



The unrecognised French BSE epidemic

Virginie Supervie, Dominique Costagliola

► To cite this version:

Virginie Supervie, Dominique Costagliola. The unrecognised French BSE epidemic. *Veterinary Research*, 2004, 35 (3), pp.349-362. 10.1051/vetres:2004016 . hal-00902786

HAL Id: hal-00902786

<https://hal.science/hal-00902786>

Submitted on 11 May 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

The unrecognised French BSE epidemic

Virginie SUPERVIE*, Dominique COSTAGLIOLA

INSERM EMI 0214, 56 bd Vincent Auriol, BP 335, 75625 Paris Cedex 13, France

(Received 1 October 2003; accepted 20 February 2004)

Abstract – In France, implementation of systematic screening programs in 2000, as a complement to the mandatory reporting of animals with clinical signs of BSE (passive surveillance), revealed certain limitations of the mandatory system. Indeed, systematic screening showed that some BSE cases were not detected by the clinical surveillance system, implying considerable BSE case under-reporting throughout the epidemic. As the most likely explanation for variant Creutzfeldt-Jakob disease (vCJD) is exposure to the aetiological agent of BSE, it is essential to reconstruct the French BSE epidemic pattern accounting for this under-reporting. We estimated age- and year-specific incidence rates of BSE by using a back-calculation method. This approach relies on the principle that the number of clinical BSE cases is the consequence of the number of BSE-infected animals after a known incubation time, defined as the time between infection and clinical onset. We generalized this model to take into account epidemiological characteristics of BSE, such as French cattle mortality, BSE case reporting probability, and age-dependent susceptibility and/or exposure to the BSE agent. We confirmed that the average BSE incubation period is five years and that the peak risk of bovine infection occurs between 6 and 12 months of age. The results also showed that the proportion of underreporting is the most influential parameter in the model, and that BSE was substantially underreported until rapid tests were introduced. Indeed, only 103 BSE cases were detected by passive surveillance up to June 2000, while we estimated that there was 301 200 (95% confidence interval (CI) [27 600–837 600]) cattle infected by the BSE agent. Despite uncertainty over the beginning of the epidemic, we showed that the French BSE epidemic in the late 1980s was completely undetected, and only the second wave, after 1990, was observed.

epidemiology / BSE / under-reporting / vCJD / back-calculation

1. INTRODUCTION

In France, BSE became a notifiable disease in June 1990. In December 1990, a mandatory passive surveillance system was set up, in which veterinary practitioners and farmers were required to report animals with clinical signs. The first case of BSE identified by this surveillance system was detected in 1991. Between 1991 and June 2000, 103 cases were identified by passive surveillance [2]. From mid-2000 until July

2001, the surveillance system underwent several changes. From mid-2000, in addition to the mandatory reporting system, a pilot study of rapid testing was implemented on cattle at risk (dead-on-farm cattle, emergency slaughtered cattle and euthanatized cattle). Then, from January 2001, systematic screening was extended to all cattle over 30 months of age entering the food chain, and this age was reduced to 24 months in July 2001. Implementation of active surveillance revealed the inefficiency of the

* Corresponding author: virginie.supervie@ccde.chups.jussieu.fr

passive surveillance, both in France and elsewhere. In France, comparison of the passive and active surveillance systems between July 2001 and June 2002 showed that only 20% of BSE cases were identified by passive surveillance. This implied considerable BSE case under-reporting throughout the epidemic.

It is now widely recognised that the most likely explanation for human variant Creutzfeldt-Jakob disease (vCJD) is exposure to the BSE agent [10, 26, 33]. As of 5th January 2004, there were 145 cases of definite or probable vCJD [16] in the United Kingdom. The future size of the vCJD epidemic in the United Kingdom is speculative, although the most recent predictions [25, 27, 31] based on statistical modelling are more optimistic than previously. The number of vCJD cases in France – 6 confirmed cases [28] – is far too small to attempt direct modelling of the vCJD epidemic in the French population. Nevertheless, a comparative assessment of the temporal pattern of exposure to the BSE agent in the United Kingdom and France could help to estimate the size of the vCJD epidemic in France. The French population has been exposed to the BSE agent from three sources: via travel to the United Kingdom and British beef imports since 1980, the likely start date of the BSE epidemic [13], and via the BSE epidemic in French cattle. A study of French blood donors showed that travel to the United Kingdom contributed very little to the overall risk in the French population [5]. Exposure of the French human population via imported British bovine products was estimated to represent between 5% and 10% of the exposure level of the British population [4]. This exposure source only posed a high risk during the period 1980–1989, i.e. the period before the British ban on specified offal from all cattle entering the human food chain (November 1989). In France, measures intended to prevent bovine infection by the BSE agent were taken from 1989. However, it was only in June 1996 that high-risk bovine tissues (“specified offal”) were excluded from

human consumption. Thus, the French population was exposed to the BSE agent via French bovine products until June 1996. However, only animals slaughtered for consumption late in the incubation period are likely to be infectious.

Another key parameter is necessary to study the exposure of the French population, namely the start date of the French BSE epidemic. BSE was first recognised in England in 1985. Supplementary feeds containing meat and bone-meal (MBM) were identified as a potential vector of the BSE agent. A French Senate report [8] states that MBM was already being imported by France from the United Kingdom in 1985 (no information is available before this date) and, according to a European report, from other European countries as early as 1980 [30]. As the earliest birth cohort of a BSE case dates back to 1983, French cattle were already potentially exposed to the BSE agent at that time. For the purposes of this study, we assumed that the French epidemic began in 1980; very similar results were obtained when a start date of 1983 was used.

We used the back-calculation method [9] to estimate longitudinal trends in the incidence of BSE infection in France, and to deduce the number of infectious animals slaughtered for human consumption. This method relies on the principle that the number of clinical BSE cases is the consequence of the number of BSE-infected animals after a known incubation time, defined as the time between infection and clinical onset. We generalised this model to take into account epidemiological characteristics of BSE, such as a time-dependent BSE case-reporting function.

