AGENCE FRANÇAISE DE SÉCURITÉ SANITAIRE DES ALIMENTS

Annex

Analysis of the BSE epidemiological situation in France, in terms of the control measures taken in November 2000

The question posed in Afssa mandate No. 2006-SA-0329 on assessing the effectiveness of the measures taken in November 2000 to control the BSE epidemic was examined by the epidemiology of animal TSEs working group at meetings on 10 January and 7 February 2007.

1. <u>Context of the request for an opinion and indication of the limits of the field of the expert review</u>

The Agence française de sécurité sanitaire (Afssa) [French Food Safety Agency] decided to carry out an assessment of the effectiveness of the measures taken in November 2000 to control the BSE epidemic:

" With the appearance of the BSE epidemic in Great Britain and demonstration of the central role played by meat and bone meal in the spread of the disease, control measures were put in place in France and Europe with the aim of preventing ruminant contamination and limiting the exposure of the human population.

In France, the ban on meat and bone meal in cattle feed dates from 1990 and was extended to all ruminants in 1994. These measures were strengthened in 1996, in the wake of the first "mad cow" crisis associated with the demonstration of the first human cases of variant Creutzfeldt-Jakob disease (vCJD), at the same time as the regulations on the removal of specified risk materials (SRM) were put in place. Other measures, including restrictions on the use of animal fats and the putting in place of systematic testing, completed this provision. Nevertheless, a large number of cases of BSE were recorded in cattle born after August 1996 (over 100 cases born after the reinforced ban [BARB] have been recorded to date), with over 20 cases born after 1 January 1998, demonstrating that the system was not totally effective.

At the end of the year 2000, following the second "mad cow" crisis, the ban on meat and bone meal was extended to all food-producing livestock and at the same time a system of systematic active surveillance was put in place at abattoirs and rendering plants for cattle aged over 30 months[1]. To date, no cases of BSE have been recorded in cattle born after 1 January 2001. Consequently, almost 6 years after these measures were put in place, there are now legitimate grounds for

[1] Exhaustive screening was implemented in January 2001 for cattle aged over 30 months. This age limit was lowered to 24 months in July 2001 and raised again to 30 months in July 2004.

a quantitative re-assessment of their effectiveness and for an examination of the possibility of eradicating BSE from France. In several opinions issued in recent years the Scientific Panel on TSEs has stated that a report on this point would be necessary, though premature before the end of 2006.[2]

Consequently, I would like the CES ESST to carry out a quantitative assessment of the effectiveness of the safety measures taken at the end of the year 2000 and to use this assessment as the basis for issuing recommendations on the measures to be taken to guarantee the future food safety of products or by-products from these animals.."

In the assessment conducted below, we have deemed that cases of BSE detected in cattle are all attributable to dietary exposure to contaminated feed. The demonstration of this feed's role or the suspicion of its role is the reason why control measures were put in place and implemented successively, with the most recent measures in November 2000 banning meat and bone meal (MBM) and certain animal fats from all feed destined for farm livestock.

Nonetheless the possibility must be considered of the existence of a spontaneous form of BSE which could not be combated by the current controls. The issue of atypical forms of BSE, whose aetiology is still not known (same risk factors as classic BSE, other risk factors, even a spontaneous form of TSE) also remains to be answered. The discovery of cases of this type (spontaneous forms, atypical forms) does not call into question the effectiveness of the current control system as regards "classic" BSE but does raise the issue of the existence of low levels of cases of TSE in cattle and the consequences this could have for public health. The issue also arises of the possible difficulty of distinguishing spontaneous cases from "classic" cases from the tail end of the epidemic.

2. Method

The working group focussed on providing a response to the first question, concerning *the quantitative assessment of the safety measures taken at the end of 2000*. It did not, however, address the second, concerning *measures to be recommended to guarantee the future food safety of products or by-products from these animals*, considering that this was the remit of the CES.

The expert review consisted of analysing the data from the active BSE surveillance programmes carried out in France since 2001, a modelling study[3] designed to produce a prospective estimate of the effectiveness of the control measures ordered in November 2000 and the scientific literature available at the present time.

[2] Opinion of the CES ESST on surveillance of the BSE epidemic in France, dated 30 June 2004.

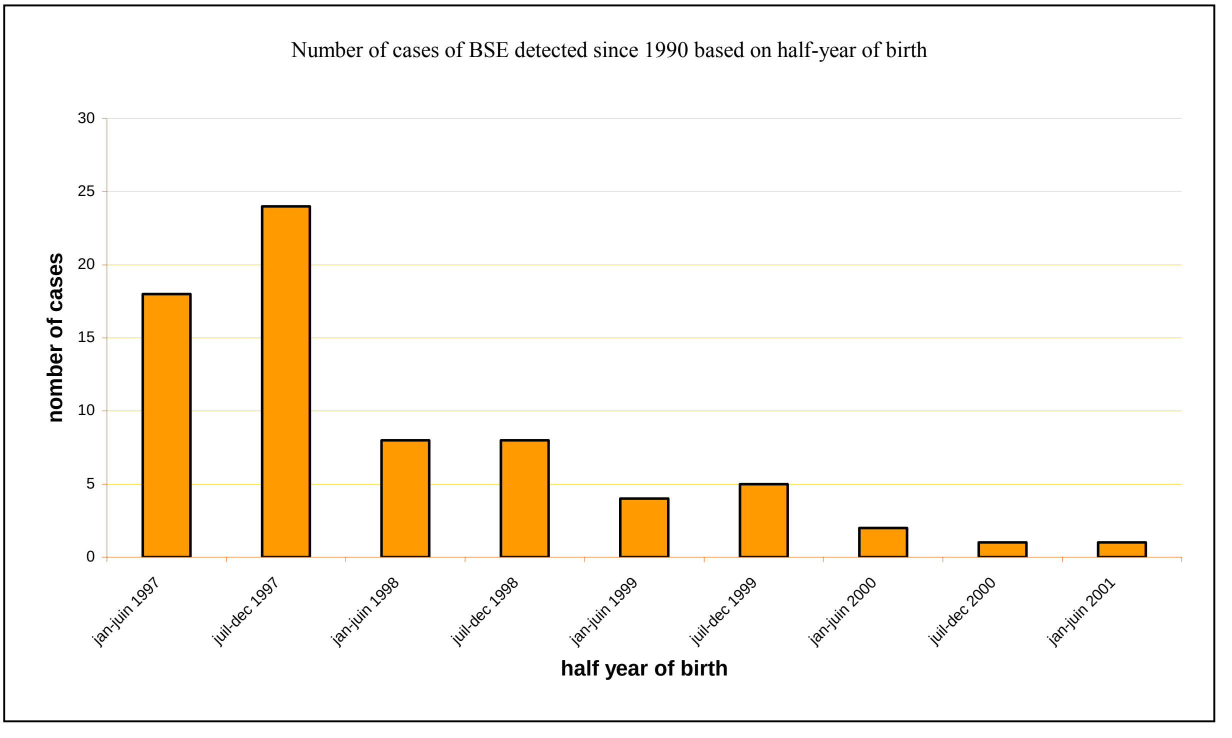
[3] Complementary approach of data analysis and modelling to estimate the pattern of the BSE epidemic: the example of France, D. Calavas, V. Supervie, E. Morignat, D. Costagliola & C. Ducrot, 2006, Risk Analysis, in press

3. Expert review

3.1 General trend of the BSE epidemic in France

The distribution of birth years of cases of BSE detected in France (cf. Figure 1) shows a marked decrease in the number of cases for the most recent birth years (1998: 16 cases; 1999: 9 cases; 2000: 3 cases; 2001[4]: 1 case, born on 1 January[5]), which can be partly explained by the distribution of incubation period.

