population. The France/UK ratio of vCJD incidence is currently approximately equal to 0.05. Further studies are needed to estimate accurately the exposure ratio between UK and France and to examine whether comparative data about exposure and incidence are fully consistent. The temporal pattern of exposure in UK and France, and possible differences in exposure to high risk bovine tissues because of food habits or risk reduction measures should be carefully considered. To cite this article: A. Alpérovitch, R.G. Will, C. R. Biologies 325 (2002) 33–36. © 2002 Académie des Sciences/Éditions scientifiques et médicales Elsevier SAS

variant Creutzfeldt-Jakob disease / incidence / bovine spongiform encephalopathy / risk assessment

Since the description of the first cases of variant Creutzfeldt-Jakob disease (vCJD) in 1996 [1], several predictions of the vCJD epidemic in Great Britain have been published [2–7]. One of the most pessimistic predictions was published by Ghani [4] who showed that vCJD mortality data by the end of 1999 (55 cases in Great Britain) were consistent with between 63 and 136 000 cases among the population known to have the susceptible genotype [4]. Under the likely hypothesis that the average annual number of vCJD cases over the period 2000–2002 will be greater than 20, the lower bound of the interval increased to 120. These numbers were obtained from extensive simulations exploring 5 million combinations of parameters regarding the dis-tribution of the vCJD incubation period, the incidence of BSE in Great Britain since the disease was recognised in cattle in 1985, the distribution of infectivity in cattle organs between contamination and clinical onset of BSE, the effectiveness of the banning of specified bovine materials and other measures taken to reduce population exposure to the BSE agent. The lower bound of the interval (120) corresponds to the most optimistic combination of parameters, in particular a mean incubation period shorter than 20 years. The upper bound (136 000) corresponds to the most pessimistic combination of parameters, in particular a mean incubation period longer than 60 years. For mean incubation periods between 20 and 60 years, and under

the hypothesis of an average number of vCJD cases in 2000–2002 greater than 20, the upper bound of the total number of deaths from vCJD falls to 6 000, the lower bound remaining equal to 120. It is more than likely that a large proportion of the 5 millions of scenarios which have been explored by Ghani et al. were consistent with the interval 120–6 000. This relatively optimistic scenario is consistent with the results of other studies [1, 5], and particularly the most recent ones [6, 7] which indicate that most likely the size of the vCJD epidemic would not exceed a few hundreds of cases in the UK.

The first modelling of the vCJD epidemic in Great Britain was performed on the basis of 14 cases [2]. The number of vCJD cases in France ($N = 4$) may appear too small to attempt to predict the size of the vCJD epidemic in this country. However, it is possible to extend the mathematical modelling used to predict the epidemic in Great Britain to France, taking into account data and assumptions about the specific pattern of exposure to BSE of the French population. A simple analysis based on the comparison of exposure and incidence ratios can also provide a crude assessment of the size of the vCJD epidemic in France.

2. Exposure to the BSE agent in France

2.1. Beef imports from the United Kingdom

Before 1996, beef imports from the United Kingdom (UK) may have constituted the main source of exposure to BSE for the French population. Available data from the French 'Office National Interprofessionnel des Viandes, de l'Elevage et de l'Aviculture' (OFIVAL), and for the UK from H M Customs & Excise, Business and Trade Statistics Limited, and the Ministry of Agriculture, Fisheries and Food (Branch D Statistics (Commodities & Food) Division) indicate that imports from the UK represented an important part of the beef consumption of the French population. Between 1985 and 1996, exports to France corresponded to approximately 10 % of the indigenous home-fed beef and veal consumption in the UK (*table*). These data provide a first crude indication of the relative exposure of the two populations. A more precise assessment should take into account quantitative and qualitative data about consumption of bovine offal and mechanically recovered meat in France and the UK over the period 1986–1995, and other parameters which may increase or decrease the risk of infection. In particular, the age distribution of animals slaughtered for exportation, and the specific tissues of British beef available for human consumption in the UK and France are important

Table. Consumption of beef of UK origin in France and UK (1985–1996).