2. MATERIALS AND METHODS

2.1. Data

Our analysis was restricted to the 103 bovine clinical cases [2] detected by passive surveillance up to June 2000 (Tab. I). All the

Table I. Distribution of clinical cases, detected by passive surveillance between January 1991 and June 2000, by age class and time at clinical onset.

Period \ Age class (years)	[3.5-4]	[4-4.5]	[4.5-5]	[5-5.5]	[5.5-6]	[6-6.5]	[6.5-7]	[7-7.5]	[7.5-8]	[8-8.5]	[8.5-9]	[9-9.5]	Total cases per six-month period
Jan.-June 1991	0	1	0	0	1	1	1	0	0	0	0	0	4
July-Dec. 1991	0	0	0	0	0	0	0	0	0	0	1	0	1
Jan.-June 1992	0	0	0	0	0	0	0	0	0	0	0	0	0
July-Dec. 1992	0	0	0	0	0	0	0	0	0	0	0	0	0
Jan.-June 1993	0	0	0	0	0	0	0	0	0	0	0	0	0
July-Dec. 1993	0	0	1	0	0	0	0	0	0	0	0	0	1
Jan.-June 1994	0	0	0	1	2	0	0	0	0	0	0	0	3
July-Dec. 1994	0	0	1	0	0	0	0	0	0	0	0	0	1
Jan.-June 1995	0	0	0	0	0	1	0	0	1	0	0	0	2
July-Dec. 1995	0	0	0	0	0	0	0	1	0	0	0	0	1
Jan.-June 1996	0	1	0	0	0	1	2	1	0	1	1	0	7
July-Dec. 1996	0	0	0	0	0	0	0	1	3	1	0	0	5
Jan.-June 1997	0	0	0	0	0	1	0	0	0	1	0	0	2
July-Dec. 1997	0	2	1	0	1	0	0	0	0	0	0	0	4
Jan.-June 1998	0	2	1	0	1	0	0	0	0	0	0	1	5
July-Dec. 1998	1	2	2	3	1	0	1	0	0	0	1	2	13
Jan.-June 1999	0	2	3	4	3	0	0	0	0	0	0	0	12
July-Dec. 1999	0	2	4	7	2	1	0	1	1	0	1	0	19
Jan.-June 2000	0	1	4	4	6	4	2	1	0	1	0	0	23
Total cases by age class	1	13	17	19	17	9	6	5	5	4	4	3	103

Jan.: January; Dec.: December.

animals were cows aged between 3.9 and 9.4 years at clinical onset; 85% were aged between 4 and 7 years, and mean age at clinical onset was 5.9 years.

Specific developments would be needed to take into account clinical cases detected after June 2000, as the multiple changes to the surveillance system between July 2000 and July 2001 could have introduced detection biases. Indeed, a retrospective clinical investigation [12] showed that some positive animals found in the pilot study should have been included in the mandatory reporting system because they had clinical signs of BSE. In addition, active surveillance improved awareness of BSE and the efficiency of mandatory reporting [14]. A pos-

sible "escape route" for BSE cases was the over 30-month-cattle destruction program. Indeed, between January 2001 and June 2001, more than 179 000 cattle over 30 months of age were destroyed without being tested. No simple models can account for such rapid changes, and we therefore decided first to develop a model based only on the period up to June 2000.

2.2. BSE epidemiological characteristics

Epidemiological data on clinical onset by age (Tab. I), assuming a long BSE incubation period [6, 24, 32], suggest that most infections occur shortly after birth. We

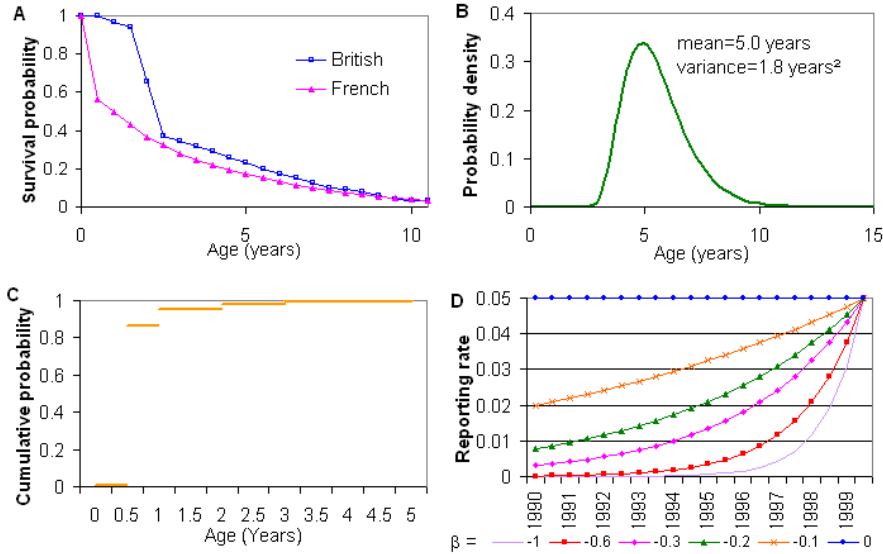


Figure 1. BSE epidemiological input data. (A) Estimated survival distributions of French (\blacktriangle) and British (\square) cattle (23). (B) Estimated probability density function of the BSE incubation period ($q = 1.667$; $p = 5$). (C) Estimated cumulative distribution function of cattle age at infection, in six classes (in years) [0–0.5], [0.5–1], [1–2], [2–3], [3–5], and [5–30]. (D) Time-dependent BSE case reporting function, assuming a 5% reporting probability in June 2000. In the sensitivity analysis, we considered β -values from 0 (\bullet) to -1 (---); $\beta = -0.6$ (\blacksquare) minimised the model-selection criterion.

therefore used age-dependent susceptibility and/or exposure to infection, as available data did not allow us to discriminate between the two.

In France, 49% of cattle are slaughtered before age one year (Fig. 1A, \blacktriangle). Thus, age at slaughter and natural mortality both need to be incorporated, as this might censor clinical onset in infected animals, or some animals could be slaughtered before being exposed to the infectious agent.