Figure 1: Distribution of birth years of cases of BSE detected in France, for cases born since 1997 (as at 1 January 2007)



It should be noted that the four cases detected in animals born in 2000 and 2001 were found at a younger age than the estimated mean incubation period.
As regards the age of the youngest case detected in each birth cohort (cf. first graph in Annex 1):

- up to the January-July 1995 cohort, surveillance was not exhaustive; therefore this indicator cannot be interpreted (for example only one case detected aged over 18 years for the January-July 86 cohort);
- after the July-December 1995 cohort, subject to exhaustive screening at death, no obvious trend can be identified from the age of the youngest case detected.

[4] 2 cases detected in rendering plants born in February 2000 and detected at 5 years 5 months and 5 years 8 months, 1 case detected in an abattoir and detected at 5 years 2 months.
[5] Case detected on 30 January 2006 in an abattoir at the age of 5 years 1 month.

The various analyses carried out to study the trend of the epidemic[6] indicate that the decrease in the exposure of the cattle population to the BSE agent began with the 95-96 cohort.

Moreover, the most recent models[7] indicate that exposure was considerably reduced for the 98-99 and subsequent cohorts (cf. Table I): for example, between the 94-95 and 98-99 cohorts, this risk was divided by 50 for dairy cattle and by 25 for suckler cattle. Despite the low number of observations (number of cases and animals tested) among the most recent cohorts, the conclusion can be drawn that there was a massive reduction in the risk of infection after the 94-95 cohort; however, the overlapping of the confidence intervals for the most recent cohorts (from the 98-99 cohort onwards) does not permit the change in risk to be quantified after that date.

Whatever the case, it should be remembered that the 2000 measures were taken in a context in which exposure had fallen very significantly since the mid 1990s.

Table I. Adjusted odds ratio and 95% confidence intervals (CI) based on birth cohorts (significant odds ratios in bold type). (extract from the model by Carole Sala).

(a) Dairy cattle

Birth cohort	Odds ratio	95% CI
88/89	0.55	0.04-8.05
89/90	0.24	0.03-2.28
90/91	0.33	0.09-1.26
91/92	**0.21**	0.06-0.73
92/93	**0.53**	0.28-0.98
93/94	0.90	0.65-1.25
94/95	1.00	Reference cohort
95/96	**0.52**	0.41-0.65
96/97	**0.09**	0.07-0.14
97/98	**0.04**	0.03-0.07
98/99	**0.02**	0.01-0.04
99/00	**0.01**	0.00-0.04
00/01	**0.01**	0.00-0.07

(b) Suckler cattle

Birth cohort	Odds ratio	95% CI
88/89	**0.06**	0.00-0.85
89/90	**0.11**	0.01-0.84
90/91	**0.07**	0.01-0.65

[6] Supervie V., Costagliola D. (2004). The unrecognised French BSE epidemic. Veterinary Research, **35**, 349-362.
La Bonnardière C., Calavas D., Abrial D., Morignat E., Ducrot C. (2004). Estimating the trend of the French BSE epidemic over six birth cohorts through the analysis of the abattoir screening in 2001 and 2002. Veterinary Research, **35**, 299-308.
Morignat E., Ducrot C., Roy P., Cohen C., Calavas D. (2004). Prevalence of BSE in Cattle found dead, euthanased or emergency slaughtered on farms in western France in 2000, 2001 and 20002. The Veterinary Record, **155**, 481-486.
[7] Sala C., Morignat E., Roy P., Ducrot C., Calavas D. (2006). Seasonality of exposure of cattle to BSE in France. In Prion 2006 - Strategies, advances and trends towards protection of society, Torino - Italy, Proceedings, 117 (RA-10).

91/92	**0.26**	0.08-0.88
92/93	0.54	0.25-1.18
93/94	0.81	0.47-1.39
94/95	1.00	Reference cohort
95/96	**0.50**	0.32-0.78
96/97	**0.11**	0.05-0.22
97/98	**0.11**	0.05-0.24
98/99	**0.04**	0.01-0.14
99/00	**0.02**	0.00-0.18
00/01	0.00	0.00-(+∞)

3.2 Age at infection and analysis of the most recent birth cohorts

To date, age at infection has only been estimated by modelling. According to the models, the preferential period of infection is between 0 and 6 months[8], or between 6 and 12 months[9]. It should be noted that this difference may be attributable to different epidemiological profiles in the United Kingdom and France, for example the type of feed used, the age at which the contaminated feed was fed, the infectious load, etc.

Even if one considers that the first year of life is when the risk is greatest, the relative uncertainty regarding age at infection would result in a similar uncertainty in estimating the effectiveness of the measures taken on a given date.

To summarise, 7 and 6 years after the cohorts born in 1999 and 2000, only 9 and 3 cases respectively have been identified, even with exhaustive surveillance. Based on the fact that the detection peak for these cases is between 6 and 8 years and based on the curves from the models, to date (cf. annex, page 18, figure 4), of the order of half the detectable animals infected in the 1999 cohort and of the order of one animal in six from the 2000 cohort (with one year less since birth) must have been recorded. Analysis of the surveillance data (cf. pages 11 and 13) shows that with 7 and 6 years elapsed respectively, of the order of three-quarters of the detectable infected animals in the 1999 cohort and half the animals from the 2000 cohort should have been detected. If one then also introduces the fact that only one positive animal out of 3 to 6 infected animals is detected, due to culling and deaths prior to the appearance of positive signs in the brain, a maximum of one hundred animals (or less than half based on less conservative observations) in 1999 and a similar number in 2000 could have been infected in France. This is consistent with the rapid decrease in frequency of infection since the cohort born in 1994.

The most recent retrospectively calculated model[10] using the data from exhaustive screening (July 2001 – June 2004), concludes, based on the assumption that contamination ceased from June 2001, that infection began to decrease in 1995 and there were no infections in 2000[11].

[8] Arnold M. E., Wilesmith J. W. (2004). Estimation of the age-dependent risk of infection to BSE of dairy cattle in Great Britain. Preventive Veterinary Medicine, **66**, 1-4, 35-47.

[9] Supervie V., Costagliola D. (2004). The unrecognised French BSE epidemic. Veterinary Research, 35, 349-362.