| | Beef of UK origin* | | |
| | UK consumption** | French consumption | |
		Source 1***	Source 2****
1985–86	1 767.2	151.5	158.8
1987–88	1 727.3	139.8	157.3
1989–90	1 612.9	136.8	163.0
1991–92	1 589.7	118.3	140.8
1993-94	1 490.6	179.4	193.8
1995-96	1 253.9	126.4	136.4
TOTAL	9 441.6	852.2	950.1

* unit: 1 000 t carcass weight equivalent,
** source: MAFF by courtesy of John Wilesmith,
*** source: UK: HM Customs & Excise Statistics,
**** source: France: OFIVAL.

parameters. Moreover, even if the UK and French data are fairly consistent (*table*), their validity should be carefully evaluated.

2.2. BSE epidemic in French cattle

The BSE epidemic in French cattle constitutes another potential source of infection for the French population. By the end of 2000, 165 BSE cases (cumulative incidence) had been diagnosed in France. Under the assumption of substantial under-reporting [8], Donnelly has estimated that between mid-1987 and 2000, 7 300 French cattle (3 700 t carcass weight equivalent) entering the food chain were infected with BSE. This number is 44 times higher than the number of BSE cases which had been diagnosed in French cattle by 'passive' surveillance during the same period, while it is generally assumed that the number of infected animals that entered the food-chain in Great Britain (750 000) was approximately 4 times higher than the number of BSE cases registered by the 'passive' surveillance system (177 000). Thus, under the hypothesis of a major under-reporting of BSE cases in France, the number of infected animals that entered the food-chain in France (7 300) would be 100 times less than in Great Britain (750 000). On another hand, data on the BSE epidemic in British cattle suggest that, approximately, only 48 000 infected animals entered the food chain before high risk tissues were excluded from human consumption (end of 1989). In France, specified bovine material have been banned from the food chain since 1994. Other current differences between the French and British risk reduction measures will not be compared in this paper, which focuses on exposure of the French population to BSE before the 1996 embargo.

2.3. Travel to Great Britain

Travel to Great Britain constitutes the third potential source of infection for French people. To assess the

importance of this source in blood donors, a survey was conducted under the auspices of the 'Agence Française de Sécurité Sanitaire des Produits de Santé' in October 1999 [9]. Although the blood donor population is not representative of the general population, this study provides a useful estimate of the potential importance of this third source of exposure. Over one week, all donors coming to give blood in 12 centres distributed throughout France completed a questionnaire about travel and residence in the UK between 1980s and 1996. One-third (33 %) of the 16 787 blood donors included in this study reported having spent at least one day in the UK during this period. The cumulative length of stay over this period was longer than 1 month for 5.6 % of the blood donors, and longer than 6 months for 1.3 %. Assuming that the probability of being exposed to beef products infected by BSE was 10 times higher in the UK than in France, it was estimated that only 2.6 % of the risk of contamination of blood donors might be attributable to travel in Great Britain, 97.4 % of the exposure to BSE being due to imported beef. In this analysis, the proportion of risk attributable to having travelled to the UK was slightly over-estimated because BSE in French cattle was not taken into account. Therefore, travel to the UK contributes very little to the overall risk of contamination of the French population by the BSE agent, while travel to the UK constitutes the major source of exposure in other countries (Canada, USA).

3. Relation between exposure to the BSE agent and incidence of vCJD

Overall, previous data suggest that exposure of the French population to BSE between the early 1980 and 1996 has been much lower than exposure of the British population during the same period. This exposure is mainly due to beef imports from the UK, the other sources of exposure (BSE in French cattle, travel to the UK) being of minor importance. Assuming that the number of vCJD cases is proportional to exposure to BSE, the vCJD epidemic in France should be therefore much smaller than the UK epidemic. As France and Great Britain have similar population size (60 million inhabitants), the vCJD incidence ratio between France and the UK gives also a valid indication of the ratio of exposure between the two countries. By the end of September 2001, the numbers of confirmed or probable vCJD cases were equal to 106 and 4 in the United Kingdom and France respectively. The vCJD incidence ratio were 0.038 (4/106), which is slightly lower than the exposure ratio suggested by a succinct analysis of the crude data about levels of exposure to the BSE agent described in this paper.