The sharp increase in BSE incidence when the first systematic screening program was instigated revealed the poor efficiency of passive surveillance; a time-dependent BSE case reporting function must thus be used. As only 20% of all BSE cases were identified by passive surveillance between July 2001 and June 2002, we

used an upper limit of 20% for the reporting probability in June 2000.

2.3. Generalised back-calculation method

The back-calculation method was extended to take into account the effect of age, using the method described by Becker and Marshner [7, 17], the cattle survival distribution, and a time-dependent probability of BSE reporting.

Let $N_{a,t}$ and $Y_{a,t}$ be the random numbers of new infected animals and new cases with age a at time t , and $E(N_{a,t})$, $E(Y_{a,t})$, their expectations. Assuming that the distribution incubation time has a density $f(t)$, that $S(a/a')$ represents the probability that an animal survives to age a from all causes of

mortality, knowing that it was alive at age a' (age at infection) and that $\Lambda(t)$ is a time-dependent probability that a given BSE case is actually reported at time t , the model becomes:

$$E_t(Y_{a,t}) = \int_0 E(N_{a-t+s,s})f(t-s)S(a/a-t+s)ds\Lambda(t).$$

The distribution incubation time was supposed to be independent on infection age and the survival distribution was supposed to be independent on time.

The incubation period was assumed to be gamma distributed, so the probability density function of the incubation period $f(t)$ was:

$$f(t) = \begin{cases} 0 & \forall t \leq 2 \\ \frac{q^p(t-2)^{p-1}\exp(-q(t-2))}{\Gamma(p)} & \forall t > 2. \end{cases}$$

In order to reproduce the observed time-lag of two years before any clinical cases are seen, we assumed that the probability of a BSE incubation period of two years or less was nil. The distribution mean was $(p/q+2)$ years and the distribution variance was p/q^2 .

The survival distribution (Fig. 1A, \blacktriangle) was estimated from three data sources: Office National Interprofessionnel des Viandes, de l'Élevage et de l'Aviculture (OFIVAL), Agence Française de Sécurité Sanitaire de l'Alimentation (AFSSA) and Direction Générale de l'Alimentation (DGAL). The OFIVAL report [29] gave the number of calves (aged between 0 and 6 months), and the number of young cattle (aged between 6 and 24 months), slaughtered in abattoirs in 2001. The DGAL dataset [18] gave the number of calves and young cattle sent for rendering in 2000. These last two data sources allowed us to estimate survival up to 24 months. The AFSSA dataset [1] gave the number of cattle aged over 24 months which were sent to abattoirs or rendering in

2001, allowing us to estimate the survival of cattle aged over 24 months. We derived conditional survival probabilities from this survival distribution. We considered survival given being alive at the time of infection, as most cattle die or are slaughtered before age one year in France. Thus, the probability of being alive at five years of age given being alive at one year age is not equal to the probability of being alive at five years age.

A logistic form was assumed for the time-dependent reporting function, starting in June 1990, with zero reporting before this date as there was no monitoring system:

$$\Lambda(t) = \begin{cases} \frac{\exp(\theta + \beta(\text{June2000} - t))}{1 + \exp(\theta + \beta(\text{June2000} - t))} & \forall t \geq 1990, \\ 0 & \forall t < 1990. \end{cases}$$

The logistic curve depended on two parameters, β the form parameter and θ the parameter determining the reporting probability in June 2000. Let $\Lambda(\text{June2000})$ be the probability of being reported in June 2000, then

$$\theta = \ln\left(\frac{\Lambda(\text{June2000})}{1 - \Lambda(\text{June2000})}\right).$$

The unknown time- and age-specific BSE infection numbers were modelled using the multiplicative model $E(N_{a,s}) = \alpha_a \lambda_s$; these parameters are defined except for a multiplicative constant; λ_s was the time-varying risk of feed-borne infection and α_a was the age-dependent susceptibility/exposure. However, we did not consider age-specific susceptibility/exposure but rather susceptibility/exposure per age class. In the absence of epidemiological data to suggest a parametric family, we did not specify a parametric form for the time-varying BSE-infection risk λ_s .

Under the assumption that the age- and time-specific new BSE-infected animal numbers, $N_{a,t}$, were independent Poisson variates then the age- and time-specific new clinical case numbers $Y_{a,t}$ were independent

Poisson variates. Then, we had the likelihood function corresponding to the age- and time-specific observed clinical BSE cases y_{at} :

$$L = L(\alpha, \lambda | y) = \prod_{t=1}^T \prod_{a=1}^A \frac{\mu_{at}^{y_{at}} \exp(-\mu_{at})}{y_{at}!}$$

where $\mu_{a,t} = E(Y_{a,t})$.

Non parametric maximum likelihood estimation to λ_s was implemented using the EM algorithm [15] to which we added a smoothing step (EMS algorithm [7]). The time-varying BSE-infection risk, λ_s , was estimated annually from 1980 to 1996. Years were defined so that, for example, 1980 consists of the period between 1 July 1980 and 30 June 1981. As we considered clinical BSE cases detected up to June 2000, we could not estimate the time-varying BSE-infection risk, or BSE infection numbers, beyond June 1997. Indeed, because of the long BSE incubation period there is little information contained in BSE incidence data about the numbers of animals infected most recently. The continuous estimates were obtained from the discrete estimates by linear interpolation.

The back-calculation method allows one to estimate the past time- and age-specific BSE infection number, $E(N_{as})$, from clinical BSE case data, $E(Y_{at})$, provided that other model parameters are known. However, the susceptibility/exposure at infection was unknown and the time-dependent reporting function and the incubation period density depended on unknown parameters. So we performed systematic sensitivity analyses for each unknown parameter.

2.4. Sensitivity analyses

We explored the sensitivity of the model results according to unknown parameter values.

We varied the mean incubation period distribution between 4 and 6 years and the variance between 1 and 3 years².

