Modelling of the French bovine spongiform encephalopathy (BSE) epidemic: use of the screening test data

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Why estimate the number of BSE infections?

- to take or not this source of exposure to the BSE agent in the estimation of the risk of the Creutzfeldt-Jakob disease of the French population

- to assess the efficiency of measures intended to prevent bovine infection by the BSE agent
OUTLINE

- The back-calculation method

- The demographic characteristics of the French cattle population and the French BSE surveillance system

- Results of the estimates of the BSE infection number from the BSE clinical cases detected up to June 2000 (before the implementation of screening tests)

- Update of this estimate from the BSE cases detected between July 2001 and June 2004 (after the implementation of screening tests)
INFECTIOUS DISEASE: example: AIDS

Often, data on reported clinical cases of a disease is the only way of tracking an epidemic.

But, at a given time, the reported clinical cases do not reflect trends in the spread of infection because incubation periods are long and variable.
THE BACK-CALCULATION METHOD

“clinical case = infection + incubation period”

\[ E(Y_t) = \int_{0}^{t} E(N_s) f(t-s) ds \]

- \( Y_t \): random numbers of new clinical cases diagnosed at time \( t \)
- \( f(\cdot) \): density function of the incubation period
- \( N_s \): random numbers of newly infected individuals at time \( s \)
- \( E(\cdot) \): expectation

Original publications:

Extension of the method to include age as a covariable:
ESTIMATION OF THE INFECTION CURVE

- If the incubation period is known, the numbers of reported clinical cases can be used to obtain an unbiased estimation of the number of past infections, provided that clinical case reporting is exhaustive.

- Regarding the BSE, we had to take account of:
  - the cattle mortality
  - the changes of BSE surveillance system
THE CATTLE MORTALITY

Median survival: 2.3 years
IQR: [0.9 year-4.8 years]

- BSE infected cattle are slaughtered or die before showing clinical signs of BSE
- Cattle may die or be slaughtered before being infected
EVOLUTION OF THE FRENCH BSE SURVEILLANCE SYSTEM

- **Clinical surveillance:** Veterinary practitioners and farmers were required to report cattle with BSE clinical signs

- **Active surveillance:**
  - Implementation of BSE screening tests:
    - first in the west of France on a sample of cattle at risk (dead-on-farm cattle, emergency slaughtered cattle and euthanatized cattle)
    - then at the national level on a sample of cattle at risk
    - then on all bovines over 30 months of age sent to the abattoir
  - BSE screening tests on all cattle, sent to the abattoir and among at risk cattle, over 24 months of age

- **Variation of the surveillance between July 2000 and June 2001 + destruction of 179086 bovines during the first six-month period of 2001 without screening tests**

- **2 periods of study:**
  - 1980 → June 2000
  - July 2001 → June 2004
We estimated that 51300[24300-84700] cattle were BSE-infected between July 1987 and June 1997 whereas 103 BSE clinical cases were reported by the clinical surveillance up to June 2000 ⇒ the BSE epidemic was censored by the cattle mortality and the under-reporting of BSE clinical cases

BSE SURVEILLANCE SYSTEM
July 2001 → June 2004

- BSE screening tests detect all BSE clinical cases and a few BSE preclinical cases (BSE-infected cattle at the end of incubation period)

- Cases of BSE detected by surveillance system:
  - Abattoir: cattle tested positive for BSE were not all preclinical cases of BSE
  - At risk: cattle tested positive for BSE were not all clinical cases of BSE

- Data were split into two groups:
  - Abattoir
  - At risk + clinical surveillance

- Retrospective study [2]:
  - Abattoir: cattle tested positive for BSE were not all preclinical cases of BSE
  - At risk: cattle tested positive for BSE were not all clinical cases of BSE

575 cases were detected between July 2001 and June 2004:
- 174 at the abattoir (median age: 7.0 years)
- 401 among at risk cattle and by the clinical surveillance (median age: 7.0 years)

BSE cases = cases detected at the abattoir + cases detected among at risk cattle and by the clinical surveillance

= K \times \text{clinical cases} + \text{preclinical cases} + (1-K) \times \text{clinical cases} + \text{preclinical cases}

K : proportion of clinical cases sent to the abattoir

\[ \text{BSE clinical cases of age } a \text{ at time } t = \]
infected of age \( a-t+s \) at time \( s \)
+ incubation period of \( t-s \)
+ survival up to the age \( a \)
+ sent to the abattoir or detected by the clinical surveillance and among at risk cattle

\[ \text{BSE preclinical cases of age } a \text{ at time } t = \]
infected of age \( a-t+s \) at time \( s \)
+ incubation period of \( t-s+u \)
+ survival up to the age \( a \)
+ sent to the abattoir or to the fallen stock at time \( u \) before the clinical onset
BACKCALCULATION ADAPTED TO THE BSE
July 2001 → June 2004

\[ E(Y_{at}) = E(Y_{at}^{ab}) + E(Y_{at}^{ar+c}) \]

\[ E(Y_{at}^{ab}) = \psi(0)K \int_{0}^{t} E(N_{a-t+s,s})f(t-s)S(a \mid a-t+s)ds + \]

\[ \mu(a)\beta(a) \int_{0}^{t} E(N_{a-t+s,s})S(a \mid a-t+s) \left( \int_{1}^{\infty} f(t-s+x)\psi(x)dx \right)ds \]

\[ E(Y_{at}^{ar+c}) = (1-K)\psi(0)\int_{0}^{t} E(N_{a-t+s,s})f(t-s)S(a \mid a-t+s)ds + \]

\[ (1-\beta(a))\mu(a) \int_{0}^{t} E(N_{a-t+s,s})S(a \mid a-t+s) \left( \int_{1}^{\infty} f(t-s+x)\psi(x)dx \right)ds \]