4. Discussion

As previously pointed out, precise comparative data about consumption of offal and mechanically recovered meat in France and the UK were not available for this analysis. Available data suggest that the temporal pattern of exposure was different in France and Great Britain, the peak of exposure occurring later in France than in the UK. The ratio between the French consumption of beef of UK origin and the UK consumption increased between 1985 and 1995. Similarly, data show that out of 30 000 tonnes of bovine offal exported from the UK to France between 1980 and 1995, 90 % was exported after 1988. Thus, the incidence of vCJD might increase later in France than in the UK.

Export statistics from various sources indicate that, between 1985 and 1995, total exports of beef of UK origin (live trade and carcass meat) were equivalent to approximately 20 % of the beef consumption in the UK. These data may appear inconsistent with the incidence of vCJD in the UK (106 cases) and outside the UK (5 cases), more vCJD cases being expected outside the UK. This apparent inconsistency might be explained in part by the fact that exported beef carcass did not include tissues with the highest infectivity, such as brain tissue. Therefore, until 1989 when specified bovine offal were excluded from human consumption in the UK, the British population was more likely to have been exposed to high risk brain tissue from British cattle than population of countries which imported British beef. On another hand, computations indicated that the potential risk of vCJD in French people having travelled to the UK was equivalent to the risk of 160 000 persons having spent 10 years in this country since the beginning of the BSE epidemic. This estimate was obtained by extrapolating data from the French blood donor survey to the whole French population in the same age range as blood donors (36 millions persons). If similar analyses were made in other countries in Europe and outside Europe, they would show that, on the whole, having travelled to the UK corresponds to several million person-years of exposure to BSE. However, so far no vCJD cases have been identified in the world-wide population of persons who have travelled to the UK, other than one case from the Republic of Ireland who had lived in the UK for four and a half years. If vCJD remained very rare in the at risk populations outside the UK, this might suggest that very specific beef products and/or early life susceptibility to exposures (i.e. before the age of travel to the UK) might explain, at least in part, the high incidence of vCJD in the UK population, in comparison to other exposed populations. The very low incidence of vCJD

outside the UK might also indicate that the most pessimistic predictions for the vCJD epidemic in the UK are not the most likely ones.

References

[1] Will R.G., Ironside J.W., Zeidler M., Cousens S.N., Estibeiro K., Alpérovitch A., et al., A new variant of Creutzfeldt-Jakob disease in the UK, Lancet 347 (1996) 921–925.

[2] Cousens S.N., Vynnycky E., Zeidler M., Will R.G., Smith P.G., Predicting the CJD epidemic in humans, Nature 385 (1997) 197–198.

[3] Ghani A.C., Donnelly C.A., Ferguson N.M., Anderson R.M., Assessment of the prevalence of vCJD through testing tonsils and appendices for abnormal prion protein, Proc. R. Soc. Lond. B Biol. Sci. 267 (2000) 23–29.

[4] Ghani A.C., Ferguson N.M., Donnelly C.A., Anderson R.M., Predicted vCJD mortality in Great Britain, Nature 406 (2000) 583–584.

[5] Cooper J.D., Bird S.M., De Angelis D., Prevalence of detectable abnormal prion protein in persons incubating vCJD: plausible incubation periods and cautious inference, J. Epidem. Biostat. 5 (2000) 209–219.

[6] Huillard d'Aignaux J., Cousens S., Smith P.G., Predictability of the UK variant Creutzfeldt-Jakob disease epidemic, Science 294 (2001) 1729–1731.

[7] Valleron A.J., Boelle P.Y., Will R., Cesbron J.Y., Estimation of epidemic size and incubation time based on age characteristics of vCJD in the United Kingdom, Science 294 (2001) 1726–1728.

[8] Donnelly C.A., Likely size of the French BSE epidemic, Nature 408 (2000) 787–788.

[9] Révision des mesures de réduction du risque de transmission des ESST par les produits sanguins, Rapport de l'Agence Française de Sécurité Sanitaire des Produits de Santé, 2000.