We fitted a flexible function to the time-dependent reporting function, dependent on two parameters. We considered values between 0 and -1 for the form parameter, β . This made it possible to explore a wide range of reporting forms, ranging from constant reporting throughout the epidemic ($\beta = 0$) to a reporting function with very low reporting probabilities in the early stages of the epidemic and a sudden increase in the recent past ($\beta = -1$). By varying the second parameter, θ , we varied the reporting probability in June 2000 between 5% and 20%.

A representative range of susceptibility/exposure forms was examined, such as constant exposure susceptibility/exposure, susceptibility/exposure decreasing with age, and no susceptibility/exposure except in the first six month of life. Also, we varied the number and spacing of the age class knots. We considered six-class susceptibility/exposure (in years): [0–0.5], [0.5–1], [1–2], [2–3], [3–5], [5–30], and compared them to five-class susceptibility/exposure: [0–1], [1–2], [2–3], [3–5], [5–30], and seven-class susceptibility/exposure: [0–0.5], [0.5–1], [1–2], [2–3], [3–5], [5–7], [7–30].

The best model was selected by using Akaike's Information Criterion (AIC) [11]: $AIC(model) = -2 \times \log(L) + 2 \times K$ where L is the model's likelihood and K is the number of estimated parameters. We considered the empiric rule of Burnham and Anderson [11], which retains a model if $(AIC(model) - \text{MinAIC}) \leq 2$ where MinAIC is the minimum AIC, i.e. the AIC of the best model.

All unknown parameters were selected to minimize the AIC. However, as all the reporting probabilities in June 2000 that we explored were compatible with a good fit (similar AIC), we needed external data to select among the hypotheses. Therefore, to establish the reporting probability in June 2000, so to determine the parameter θ , we compared annual predicted clinical BSE cases with observed clinical cases.

To determine precision, we used bootstrap [21] estimates considering that the

observed age- and year-specific incidence of BSE cases arose from a Poisson distribution. The 95% confidence interval for each parameter was obtained by excluding the 5% most extreme values obtained from 100 bootstrap samples.

2.5. Predictions

To obtain the number of new clinical cases at time t , we used the following function:

$$\int_0^A E(Y_{at}) da = \int_0^A \int_0^t E(N_{a-t+s,s}) f(t-s) S(a/a-t+s) ds \Lambda(t) da.$$

Up to June 1997 we used estimates of $E(N_{a,t})$ and beyond June 1997 we assumed that no new infections occurred. Regarding the time-dependent reporting function, beyond June 2000 we assumed that the reporting probability of clinical cases was 20%.

2.6. Number of late-stage BSE cases slaughtered for consumption

To compare exposure of the British and French populations to the BSE agent, we defined late-stage animals as animals slaughtered within 12 months of clinical onset, as in the British study [23]. From the estimated number of BSE-infected cattle, we ascertained by simulation the number of late-stage animals slaughtered for consumption. To each infected animal, we randomly assigned an age at infection, an incubation period, and a lifetime, given that the animal was alive at the age of infection. Bearing in mind mortality directly attributed to clinical cases, we imposed that lifetime ranges between age at infection and age at infection plus incubation period.

We thus obtained the number of BSE-infected cattle between times s and $s + \Delta$ aged between a and $a + \Delta$ at infection with

an incubation period between d and $d + \Delta$, and a lifespan between a' and $a' + \Delta$. We were thus able to deduce the number of infected cattle slaughtered between times t and $t + \Delta$ ($t = s + (a' - a)$), between x and $x + \Delta$ times before the clinical onset of BSE ($x = d - (a' - a)$), and aged between a' and $a' + \Delta$ at slaughter.

The method of back-calculation, the EMS algorithm and the simulations were implemented using computer programs written in C++ for this purpose.

As the likelihood is no longer maximised when the smoothing step is included in the EM algorithm, we used a convergence criterion based on the values of the parameter as Becker and Marshner [7].

3. RESULTS

The best model, according to Akaike's Information Criterion, suggests that the average BSE incubation period is five years (Fig. 1B) and that most infections occur between 6 and 12 months of age (Fig. 1C).

With reference to the form parameter of the reporting curve, $\beta = -0.6$ minimises the AIC, we also present results for $\beta = -0.5$ and $\beta = -0.7$ as they satisfy the empiric rule of Burnham and Anderson. To establish the reporting probability in June 2000, we compared annual predicted clinical BSE cases (Tabs. II and III) with observed clinical cases. Passive surveillance detected 134 clinical BSE cases between July 2000 and June 2001 and 60 clinical BSE cases between July 2001 and June 2002 (respectively 75 and 161 BSE cases were detected among cattle at risk). Table II shows short-term projections of the clinical BSE case incidence according to the form parameter and the level of the reporting curve in June 2000. Table III illustrates longer-term projections according to the reporting probability in June 2000, the form parameter β being fixed at -0.6 . Comparison of predicted cases with the 134 and 60 clinical cases detected in the periods from July 2000 to June 2001 and

Table II. Predicted incidence of clinical BSE cases in French cattle (with 95% bootstrap CIs) for the periods July 2000 to June 2001 (2000–2001) and July 2001 to June 2002 (2001–2002) according to the form parameter, β , and the reporting probability in June 2000 ($\Lambda(\text{June}2000)$). We assumed that no animals born after June 1997 became infected.

	Predicted incidence of clinical BSE cases (with 95% CI)					
	$\beta = -0.7$		$\beta = -0.6$		$\beta = -0.5$	
	2000–2001	2001–2002	2000–2001	2001–2002	2000–2001	2001–2002
$\Lambda(\text{June}2000) = 0.05$	139 [99–207]	69 [47–108]	132 [95–199]	67 [45–105]	127 [90–191]	64 [43–102]
$\Lambda(\text{June}2000) = 0.10$	69 [49–103]	34 [23–54]	66 [47–99]	33 [22–52]	63 [45–95]	32 [21–51]
$\Lambda(\text{June}2000) = 0.15$	45 [32–68]	23 [15–35]	43 [31–65]	22 [15–34]	41 [29–63]	21 [14–34]
$\Lambda(\text{June}2000) = 0.20$	33 [24–50]	17 [11–26]	32 [23–48]	16 [11–26]	31 [22–47]	16 [11–25]

Table III. Predicted annual incidence of asymptomatic and clinical BSE cases, (with 95% bootstrap CIs) according to the reporting probability in June 2000 ($\Lambda(\text{June}2000)$). We assumed that parameter β of the reporting curve was -0.6 and that no animals born after June 1997 became infected.