[10] SupervieV., Costagliola D. (2007). Estimating incidence of the French BSE infection using a joint analysis of both asymptomatic and clinical BSE surveillance data, Mathematical Biosciences (in press)

3.3 Date of actual implementation of the 2000 measures

Since no feed recall was organised when the 2000 measures were put in place (source: DGAl), these measures did not fully take effect until later. In one of the mandates received by Afssa, the DGAL (Direction Générale de l'Alimentation (Directorate General for Food)) gave the end of 2001 as the date to be used as the actual implementation date of the 2000 measures. This arbitrary period was determined based on a very wide safety margin. In effect, roughly speaking, feed supplied in bags can generally be stored by the manufacturers for 3 to 4 months, but is consumed rapidly once on the holding; as regards feed in bulk, this is manufactured to order when a delivery is due and can generally be stored for 3 to 4 months on the holding. Therefore, in view of the fact that the date to be used for the actual implementation of the 2000 measures has a major impact on the reply to the question asked, a more reasonable period of 6 months rather than one year was used in the reply to the mandate, resulting in an implementation date for the measure of mid-2001. This approach is made all the more logical by the fact that we now know, with hindsight, that the risk of infection had already been falling fast for five years at the point when the measures were put in place at the end of the year 2000.

3.4. Probability of detection over time based on the number of animals infected

Another way of examining the question regarding the effectiveness of the 2000 measures used a model of the probability of detecting at least one positive over time, based on the number of animals infected. To do this we used an updated version of the approach used in 2004[12].

The key points of this approach are as follows (see Annex 2 for more details):

1. using an arbitrary number of animals infected during a short period of time (1, 10, 100, 1000);
2. using the parameters estimated for the models of the BSE epidemic in France (distribution of age at infection, distribution of incubation period) and the survival curve for the animals (based on the mortality and slaughter of adult animals);
3. an estimate is made based on 1 and 2, using binomial distribution, of the probability of detecting at least one positive animal after a certain period of time after infection (from 3 to 15 years in ½ years).

The fact that the simulation process uses the date of infection and not the date of birth complicates the usefulness of this study for the reply to the question asked, given the estimated variability of age at infection. It would have been preferable to have a table based on dates of birth rather than dates of infection: however, this would greatly complicate the model which must include the distribution of birth dates of animals kept for breeding, a distribution of age at infection, as this takes account of probable seasonal variations in farm management practice.

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[11] The upper limit of the CI of the prevalence estimated by the model for 2000 does not include the number of cases observed.

[12] Epidemiology of TSEs working group report in response to the mandate issued by AFSSA on 11 March 2004: Calavas D., Costagliola D., Ducrot C. (2004). Suivi de l'épizootie d'ESB en France, 12pp.

If one accepts the situation of an actual implementation of the measures on 1 July 2001, on 1 January 2007 one would have five and a half years of retrospection from that date.

The examination was conducted on the basis that infections could have occurred after that date of 1 July 2001 (for example during the half-year July-December 2001). In view of the fact that the great majority of animals are contaminated at between 6 months and 1 year, the animals principally concerned by this absence of controls would be those born between July 2000 and July 2001 (cf. Figure 2). Nevertheless, some of these animals, in this case those born in the second half of 2000, could also have been infected before July 2001. To restrict the calculation to those likely to have been contaminated after the date selected (1 July 2001), we only considered animals born during the first half of 2001. It should therefore be noted that the case born most recently (case born on 1 January 2001 and detected on 30 January 2006, so relatively young at 5 years 1 month) is at the extreme end of the category concerned, unless other hypotheses can be put forward for its contamination.

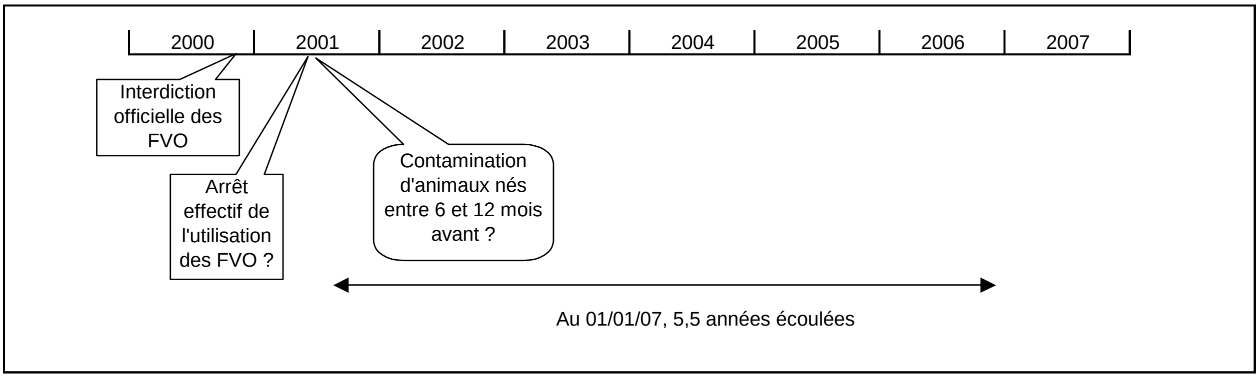


Figure 2: Situation in which the November 2000 measures only took effect at the end of 2001.

If however, this case is ignored, then using the model one can estimate, based on a period of five and a half years, that there is (Table II of Annex 2):

- 100% probability that the number of animals infected after 1 July 2001 is less than 1000;
- 89% probability that the number of animals infected after 1 July 2001 is less than 100.

With 6 months' additional retrospection, so working from June 2007, assuming that no case born after January 2001 is detected, the probability that the number of animals infected after 1 July 2001 would be less than 100 increases to 98.7 %.

3.5. Cases of atypical BSE

Cases of atypical BSE have recently been described in France, as well as in other countries in Europe and North America. In France, 13 cases of atypical BSE have been detected to date[13]. Typing of BSE cases has only been exhaustive in France since 2003. Atypical cases are very rare, but given the defects in surveillance prior to mid-2001, the higher age of these cases (to date over 7.5 years), and therefore the lack of retrospection at the present time, it is

[13] Type H: 2000: 1 case; 2001: 1 case; 2002: 2 cases; 2003: 3 cases; then 1 case per year from 2004 to 2007 (to 1 February). Type L: 2002: 1 case; 2003: 1 case.

impossible to estimate a trend for their occurrence. Their aetiology is also completely unknown: a variant phenotype of classic BSE and which would then result from the same modes of exposure, a TSE distinct from classic BSE and which could then have other determining factors ("spontaneous" form, exposure to other factors, etc.).

Consequently, no estimate can be given of any developments in numbers of these cases over the next few years.

3.6. Conclusion

To summarise, the estimates based on the model are very comparable with the results of the analysis of the surveillance data.

Overall, current data on the cohorts predating the 2001 cohort and the absence of cases born after 1 January 2001 provide strong grounds for estimating that the number of animals infected in past years was less than one hundred per year, since only some (15 to 30%) of these animals can be or were detected, due to culling and death. Once more time has elapsed, and if the number of cases detected in animals born after 2000 remains low, this estimate could gradually be refined, probably down to an annual number of infections of less than twenty.