- \( \mu(a) \): hazard of death for a cattle of age \( a \)
- \( \beta(a) \): age-specific proportion of cattle mortality resulting from the abattoir
- \( K \): proportion of clinical cases sent to the abattoir
- \( S(a\mid a') \): probability that a cattle survives to age \( a \) knowing that it was alive at the age \( a' \), \( a' \) is the age at infection
- \( \psi(x) \): probability that the screening test detects the infection at time \( x \) before the clinical onset

The dependence on age is incorporated via the multiplicative model:

\[ E(N_{as}) = \pi_{a} \alpha_{a} \lambda_{s} \]

- \( \pi_{a} \): proportion of cattle in the population who are of age \( a \)
- \( \alpha_{a} \): susceptibility/exposure of cattle of age \( a \)
- \( \lambda_{s} \): BSE infection intensity at time \( s \)
PARAMETER ESTIMATION, MODEL SELECTION AND PRECISION

\{Y_{a,t}\}_{a=1,\ldots,A; t=1,\ldots,T} \rightarrow \text{independent Poisson variates of expectation } \mu_{at} = E(Y_{a,t})

Observations \(y_{a,t}\) yield the likelihood function:

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

- **EM algorithm** [1] was used to estimate the age at infection, \(\alpha\), and the infection intensity, \(\lambda\)

- **Criterion of model selection:**
  - **Akaike's Information criterion (AIC):** \(AIC = -2\log L + 2K\)
    - \(\log L\) : likelihood and \(K\) : number of parameter model
  - **Empiric rule of Burnham and Anderson** [2] : \(AIC(\text{model}) - \min(AIC) \leq 2\)

- 95% bootstrap confidence intervals [3]

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SENSITIVITY ANALYSES

- Sensitivity profiles of screening test:

<table>
<thead>
<tr>
<th>Months before the clinical onset</th>
<th>Sensitivity profiles(P)</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
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</table>

- K: proportion of clinical cases sent to the abattoir
  - between 0.05 and 0.50
INCREASE OF AGE OF BSE CASES: A FEW POSSIBLE SCENARIOS

- Median age of BSE cases:
  - Before June 2000: 5.5 years
  - From July 2001 and June 2004: 7 years
  ⇒ Increase of age of BSE cases (Mann-Whitney test: p < 0.00001)

- A problem of "identifiability": non uniqueness of solutions, because there is no way of distinguishing between infection at birth with a 5-year incubation period and infection at 1 year with a 4-year incubation period

- Three possible SCENARIOS:
  - **SCENARIO 1:**
    - no change of infection age (between 6 and 12 months)
    - lengthening of the incubation period
  - **SCENARIO 2:**
    - infection occurred later
    - no change of the period incubation (mean: 5 years and variance: 1.8 years²)
  - **SCENARIO 3:**
    - end of the epidemic ⇒ no change of infection age (between 6 and 12 months); no change of incubation period (mean: 5 years and variance: 1.8 years²)
## RESULTS (1)  July 2001 → June 2004

### SCENARIO 1
Lengthening of the incubation period (IP)

<table>
<thead>
<tr>
<th></th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
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### SCENARIO 2
Infection occurred later

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<td>Proportion of infection</td>
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<td>[3-5]</td>
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<td>[5-30]</td>
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### SCENARIO 3
No change

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RESULTS (2)  July 2001 → June 2004

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<th>P2</th>
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SCENARIO 1

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SCENARIO 2

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<th>AR</th>
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</table>

AB : abattoir; AR+C: at risk + clinical surveillance
RESULTS (3)  July 2001 → June 2004

**SCENARIO 1**
- Profiles: P1, P2, P3, P4, P5, P6
- Curve obtained for the period 1980 → June 2000
- 95% bootstrap confidence intervals

**SCENARIO 2**

**SCENARIO 3**
DISCUSSION(1)

- Problem of identifiability ⇒ 3 SCENARIOS

SCENARIO 1: lengthening of the incubation period
- best fit
- consistent dynamics

SCENARIO 2: infection occurred later
- another source of infection ???

SCENARIO 3: no change

⇒ SCENARIO 1
Without fixing either the proportion of BSE clinical cases sent to the abattoir or the screening test sensitivity, it was not possible to choose one situation rather than another.

If the assumed sensitivity was very low then the proportion of BSE clinical cases sent to the abattoir was high, and vice versa. This proportion varies between 15 and 30% according to the test sensibility.

Independent sources of information:
- Experimental study [1]: rapid tests may become positive only three months before clinical onset.
- Comparison of age of BSE cases detected at the abattoir and by the clinical surveillance:
  - Median age of BSE cases detected at the abattoir: 7.04 years
  - Median age of BSE cases detected by the clinical surveillance: 6.87 years

⇒ Low preclinical sensitivity of rapid tests: profiles of sensitivity P2 or P3.

CONCLUSIONS

- Data do not allow to choose a preclinical sensitivity profile of rapid test but this sensitivity is likely low.
- Probable lengthening of the incubation period.
- Between 15 and 30% of BSE clinical cases would be sent to the abattoir.
- The number of infections was very low at the end of the 1990s and zero from 2000⇒ the impact of the meat and bone meal ban impose in 2000 for all animal species in 2000 will never be assessable.