	Predicted annual incidence of asymptomatic and clinical BSE cases (with 95% CI)			
	$\Lambda(\text{June}2000) = 0.05$	$\Lambda(\text{June}2000) = 0.10$	$\Lambda(\text{June}2000) = 0.15$	$\Lambda(\text{June}2000) = 0.20$
July 2002/ June 2003	127 [82–205]	63 [40–102]	42 [27–68]	31[20–50]
July 2003/ June 2004	40 [25–66]	20 [12–33]	13 [8–22]	10[6–16]
July 2004/ June 2005	11 [6–18]	5 [3–9]	4 [2–6]	3 [2–4]
July 2005/ June 2006	2 [1–4]	1 [1–2]	1 [0–1]	1 [0–1]
July 2006/ June 2007	1 [0–1]	0 [0–0]	0 [0–0]	0 [0–0]

July 2001 to June 2002, respectively, reveals that the reporting probability in June 2000 was no higher than 10% (Tab. II). In addition, the comparison of annual predicted clinical or asymptomatic cases for the period July 2002 to June 2003 (Tab. III) with the 172 clinical or asymptomatic BSE cases recorded between July 2002 and June 2003 shows that the assumption of a reporting

probability of 10% or more in June 2000 would underestimate the true situation. Thereafter, we inferred that the best estimate of the reporting probability in June 2000 was 5% and that the form parameter of the reporting curve was -0.6 (Fig. 1D, ■).

Under the previous assumptions, we estimated that 301 200 (CI = [27 600–837 600]) cattle were infected by the BSE

Table IV. Estimated numbers of infections in French cattle (with 95% bootstrap CI) from June 1980 to June 1997 (**A**) and from June 1987 to June 1997 (**B**) according to the form parameter, β , and the reporting probability in June 2000 ($\Lambda(\text{June}2000)$).

	Estimated numbers of infections in French cattle (with 95% CI)		
	$\beta = -0.7$	$\beta = -0.6$	$\beta = -0.5$
(A)			
$\Lambda(\text{June}2000) = 0.05$	656 400 [41 600–1 872 800]	301 200 [27 600–837 600]	141 100 [18 800–377 200]
$\Lambda(\text{June}2000) = 0.10$	311 400 [20 000–888 000]	143 000 [13 300–397 300]	67 200 [9 100–179 200]
$\Lambda(\text{June}2000) = 0.15$	196 500 [12 700–560 000]	90 300 [8 500–250 800]	42 500 [5 800–113 200]
$\Lambda(\text{June}2000) = 0.20$	138 900 [9 100–395 700]	64 000 [6 100–177 300]	30 200 [4 200–80 200]
(B)			
$\Lambda(\text{June}2000) = 0.05$	78 900 [34 500–135 400]	51 300 [24 300–84 700]	34 200 [17 300–54 800]
$\Lambda(\text{June}2000) = 0.10$	37 700 [16 600–64 700]	24 600 [11 700–40 600]	16 500 [8 400–26 400]
$\Lambda(\text{June}2000) = 0.15$	24 000 [10 600–41 100]	15 700 [7 500–25 900]	10 600 [5 400–16 900]
$\Lambda(\text{June}2000) = 0.20$	17 100 [7 600–29 300]	11 300 [5 400–18 500]	7 600 [3 900–12 200]

agent since 1980 (Tab. IV(A)). Table IV shows estimates of BSE-infected cattle numbers according to the two parameters of the reporting function. It should be noted that these estimates are strongly dependent on reporting probabilities. Also, the under-reporting proportion was the parameter of the model with most influence on these estimates.

The confidence intervals (Fig. 2A, dotted lines) reflect the uncertainty in the estimated number of infections occurring during the 1980s. From 1987 onwards, estimates become more precise as the confidence interval amplitude is lower. The infection number rises between 1987 and 1990, then falls between 1990 and 1992; 1992 to 1995 saw another rise but smaller than the previous one and, finally, we observed a new fall after 1995. Between July 1987 and June

1997, an estimated 51 300 (CI = [24 300–84 700]) cattle were infected (Tab. IV(B)). Very similar estimates were obtained when the epidemic start date was assumed to be 1987 (results not shown).

From these infection number estimates, we ascertained the number of late-stage animals slaughtered for consumption, i.e. animals slaughtered in the late stage of incubation when it is hypothesized that infected tissues are infectious. Between July 1980 and June 1997, we estimated that 301 200 (CI = [27 600–837 600]) cattle were infected by the BSE agent. Only 47 300 (CI = [3 000–135 000]) late-stage animals were slaughtered for consumption before the French specified-bovine-offal ban in June 1996 and 1 500 (CI = [900–2 300]) between July 1996 and June 2000. If we restrict the study interval from July 1987 to June 1997,