Nevertheless, another major element to be taken into account is that one cannot currently rely on the number of positive animals being nil. Each year, a minimum of one to three cases of atypical BSE are discovered, which could be the result of another determining factor. To these can be added a few cases of classic BSE, which, while they are being observed, could be the result of very low levels of a spontaneous type of the disease.

Finally, based on the detection capacities of the current system (exhaustivity of tests at rendering plants and abattoirs on cattle aged over 24 and 30 months respectively[14] and the detection capacity of the rapid tests on the barin stem approved for use at the present time), the characteristics of the disease (age at infection and incubation period) and the demographic structure of the cattle population, the absence of cases detected in a given birth cohort is compatible with twenty infected animals in that cohort (with 95% probability).

The result of these three additional pieces of information is that if no cases of BSE have been detected, when considering subsequent years one can work on the basis of a maximum of twenty infected cattle per year in France. A review of any changes to the infection control measures and of how the risk to humans is managed can be carried out on that basis.

[14] It should be noted that this capacity would not be altered by raising the minimum age for screening at the abattoir, cf. Opinion of the Scientific Panel of 21 November 2005, in reply to mandate No. 2005-SA-0291.

ANNEX 1: AGE DISTRIBUTION OF BSE CASES BASED ON THEIR BIRTH COHORT (C SALA – AFSSA LYON)

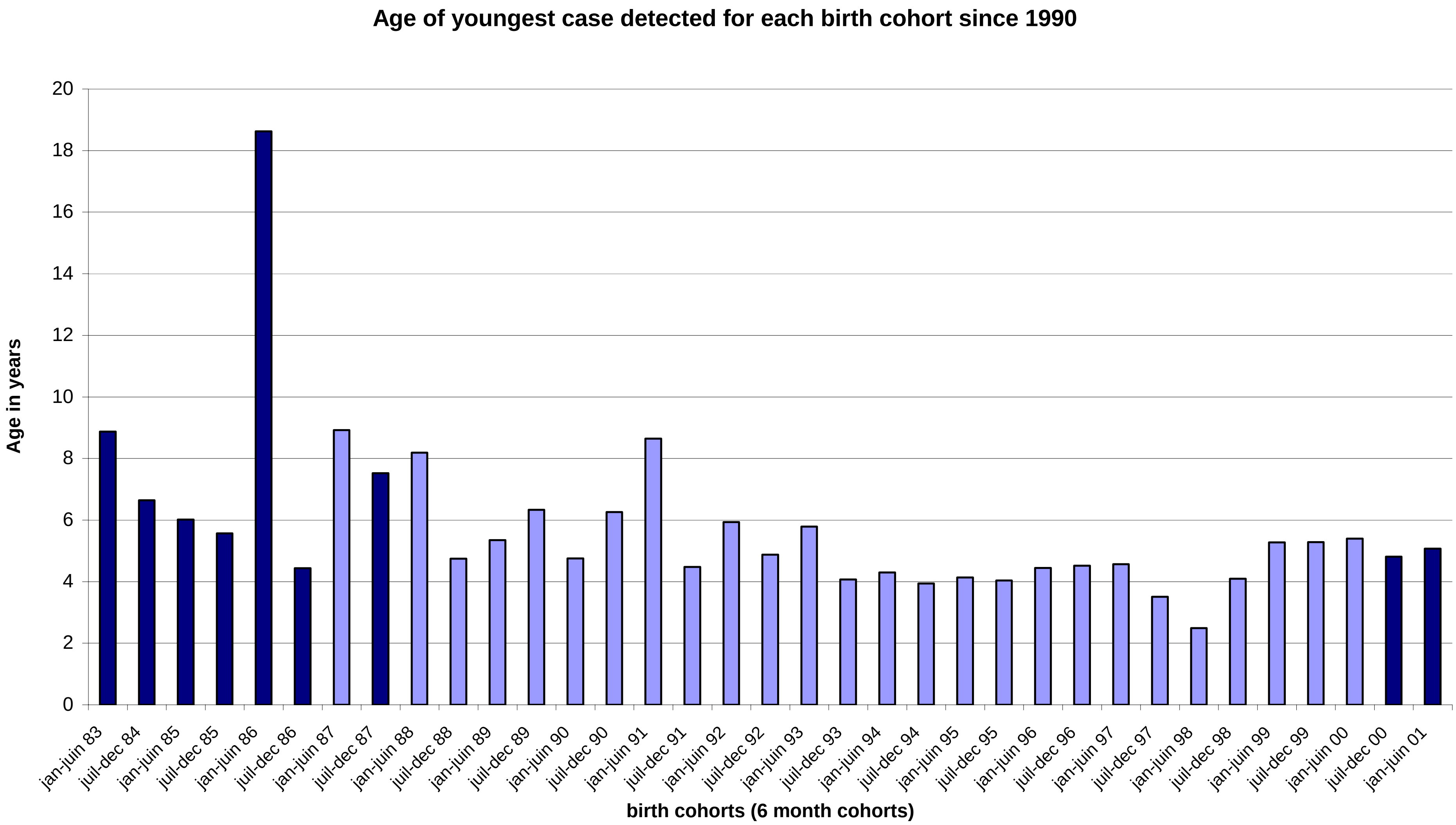
The birth cohorts are cohorts of 6 months, e.g. Jan-June 83: animals born from 1 January 1983 to 30 June 1983; Jul-Dec 83: animals born from 1 July 1983 to 31 December 1983

I. Age of first case detected in each birth cohort since 1990

Year of detection	Birth cohort	Age in days	Type of production	Age in years
1991	Jan-June 83	3246	D	8.9
1991	July-Dec 84	2432	D	6.6
1991	Jan-June 85	2202	D	6.0
1991	July-Dec 85	2037	D	5.6
2004	Jan-June 86	6817	S	18.6
1991	July-Dec 86	1625	D	4.4
1996	Jan-June 87	3265	D	8.9
1995	July-Dec 87	2753	D	7.5
1996	Jan-June 88	2996	S	8.2
1993	July-Dec 88	1737	S	4.7
1994	Jan-June 89	1958	D	5.3
1996	July-Dec 89	2318	D	6.3
1994	Jan-June 90	1739	D	4.8
1997	July-Dec 90	2292	D	6.3
1999	Jan-June 91	3165	S	8.6
1996	July-Dec 91	1638	D	4.5
1997	Jan-June 92	2172	D	5.9
1997	July-Dec 92	1784	D	4.9
1998	Jan-June 93	2118	S	5.8
1998	July-Dec 93	1490	S	4.1
1998	Jan-June 94	1573	D	4.3
1998	July-Dec 94	1441	D	3.9
1999	Jan-June 95	1513	S	4.1
1999	July-Dec 95	1479	D	4.0
2000	Jan-June 96	1626	D	4.4
2001	July-Dec 96	1653	D	4.5
2001	Jan-June 97	1670	D	4.6
2001	July-Dec 97	1284	D	3.5
2000	Jan-June 98	913	D	2.5
2002	July-Dec 98	1499	D	4.1
2004	Jan-June 99	1930	S	5.3
2004	July-Dec 99	1933	D	5.3
2005	Jan-June 00	1974	S	5.4
2005	July-Dec 00	1761	D	4.8
2006	Jan-June 01	1855	S	5.1

Type of production: L for dairy and mixed. A for suckler and cross or not recorded.

