Sensitivity-adjusted BSE Prevalence can be Estimated Using Surveillance Data Without External Information on Incubation Time and Age at Infection

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Abstract

We have developed a Bayesian model for estimating the true prevalence of bovine spongiform encephalopathy (BSE) by adjusting for diagnostic sensitivity. The model considers the observed number of detected cases per year of testing and age at testing as a Poisson variate. The Poisson density parameter is a function of a) the unknown prevalence of the given birth cohort, b) the observed number of tested cattle per test year and age at testing and c) the Gompertz function with two unknown parameters for the age-dependent diagnostic sensitivity. We have applied the model to the German BSE surveillance data (19.5 mil. test results obtained between 1997 and 2009, with partially censored data on age at testing). The unknown parameters could be estimated without external information on incubation time and age at infection. The results indicate a BSE prevalence peak in the 1996 birth cohort of 13.9 (upper limit 17.2 of 95% credible interval) cases per 100,000 with a ratio of undetected to detected cases of 1.0. From 1996 onwards, the true prevalence exhibits a continuously decreasing trend. We can also show that the ratio of undetected to detected cases increases for younger birth cohorts.

Keywords: BSE, prevalence, sensitivity, Bayesian model.

Introduction

The BSE infection prevalence is an important input parameter for BSE risk assessments. In this context, it is important to realise that observed prevalence rates may be biased due to false negative test results occurring in BSE infected cattle during the early stages of incubation [1-3]. The age-dependent diagnostic sensitivity of BSE testing [4] has been derived from the distribution of the incubation time period and age-at-infection estimated using UK data [5]. The age-dependent sensitivity is a proxy for the combined effect of the age-at-infection and the incubation period length [4]. However, it is not known whether such sensitivity estimates are generally applicable irrespective of the target cattle population. Therefore, we aimed at estimating BSE prevalence for the German cattle population adjusted for diagnostic sensitivity without using such external information. Our case definition refers to the status "BSE infected" irrespective of the tissue distribution of infectious BSE prions.

Materials and methods

Data: We have used the complete German BSE surveillance data collected between 2001 and 2009 supplemented with BSE test data collected in Germany prior to 2001. The total number of BSE cases and total sample size are 413 and 19,449,774, respectively [6]. We have organised the data by year of testing and birth cohort. The number of BSE tests conducted in 2001 and later was reported in one age category for all cattle slaughtered with an age of 0-24 months (interval censoring). For the purpose of our model, we assigned an age of 0-12 months to all animals in this category. Furthermore, the age at testing is left-censored with variable censoring limits. The censoring limits are 2, 8, 8 and 13 years for the BSE testing reported in 2001, 2002, 2003 and after 2003, respectively. For example, in 2001, a total number of 2,354,527 BSE tests have been reported in cattle of the age category ">24 months". For consistency, we assigned the censored age category to a number of 125 and 6 BSE cases detected in 2001 and 2002, respectively. The number of animals born in cohort i and tested in year j and the corresponding number of positive BSE test results are denoted as n_{ij} and X_{ij}, respectively.

Age-dependent sensitivity (Se). We considered a Gompertz function with the unknown parameters β_1 and β_2 to reflect the *Se* as a function of age (a_{ij}) in years,

$$Se(a_{ij}) = \exp[\beta_1 \exp(\beta_2 a_{ij})].$$

Response variable. We modeled the number of BSE cases from cohort i detected in year j as a Poisson variate with a parameter λ_{ij} expressed as function of the sample size n_{ij}, the unknown true BSE prevalence π_i and sensitivity $Se(a_{ij})$,

$$X_{ij} \sim \text{Poi}(\lambda_{ij})$$
$$\lambda_{ij} = n_{ij}\, \pi_i\, Se(a_{ij}).$$

Model fitting. The parameters of the Gompertz function for age-dependent sensitivity and the cohort specific true BSE prevalence (π_i) have been estimated using a Bayesian model (see details in 7). Beta distributions with parameters (1,1) were chosen as priors for the cohort specific prevalences. The model has been implemented in R [8] using the BRugs package for Markov chain Monte Carlo (MCMC) modelling [9]. The reported point estimates are median values of the corresponding posterior distributions.

Results and discussion

The estimates of the Gompertz parameters β_1 and β_2 were -12.2 (-22, -8; 95% credible interval) and -1.73 (-1.89, -1.43; 95% credible interval), respectively. The estimates of the BSE infection prevalence for birth cohorts 1994-2005 are shown in Table 1.

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We found a peak of Se-adjusted prevalence estimate of 13.9 cases per 100,000 cattle for the 1996-cohort with an upper limit of a 95% credible interval of 17.2 cases per 100,000. The estimated ratio of undetected to detected cases for the same cohort is 1.0 with upper limit of 1.4. It is noted that the cohort specific prevalence estimates are based on all surveillance results accumulated over all available years of testing.

Table 1: Estimate of BSE infection prevalence adjusted for sensitivity (cases per 100,000) and ratio of undetected to detected cases for German birth cohorts 1994-2005.

Cohort	Prevalence (UL)*	Ratio (UL)
1994	3.4 (5.7)	1.0 (2.3)
1995	4.5 (6.4)	1.0 (1.7)
1996	13.9 (17.2)	1.0 (1.4)
1997	6.5 (8.4)	1.0 (1.5)
1998	4.0 (5.3)	1.0 (1.6)
1999	6.4 (7.8)	1.3 (1.6)
2000	1.3 (1.9)	1.2 (2.1)
2001	0.2 (0.5)	1.4 (8.0)
2002	0.0 (0.2)	1.6 (66.8)
2003	0.1 (0.3)	1.5 (61.7)
2004	0.1 (0.3)	1.5 (58.5)
2005	0.1 (0.5)	1.2 (44.9)

*UL=upper limit of 95% credible interval.

The ratio (undetected to detected BSE cases) estimates showed an increasing trend. We interpret this trend as an effect of an increasing proportion of younger animals tested when age-dependent sensitivity is still low.

The number of cattle slaughtered and tested at age of three years and older declined markedly for birth cohorts 2006 and thereafter. Our model provided increasing BSE prevalence estimates for these younger cohorts, which finally reached 50,000 cases per 100,000 for the 2009-cohort (results not shown). We interpret this as an increasing effect of the prior cohort-specific prevalence (expected value of 0.5), which is finally reached in the absence of suitable testing data for the youngest cohort.

Both interval censoring and left censoring occurred in the reporting of age at testing for the BSE surveillance data. In these cases, we have assumed the minimum age (in years) within the known censoring interval. We believe that this is a conservative approach under the assumption that age-dependent sensitivity increases with age. On the other hand, due to collapsing the ages of 125 BSE cases detected in 2001 into a single censored age category of three years (25-36 months) we may expect that the estimated function for age-dependent *Se* is shifted to the left. This calls for additional sensitivity analyses which can be addressed using alternative approaches for dealing with the age censoring.

We can conclude that the parameters of the latent (non-observable) function for age-dependent BSE testing sensitivity could be estimated without external data. The model in its generic form is capable to estimate parameters of a latent function underlying the data-generating process.

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