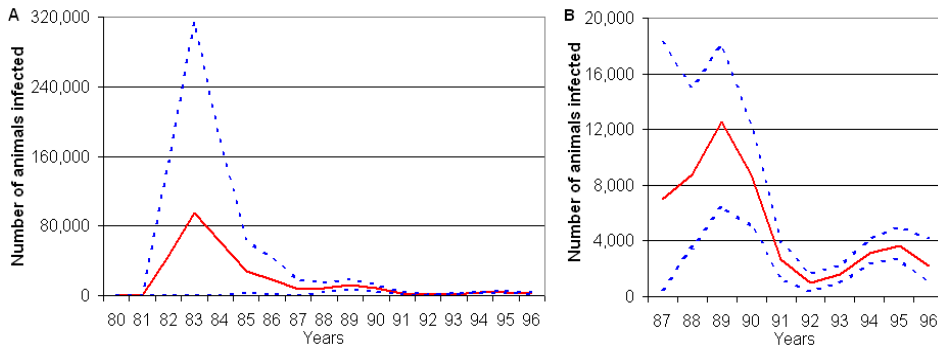


Figure 2. Estimated (—) annual incidence of BSE infection since 1980 (A) and since 1987, using different scales to visualize the dynamics of the epidemic (B), assuming a reporting probability of 5% in June 2000 and parameter β of the reporting curve = -0.6 . Assuming a reporting probability of 10% in June 2000, the amplitude of the curve changes but its shape is unaffected. The dotted lines (---) represent 95% bootstrap confidence intervals.

we estimated that 51 300 (CI = [24 300–84 700]) cattle were infected. In this case, only 6 100 (CI = [2 500–10 600]) late-stage animals were slaughtered for consumption between July 1987 and June 1996 and 1 500 (CI = [900–2 300]) between July 1996 and June 2000.

With regard to predictions, under the model constraint that no animals born after June 1997 became infected, all our fitted models predict that BSE cases will continue to be diagnosed at least until 2006 (Tab. III).

4. DISCUSSION

The agreement of our results with those resulting from modelling of the British BSE epidemic [6, 23], with respect to the distribution of the BSE incubation period and age at infection, even though the BSE epidemic dynamics and the model used to estimate the parameters were different in France and the United Kingdom, suggests they are robust. As Anderson has already shown that, whatever the distribution used (Weibull, Gamma, etc.), the estimated mean was always in the range 4.5–5.5, and as we found a similar result with a Gamma distribution, we decided not to explore the

impact of the distribution type. The estimated infection age distribution rules out calf milk substitutes [3] as a major source of BSE infection. Indeed, this distribution suggests that no infections occur before six months of age, whereas calf milk substitutes are given before this age. In addition, susceptibility after age one year was not negligible and must therefore be considered when designing targeted culling policies. Also, the age-risk function form that we derived resembles that postulated for vCJD [31], namely, no susceptibility (or exposure) in the first months (or years) of life; high susceptibility (or exposure) during young age; and then an abrupt decline in susceptibility (or exposure), suggesting that it could be a feature of both BSE and its human variant.

Our results show that the proportion of underreporting is the most influential parameter in the model and that there was substantial underreporting across the BSE epidemic until rapid tests were introduced. Indeed, comparison of the annual incidence prediction with the number of observed cases suggests that the reporting probability in June 2000 was no higher than 5%. A parametric function for the time-dependent reporting function is a strong assumption.

However, in the absence of independent data on reporting probabilities it is not possible to reliably estimate reporting non-parametrically. Nevertheless, we chose an extremely flexible function. Indeed, we fitted a wide range of reporting forms, ranging from constant reporting throughout the epidemic to a reporting function with very low reporting rates in the early stages of the epidemic and a sudden increase in the recent past. With reference to the reporting probability in June 2000, the value of 5% was far lower than that assumed in previous models [19, 20] but is consistent with the observed rate of 20% for the period from July 2001 to June 2002. This value is also consistent with an index evaluating the strength of BSE clinical surveillance, namely the ratio of negative clinical suspicions of BSE reported by veterinarians to the adult cattle population. Between 1990 and 1999, the average number of negative suspicions was 10.7 per million adult cows per year, then there was a sharp increase in 2000 to about 80 negative suspicions per million adult cows per year [14]. These numbers can be compared to the Office International des Épizooties recommendations for effective surveillance of BSE, which are to carry out a minimum of 100 annual investigations of animals showing clinical signs compatible with BSE per million cattle over 30 months of age. This is ten times higher than the French data during the period from 1990 to 1999, which indicates a lack of BSE surveillance in that period and thus points in the same direction as our results.

The confidence intervals of the estimated total number of infections in cattle born between mid-1987 and mid-1997 show less variability than estimates for the 1980s. From 1987 onwards, the epidemic pattern was consistent with the control measures adopted to prevent the BSE epidemic (Fig. 2B). Imports of British MBM increased strongly in the late 1980s, possibly explaining the rise in the number of infections between 1987 and 1990. Initial control measures, such as the French embargo

on British MBM (August 1989), and the embargo on live cattle and the ban of MBM in cattle feed (September 1990), could explain the fall observed between 1990 and 1992. Feed cross-contamination and recycling of infectious material within the feed industry may explain the rise observed between 1992 and 1995. It is too early to judge the effectiveness of measures taken in 1994 (extension of the MBM ban to ruminant feed) and 1996 (specified-offal ban), based on data reported up to June 2000.

Our estimates are different from those recently published by Donnelly [19], probably owing to differences in the assumptions and data used. Indeed, in her analysis, Donnelly considered clinical cases detected by passive surveillance up to June 2001; she thus took into account the 134 BSE cases detected between July 2000 and June 2001 (103 BSE cases were detected between 1991 and June 2000). She assumed a continuous trend in monitoring efficiency, despite biases induced by the introduction of active surveillance in mid-2000 and despite the fact that 179 000 cattle over 30 months of age were destroyed between January and June 2001 without being tested. Therefore, specific developments of the back-calculation method will be necessary to incorporate the additional cases detected after the outset of the targeted screening program. Also, these developments should take into account the heterogeneity of BSE exposure related to breeding practices. We could not take into account this heterogeneity as almost all cases considered in this analysis were bred in the west of France. Nevertheless, the accumulation of additional years of data, even with perfect reporting of all cases, would not substantially reduce the uncertainty about the early trends in incidence of BSE infection. In addition, Donnelly assumed complete notification of BSE cases from 2001 onwards, whereas passive surveillance only detected 20% of BSE cases between July 2000 and June 2001. This assumption implies a major underestimation of the BSE case number.