The graph below shows the age of the youngest case detected in each birth cohort.
Dark blue is used for cohorts in which only one case has been detected since 1990.


Age of youngest case detected for each birth cohort since 1990
Age in years
20
18
16
14
12
10
8
6
4
2
0
jan-juin 83
juil-dec 84
jan-juin 85
juil-dec 85
jan-juin 86
juil-dec 86
jan-juin 87
juil-dec 87
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juil-dec 00
jan-juin 01
birth cohorts (6 month cohorts)

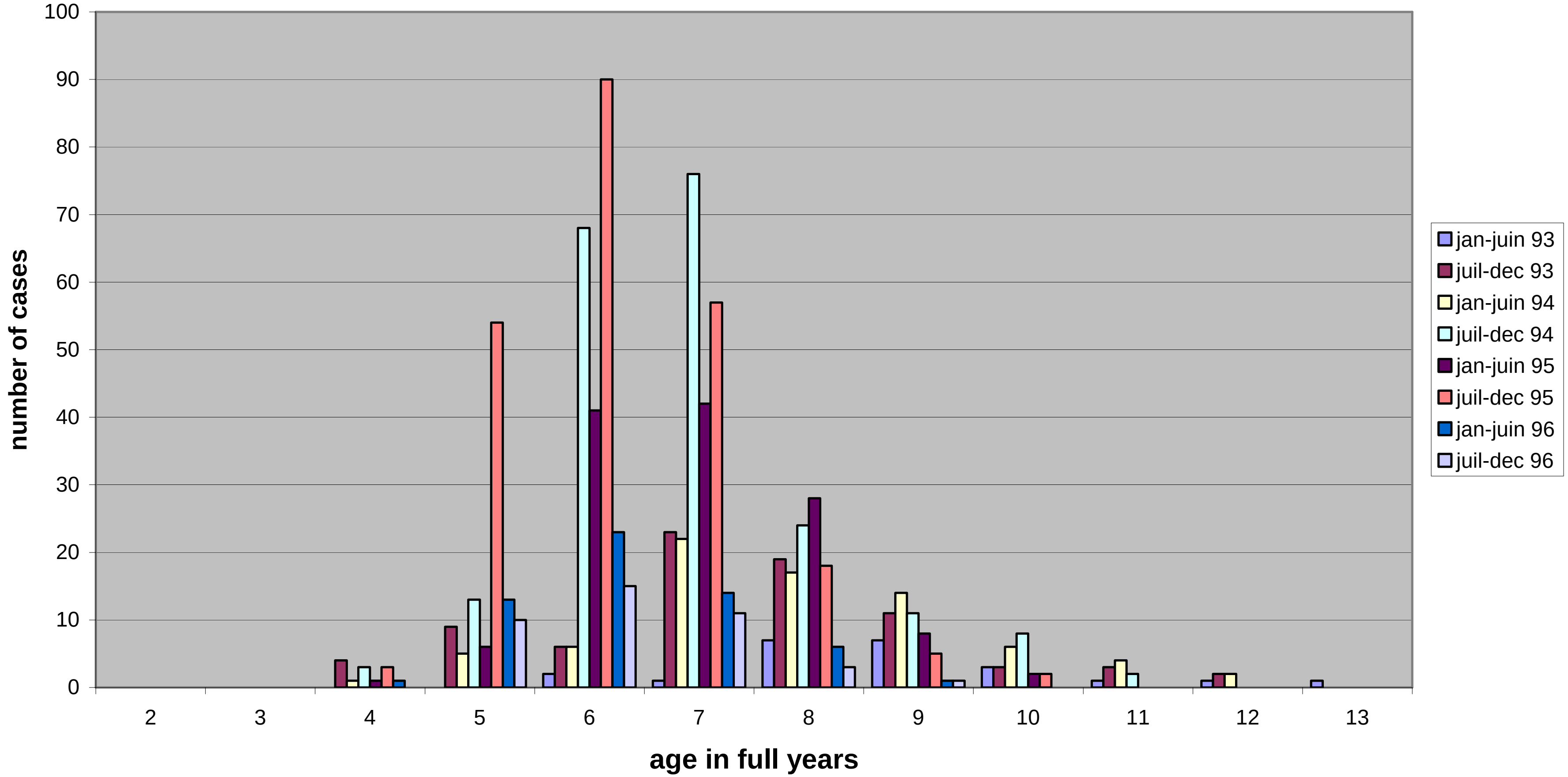
II. Distribution of cases by age based on birth cohort

A. Distribution of numbers of cases

age in years	cohort Jan-June 88	July-Dec 88	Jan-June 89	July-Dec 89	Jan-June 90	July-Dec 90	Jan-June 91	July-Dec 91	Jan-June 92	July-Dec 92	Jan-June 93	July-Dec 93
2												
3												
4								1				4
5		3	1		1					1		9
6		1		1		6			1	1	2	6
7		1	3	1				1		2	1	23
8	1	4	1						2	2	7	19
9		1	1	2			1	2		2	7	11
10						1			1	2	3	3
11							1	1	2	2	1	3
12					1		3		3	1	1	2
13	1	1			1					1	1	
14												
15			1		1							

	Jan-June 94	July-Dec 94	Jan-June 95	July-Dec 95	Jan-June 96	July-Dec 96	Jan-June 97	July-Dec 97	Jan-June 98	July-Dec 98	Jan-June 99	July-Dec 99
2									1			
3												
4	1	3	1	3	1			6	3	1		
5	5	13	6	54	13	10	4	4	2	4	2	2
6	6	68	41	90	23	15	9	9	3	3	2	1
7	22	76	42	57	14	11	4	5		1		
8	17	24	28	18	6	3						
9	14	11	8	5	1	1	1					
10	6	8	2	2								
11	4	2										
12	2											
13												
14												
15												

Distribution by age and birth cohort
(in numbers of animals)



B. Distribution of cases in proportion to total number of cases in a cohort (%)

age in years	Jan-June 93	July-Dec 93	Jan-June 94	July-Dec 94	Jan-June 95	July-Dec 95	Jan-June 96	July-Dec 96	Jan-June 97
4	0.0	5.0	1.3	1.5	0.8	1.3	1.7	0.0	0.0
5	0.0	11.3	6.5	6.3	4.7	23.6	22.4	25.0	22.2
6	8.7	7.5	7.8	33.2	32.0	39.3	39.7	37.5	50.0
7	4.3	28.8	28.6	37.1	32.8	24.9	24.1	27.5	22.2
8	30.4	23.8	22.1	11.7	21.9	7.9	10.3	7.5	0.0
9	30.4	13.8	18.2	5.4	6.3	2.2	1.7	2.5	5.6
10	13.0	3.8	7.8	3.9	1.6	0.9	0.0	0.0	0.0
11	4.3	3.8	5.2	1.0	0.0	0.0	0.0	0.0	0.0
12	4.3	2.5	2.6	0.0	0.0	0.0	0.0	0.0	0.0
13	4.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

It is standard practice for a birth cohort to concern the animals born between 1 July in one year and 30 June the next. The following graph also shows greater homogeneity between the half-cohorts belonging to two successive years (July-Dec 95 and Jan-June 96 for example) than between two half-cohorts belonging to the same year (Jan-June 95 and July-Dec 95 for example).