Comparison of estimated survival distributions (Fig. 1A) between British (\square) and French (\blacktriangle) cattle suggests that French cattle have a shorter lifespan. Donnelly's models of the French BSE epidemic did not take this specificity into account. Indeed, she assumed that the "French cattle" survival up to 2.5 years of age was equal to that in the British cattle, and survival beyond this age was estimated from data on a single French cow herd (\square). Even if survivorship to the age classes with most cases of clinical BSE (4 to 7 years) looks quite similar, the use of Donnelly's survival figures does not yield the same BSE infection numbers. Indeed, as almost all cattle are infected before one year of age and as almost all British cattle survive until this age, the estimated BSE infection number will be higher using Donnelly's survival rates.

With regard to predictions, all our fitted models predict that BSE cases will continue to be diagnosed at least until 2006. These predictions are a lower bound as they were obtained under the model constraint that no infections occurred after June 1997. However, as of 8th January 2004, 26 BSE cases have already been reported in cattle born after that date [2]. These cases are probably due to cross-contamination between ruminant and not-ruminant feed, as the MBM ban was only extended to all animal species in November 2000. Hence, BSE infections are likely to have occurred until at least this date. However, the comparison of our predictions with observed clinical cases will allow us to judge the effectiveness of measures taken in 1994 (extension of the MBM ban to ruminant feed) and 1996 (specified-offal ban). Updated back-calculation will also be necessary to obtain updated projections of the BSE incidence, which will allow the impact of potential changes to current control measures to be assessed.

Between July 1980 and June 1997, we estimated that 301 200 (CI = [27 600–837 600]) cattle were infected by the BSE agent. Only 47 300 (CI = [3 000–135 000]) late-stage animals were slaughtered for

consumption before the French specified-bovine-offal ban in June 1996, and 1 500 (CI = [900–2 300]) between July 1996 and June 2000. If we restrict the study interval from July 1987 to June 1997, an estimated 51 300 (CI = [24 300–84 700]) cattle were infected. In this case, only 6 100 (CI = [2 500–10 600]) late-stage animals were slaughtered for consumption between July 1987 and June 1996 and 1 500 (CI = [900–2 300]) between July 1996 and June 2000.

In their first study of the British BSE epidemic [23], Anderson and his team estimated that 766 000 (CI = [745 000–799 000]) British cattle had been infected by BSE. Among these, only 8 000 late-stage animals were slaughtered before November 1989 (date of the British specified-offal ban) and 43 500 in the period 1990–1995. In their last study [22], they estimated that 4 000 000 animals were BSE-infected but the number of late-stage animals slaughtered for consumption was not specified. In our study, we estimated that 301 200 (CI = [27 600–837 600]) French cattle were infected by the BSE agent. Among these, 47 300 (CI = [3 000–135 000]) late-stage animals were slaughtered for consumption before the French specified-offal ban in June 1996 and 1 500 (CI = [900–2 300]) between July 1996 and June 2000. If we restrict the study interval from July 1987 to June 1997, an estimated 51 300 (CI = [24 300–84 700]) French cattle were infected. In this case, only 6 100 (CI = [2 500–10 600]) late-stage animals were slaughtered for consumption between July 1987 and June 1996 and 1 500 (CI = [900–2 300]) between July 1996 and June 2000.

On the sole basis of raw estimates of late-stage animals in France and the United Kingdom, exposure of the French population to the BSE agent via French bovine products was not negligible compared to exposure of the French population via the imports of British bovine products. In addition, the specified-offal ban on all cattle entering the human food chain was only instigated in June 1996 in France, compared

to November 1989 in the United Kingdom. Consequently, French population exposure to the BSE epidemic in French cattle lasted until June 1996, and there was a shift of the temporal pattern of exposure to infectious animals in France and the United Kingdom. Nevertheless, possible differences between these two countries in exposure to high-risk bovine tissues (because of eating habits or risk reduction measures) should be carefully considered before reaching conclusions. Further work will compare global exposure to the BSE agent in the French population with that in the British population, taking these differences into account.

Finally, modelling indicates substantial under-reporting until active surveillance was introduced. This could explain why more cases of BSE were reported among cattle born after the MBM ban than before it. Because of this under-reporting, the French BSE epidemic in the late 1980s was completely undetected, and only the second wave, after 1990, was observed. Also, exposure of the French population to the BSE agent via French bovine products was not negligible compared to exposure of the French population via the imports of British bovine products.

ACKNOWLEDGEMENTS

We thank Sylvie Deffic-Burban for discussions on back-calculation methods, and Alain-Jacques Valleron for helpful comments on the manuscript. This work was funded by a grant from GIS prion.

REFERENCES

- [1] Agence Française de Sécurité Sanitaire de l'Alimentation (AFSSA), Épidémiosurveillance de l'ESB en France. Tableau de bord au 28/02/02, in: AFSSA Documents.
- [2] AFSSA, Liste des cas ESB en France au 08/01/04, in: AFSSA Documents (9 January 2004) <http://www.afssa.fr/ftp/basedoc/Cas1ESB040108.pdf> [consulted 26 January 2004].
- [3] AFSSA, Farines et graisses d'origine animale, in: AFSSA Documents http://www.afssa.fr/dossiers/index.asp?id_dossier=4029 [consulted 22 September 2003].
- [4] Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), Révision des mesures de réduction du risque de transmission des ESST par les produits sanguins, in: AFSAPS Documents <http://agmed.sante.gouv.fr/pdf/6/nvmcj.pdf> [consulted 22 September 2003].
- [5] Alperovitch A., Will R.G., Predicting the size of the vCJD epidemic in France, *C. R. Acad. Sci. III-Vie* 325 (2002) 33–36.
- [6] Anderson R.M., Donnelly C.A., Ferguson N.M., Woolhouse M.E., Watt C.J., Udy H.J., MaWhinney S., Dunstan S.P., Southwood T.R., Wilesmith J.W., Ryan J.B., Hoinville L.J., Hillerton J.E., Austin A.R., Wells G.A., Transmission dynamics and epidemiology of BSE in British cattle, *Nature* 382 (1996) 779–788.
- [7] Becker N.G., Marschner I.C., A method for estimating the age-specific relative risk of HIV infection AIDS incidence data, *Biometrika* 80 (1993) 165–178.
- [8] Bizet J., Dériot G., Farines : l'alimentation animale au cœur de la sécurité sanitaire Tome I, in: Senat information reports 2000–2001 <http://www.senat.fr/rap/r00-321-1/r00-321-1.html> [consulted 22 September 2003].
- [9] Brookmeyer R., Gail M.H., A method for obtaining short-term projections and lower bounds on the size of the AIDS epidemic, *J. Am. Stat. Assoc.* 83 (1988) 301–308.
- [10] Bruce M.E., Will R.G., Ironside J.W., McConnell I., Drummond D., Suttle A., McCardle L., Chree A., Hope J., Birkett C., Cousens S., Fraser H., Bostock C.J., Transmissions to mice indicate that "new variant" CJD is caused by the BSE agent, *Nature* 389 (1997) 498–501.
- [11] Burnham K., Anderson D., Information theory and Log-likelihood: Akaike's Information Criterion, in: Model selection and inference: A practical information-Theoretic approach, Springer-Verlag, New York, 1998, pp. 43–48.
- [12] Calavas D., Ducrot C., Programme pilote de surveillance de l'ESB. Enquête clinique retrospective concernant les bovins positifs, in: Afssa documents (22 may 2000) <http://www.afssa.fr/ftp/basedoc/annexe2esb30mai.pdf> (AFSSA, Maison-Alfort, 2001).
- [13] Cohen C.H., Valleron A.J., When did bovine spongiform encephalopathy (BSE) start? Implications on the prediction of a new variant of Creutzfeldt-Jakob disease (nvCJD) epidemic, *Int. J. Epidemiol.* 28 (1999) 526–531.
- [14] Cuenot M., Calavas D., Abrial D., Gasqui P., Cazeau G., Ducrot C., Temporal and spatial

- patterns of the clinical surveillance of BSE in France, analysed from January 1991 to May 2002 through a vigilance index, *Vet. Res.* 34 (2003) 261–272.
- [15] Dempster A.P., Laird N.M., Rubin D.B., Maximum likelihood from incomplete data via the EM algorithm (with discussion), *J. R. Stat. Soc. B* 39 (1977) 1–38.
- [16] Department of health, monthly Creutzfeldt Jakob Disease statistics, in: What's New (5 January 2004) <http://www.info.doh.gov.uk/doh/intpress.nsf/page/2004-0004?OpenDocument> [consulted 26 January 2004].
- [17] Deuffic S., Costagliola D., Is the AIDS incubation time changing? A back-calculation approach, *Stat. Med.* 18 (1999) 1031–1047.
- [18] DGAL, Bilan du Service public de l'équarrissage de l'année, 2000.
- [19] Donnelly C.A., BSE in France: epidemiological analysis and predictions, *C. R. Acad. Sci. III-Vie* 325 (2002) 793–806.
- [20] Donnelly C.A., Likely size of the French BSE epidemic, *Nature* 408 (2000) 787–788.
- [21] Efron B., The jackknife, the bootstrap, and other resampling plans, SIAM, Philadelphia, 1982.
- [22] Ferguson N.M., Donnelly C.A., Assessment of the risk posed by bovine spongiform encephalopathy in cattle in Great Britain and the impact of potential changes to current control measures, *Proc. R. Soc. Lond. B Biol. Sci.* 270 (2003) 1579–1584.
- [23] Ferguson N.M., Donnelly C.A., Woolhouse M.E.J., Anderson R.M., The epidemiology of BSE in cattle herds in Great Britain. II. Model construction and analysis of transmission dynamics, *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 352 (1997) 803–838.
- [24] Ghani A.C., Donnelly C.A., Ferguson N.M., Anderson R.M., The transmission dynamics of BSE and vCJD, *C. R. Acad. Sci. III-Vie* 325 (2002) 37–47.
- [25] Ghani A.C., Ferguson N.M., Donnelly C.A., Anderson R.M., Factors determining the pattern of the variant Creutzfeldt-Jakob disease (vCJD) epidemic in the UK, *Proc. R. Soc. Lond. B Biol. Sci.* 270 (2003) 689–698.
- [26] Hill A.F., Desbruslais M., Joiner S., Sidle K.C.L., Gowland O., Collinge J., The same prion causes vCJD and BSE, *Nature* 389 (1997) 448–450.
- [27] Huillard d'Aignaux J.N., Cousens S.N., Smith P.G., Predictability of the UK variant Creutzfeldt-Jakob Disease epidemic, *Science* 294 (2001) 1729–1731.
- [28] Institut de veille sanitaire, Nombre de cas de maladie de Creutzfeldt-Jakob, in: Surveillance, Données du Réseau national de surveillance de la Maladie de Creutzfeldt-Jakob et maladies apparentées (2 September 2003) http://www.invs.sante.fr/display/?doc=publications/mcj/donnees_mcj.html [consulted 22 September 2003].
- [29] Office national Interprofessionnel des Vian-des, de l'Élevage et de l'Aviculture, cahier statistique bovin n° 36, in: OFIVAL statistic <http://www.ofival.fr/statistiques/statistique1.htm> [consulted in January 2003].
- [30] The European Union, Report on the assessment of the Geographical BSE-Risk of France (July 2000) http://europa.eu.int/comm/food/fs/sc/ssc/out119_en.pdf [consulted 22 September 2003].
- [31] 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.
- [32] Wilesmith J.D., Wells G.A.H., Ryan J.B.M., Gavier-Widen D., Simmons M.M., A cohort study to examine maternally-associated risk factors for bovine spongiform encephalopathy, *Vet. Rec.* 141 (1997) 239–243.
- [33] Will R.G., Ironside J.W., Zeidler M., Cousens S.N., Estibeiro K., Alperovitch A., Poser S., Pocchiari M., Hofman A., Smith P.G., A new variant of Creutzfeldt-Jakob disease in the UK, *Lancet* 347 (1996) 921–925.