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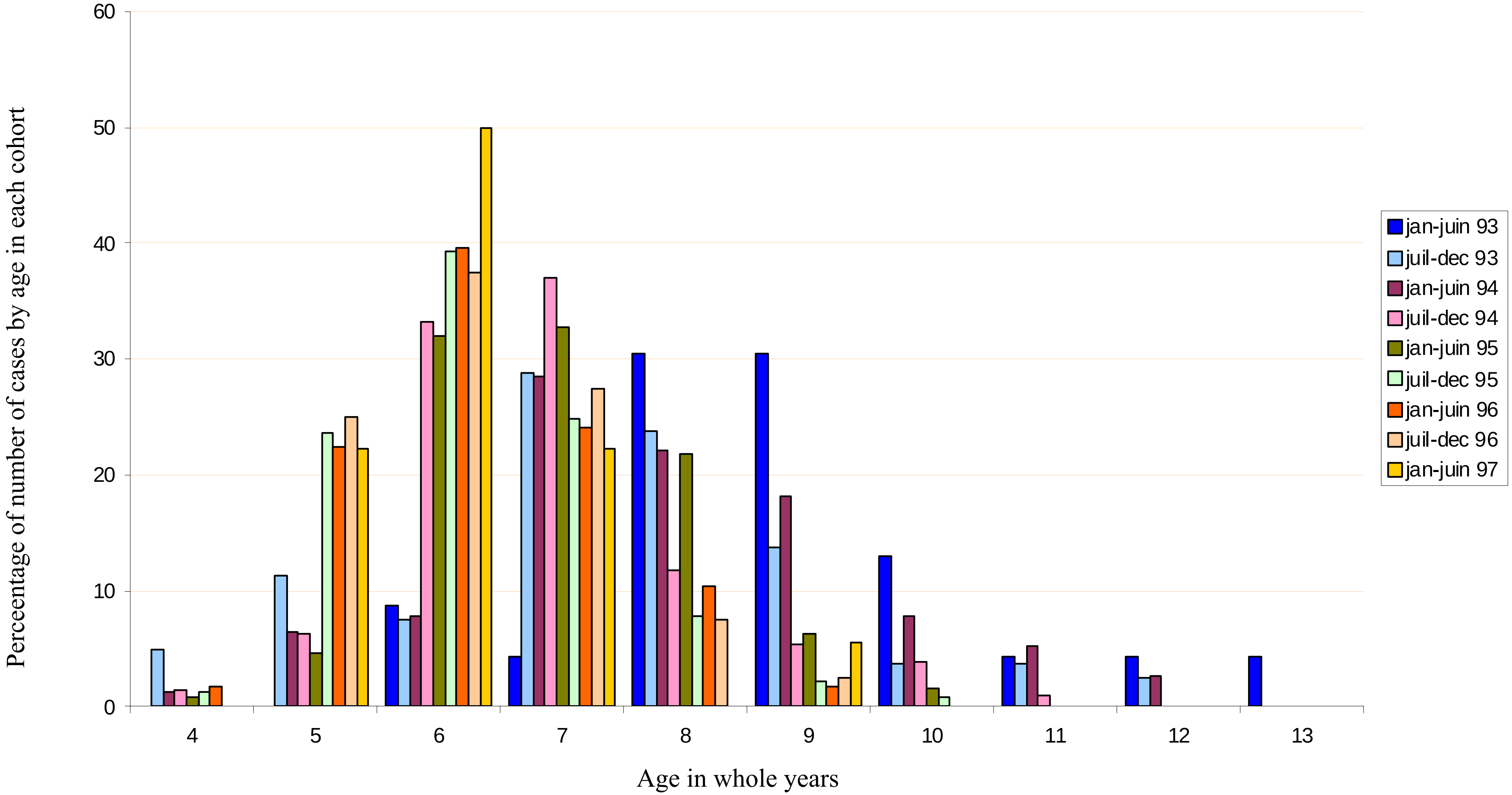
Distribution of number of cases by age each birth cohort (percentage)



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ANNEX 2: EXTRACT FROM THE SCIENTIFIC ARTICLE SENT FOR PUBLICATION

Section 3: Binomial modelling to estimate prospectively the efficiency of the 2000 ultimate feed ban

The MBM ban extended to all farm species in November 2000 should have prevented and even entirely suppressed exposure to the BSE agent. Nevertheless, few bovines born after this date could be infected by the BSE agent in the same way as it has been observed in the United-Kingdom (UK), where some BSE cases were born after the ban of MBM extended to all farm species in August 1996, also called the born after the reinforced feeding ban cases (BARB); as of 1st September 2006, there had been 152 BARB cases (21 born in 1996, 51 in 1997, 41 in 1998, 26 in 1999, 7 in 2000, 5 in 2001 and 1 in 2002). Farms in the UK, not fully cleared out in 1996 of feed potentially containing MBM and imported feed from countries where the MBM were always allowed for certain farm animals, could be infection sources of the first BARB cases.[(30)] Indeed, there is some evidence from the epidemiological investigations in one herd that two BSE cases born in 2001 and the case born in 2002 may have resulted from the persistence of infection in farm feed bins beyond the dates of the official feed ban.[(31)] However, similar evidence has not been found to explain the other BSE cases in cattle born in 2001. Moreover, these cases were born after MBM was banned to all farm species throughout Europe in January 2001. It could remain BSE infections at a low level, due to non feed-borne sources or even spontaneous occurrence. This latter hypothesis has been recently reconsidered by the recent finding of atypical cases of BSE (atypical phenotypes) whose frequency might well be consistent with the occurrence of sporadic disease.[(32)] Nevertheless, to date, nothing confirmed or invalidated these assumptions.
In view of the long incubation period of BSE, it is not possible to precisely assess the global impact of any control measure before several years. Nevertheless, it is possible to assess by modelling the minimum time to first detection if infections still occurred. In order to assess this time, we used parameters about age at infection and incubation time estimated in a study where we updated the estimate of the BSE infection epidemic from BSE cases detected since July 2001,[(19)] and updated data on cattle survival (Fig. 1▲). The distribution of age at infection was the same as that presented in Section 1 (Fig. 2). In contrast, the average BSE incubation period was 6.3 years and the variance 3.3 years^2.
We formulated the problem in discrete time units, where the unit is half year. The convolution of the probability density function of age at infection and of the incubation time allows calculating the cumulative distribution of the age at clinical onset:

$$H_a = \sum_{x=1}^{a} \sum_{s=1}^{x} g_s f_{x-s}$$

where g_s is the probability of being infected at age *s*, and f_x is the probability that the incubation period lasts *x* units of time. However, the cattle survival is not taken into account in this distribution. In France, a large part of cattle are slaughtered or die young; as a result, animals with long BSE incubation times die or are slaughtered before the clinical onset. This means that the age at slaughter or death needs to be taken into account. In addition, only some cattle were exposed to the BSE agent, as other died or were slaughtered shortly after birth. It was therefore necessary to consider survival among animals that were alive at the time of infection. Assuming that $S_{x|s}$ represents the probability that an animal will survive to age *x*, knowing that the same animal was alive at age *s* (the age at infection), the cumulative proportion of infected animals being detected as clinical cases at age *a* is:

$$H'_a = \sum_{x=1}^{a} \sum_{s=1}^{x} g_s f_{x-s} S_{x|s}$$

The graph of this cumulative proportion is presented on Figure 4. To estimate the probability of detecting at least one case among a given number of infected animals, within a given period, we used the binomial distribution. Its parameters are the number of infections, all these infections occurring within a short period of time, and the cumulative proportion of being detected as a clinical case at age *a*. We varied the number of infections between 1 and 1000.

The results of this modelling are presented in Table II. The time to first detection, with a 95% probability of detecting at least one clinical BSE case, is 5 years for 1000 infections, and 6 years for 100 infections. We highlighted that the probability of detecting one BSE case after 15 years if there were 10 infections is only 0.80 and only 0.15 if there was one infection.

In France, the ban of MBM was extended to all farm species five years ago in November 2000. As of 1st September 2006, only one BSE case born after November 2000 has been detected. It was born the 1st January 2001. The finding of one BSE case born one month after the ban of MBM extended to all species shows that this measure was not fully effective immediately. That could be explained by the fact that no stock recall of feed containing MBM was done in France. However, as not a single BSE case born within six months after January 2001 was detected by June 2006, we can conclude from the model, with a 95 % probability, that less than 1000 infections occurred among the French cattle population of 8.5 million adult cows during the six months following January 2001. In addition, if not a single BSE case born within six months after January 2001 is detected by June 2007, we could conclude from the model, with a 95 % probability, that less than 100 infections occurred among the French cattle population during the six months following January 2001. If we suppose that the ultimate control measure was efficient only six months later (in July 2001) we need to wait until December 2006 (respectively December 2007) to conclude with a 95 % probability that less than 1000 infections (respectively 100 infections) occurred among the French cattle population during the six months following June 2001.

This model does not account for the fact that cattle infected by the BSE agent can be detected by a screening test before developing clinical signs. We made this assumption because the preclinical sensitivity of screening test is not precisely known. However, a study suggested that screening tests could become positive three months before clinical onset.[(33)] Taking into account a preclinical detectability for the screening tests would imply that time period to detect one BSE case with a certain probability would be slightly shorter. Consequently our model is a worst case scenario of the number of infections. In contrast, results of this model were obtained under the assumption that the age at infection and the incubation period will not change. However, it could again lengthen and then increase the time to wait before detecting a case.

LEGEND FIGURES

Figure 1. Estimates of survival distribution of French cattle. (■) estimated from three data sources and (▲) estimated from demographic data of the French reference database for bovine identification in 2002.

Figure 2. (**A**) Cumulative distribution of cattle age at infection; (**B**) Probability density function of the BSE incubation period.

Figure 3. Estimated (——) annual incidence of BSE infection since 1980 (**A**) and since 1987 (**B**), using different scales to visualize the dynamics of the epidemic. The dotted lines (-----) represent 95% bootstrap confidence intervals. Years were defined so that, for example, 1990 consists of the period between 1st July 1990 and 30th June 1991

Figure 4: Cumulative proportion of infected bovines being detected as clinical cases according the age of clinical onset.

FIGURES

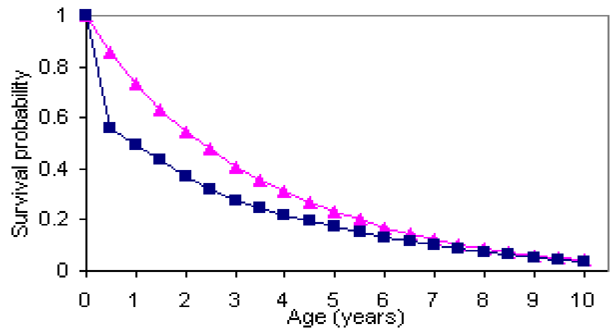


Figure 1

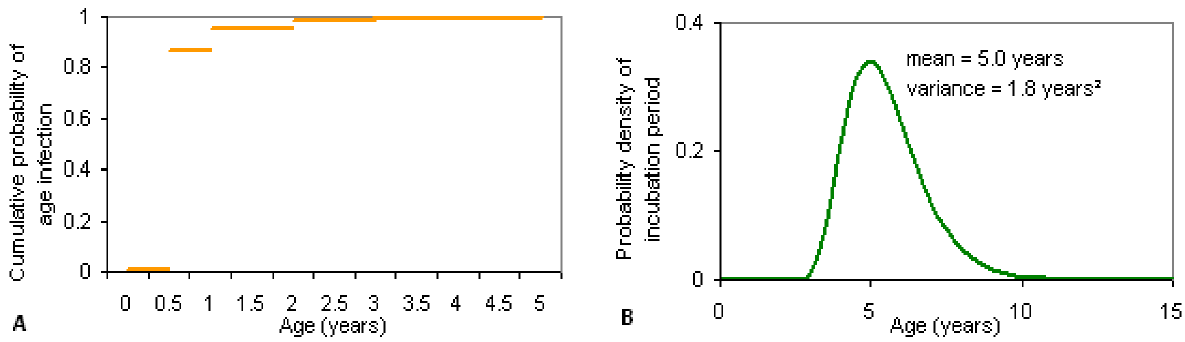
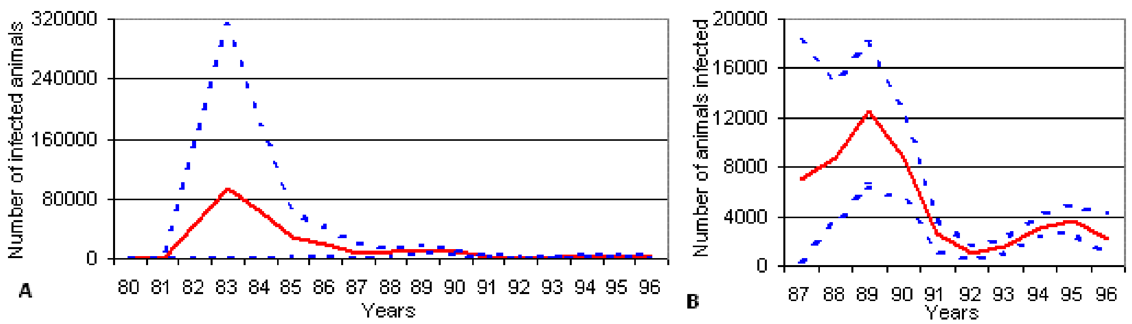


Figure 2



4.

Figure 3

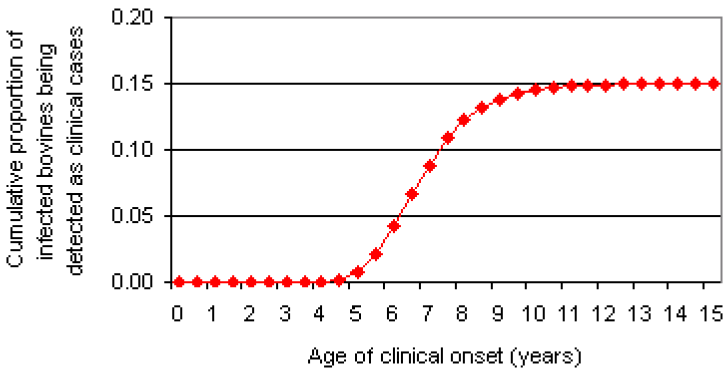


Figure 4

Table II: Cumulative probability of detecting at least one case according to the number of infections, all infections occurring within a short period of time, and according to the time after the date of infection.

Time after the date of infection (years)	Number of infections: 1000	100	10	1
3	0.0%	0.0%	0.0%	0.0%
4	12.5%	1.3%	0.1%	0.0%
4.5	79.4%	14.6%	1.6%	0.2%
5	100.0%	54.0%	7.5%	0.8%
5.5	100.0%	89.1%	19.9%	2.2%
6	100.0%	98.7%	35.4%	4.3%
6.5	100.0%	99.9%	49.7%	6.6%
7	100.0%	100.0%	60.2%	8.8%
7.5	100.0%	100.0%	68.5%	10.9%
8	100.0%	100.0%	72.8%	12.2%
8.5	100.0%	100.0%	75.6%	13.2%
9	100.0%	100.0%	77.4%	13.8%
9.5	100.0%	100.0%	78.5%	14.2%
10	100.0%	100.0%	79.2%	14.5%
10.5	100.0%	100.0%	79.6%	14.7%
11	100.0%	100.0%	79.8%	14.8%
11.5	100.0%	100.0%	80.0%	14.9%
12	100.0%	100.0%	80.1%	14.9%
12.5	100.0%	100.0%	80.2%	14.9%
13	100.0%	100.0%	80.2%	14.9%
13.5	100.0%	100.0%	80.2%	15.0%
14	100.0%	100.0%	80.2%	15.0%
14.5	100.0%	100.0%	80.2%	15.0%
15	100.0%	100.0%	80.2%	15.0%

ANNEX 3: ADDITIONAL CALCULATIONS BASED ON THE PRECEDING MODEL (B DURAND – AFSSA ALFORT)

1- The model used (cf. Annex 2) permits the calculation of the probability p that an infected animal would be detected based on time elapsed since contamination which is the convolution of age at infection, incubation period and culling of the animals.
2- It is assumed that the number of animals detected in a cohort follows a binomial distribution based on parameters p (which vary according to age, see 1) and n (number of infected animals).
3- If 10 animals are infected, the probability of detecting at least 1 is: $1 - (1 - p)^{10}$.
4- In a binomial process, assuming a non-informative distribution (i.e. uniform) for the number of infected animals, the distribution then becomes a negative binomial distribution: n ~ NegBinom(s + 1, p) in which s is the number of successes (0 in this case) and p is the probability of being detected, calculated using the model, and assumed to be fixed (non-random).
5- A distribution of probabilities is obtained for the number of animals infected n and the unilateral quantiles can be calculated (N when Prob(n < N) = quantile) for example for 50 %, 75 %, 95 % and 99 %.

Table: Cumulated probabilities based on time elapsed after infection before detection of at least one case, based on number of infections, all infections occurring during a short period and maximum number of infections if no animals have been detected as positive.

Time elapsed after infection (years)	Number of infections*				Quantiles**			
	1000	100	10	1	50	75	95	99
4	0.13	0.01	0.00	0.00	5190	10381	22434	34487
4.5	0.79	0.15	0.02	0.00	438	877	1896	2914
5	1.00	0.54	0.07	0.01	89	178	385	593
5.5	1.00	0.89	0.20	0.02	31	62	134	207
6	1.00	0.99	0.36	0.04	15	31	68	104
6.5	1.00	1.00	0.49	0.07	10	20	43	67
7	1.00	1.00	0.60	0.09	7	15	32	49
7.5	1.00	1.00	0.68	0.11	6	12	25	39
8	1.00	1.00	0.73	0.12	5	10	23	35
8.5	1.00	1.00	0.76	0.13	4	9	21	32
9	1.00	1.00	0.77	0.14	4	9	20	31
9.5	1.00	1.00	0.78	0.14	4	9	19	30
10	1.00	1.00	0.79	0.14	4	8	19	29
10.5	1.00	1.00	0.80	0.15	4	8	18	28
11	1.00	1.00	0.80	0.15	4	8	18	28
11.5	1.00	1.00	0.80	0.15	4	8	18	28
12	1.00	1.00	0.80	0.15	4	8	18	28
12.5	1.00	1.00	0.80	0.15	4	8	18	28
13	1.00	1.00	0.80	0.15	4	8	18	28
13.5	1.00	1.00	0.80	0.15	4	8	18	28
14	1.00	1.00	0.80	0.15	4	8	18	28
14.5	1.00	1.00	0.80	0.15	4	8	18	28
15	1.00	1.00	0.80	0.15	4	8	18	28

* these numbers correspond to Table 2 in Annex 2, rounded to nearest whole number.

** the 50, 75, 95 and 99 quantiles are the quantiles for the distribution when number of infected numbers is known.

For example, in the knowledge that no animals have been found to be positive:

- 5.5 years after infection, there is 50% probability that the number of infected animals is less than 31, 75% probability that it is less than 62, 95% probability that it is less than 134, and 99% probability that it is less than 207;
- 6.0 years after infection, there is 50% probability that the number of infected animals is less than 15, 75% probability that it is less than 31, 95% probability that it is less than 68, and 99% probability that it is less than 104.

This approach also permits an estimate of the lowest capacity of the current screening system[15]. Assuming that a birth cohort has been exhaustively tested (cattle can live for over 20 years in current conditions but estimates can only take account of a margin with 10 years retrospective calculation) and that no animal from this cohort has tested positive, one can be confident that in this cohort there were fewer than:

- 4 infected animals with 50% probability;
- 8 infected animals with 75% probability;
- 18 infected animals with 95% probability;
- 28 infected animals with 99% probability.

[15] Meaning exhaustive screening of cattle aged 24 months at rendering plants and abattoirs, using the currently approved rapid tests.