



## Assessing the time taken for a surveillance system to detect a re-emergence of bovine spongiform encephalopathy in cattle



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### ABSTRACT

During the bovine spongiform encephalopathy (BSE) epidemic in July 2001 the European Commission established a surveillance scheme for the comprehensive sampling of all BSE clinical suspects, healthy slaughter (HS) animals >30 months, and all emergency slaughter and fallen stock animals tested when >24 months. With the exponential decline in classical BSE cases, this comprehensive surveillance system has been successively modified to become risk-based, targeting those exit streams and ages where cases from the original epidemic are most likely to be detected. Such reductions in testing are not without losses in the information subsequently collected, which could affect the sensitivity of the surveillance system to relatively small changes in the underlying prevalence of BSE across the European Union (EU). Here we report on a cohort-based approach to estimate the time taken for EU surveillance to observe a theoretical re-emergence of BSE in cattle. A number of surveillance schemes were compared. The baseline scheme considered detection being triggered by at least one case in the 'age window' 48–72 months in the fallen stock or emergency slaughter exit streams. Alternative schemes changed the start and end of this age window as well as considering testing for HS cattle. Under the baseline scheme, an estimated 15 years would lapse ([2.5th, 97.5th] percentiles = [10,24]) prior to detection, during which time 2867 infected animals ([2.5th, 97.5th] = [1722,6967]) would enter the slaughter population. These animals would be predominantly young animals (majority <24 months) showing no clinical signs. This baseline scheme reduced the time to detection by 2 years, compared to a scheme where only clinical suspects were tested assuming BSE symptoms are recognised to the same degree by veterinary surgeons. Additional testing of younger animals did not improve detection as young infected animals were unlikely to test positive, but testing of older animals reduced the time to detection. Testing of HS animals >72 months reduced the time to detection by one year compared to the baseline model, but would incur a high financial cost, e.g. testing HS animals >72 months of age for 14 years would entail approximately 50.4 million additional tests. A limitation of the results is that there is no guarantee that current detection methods, optimised for detection of classical BSE, would identify a novel prion disease in cattle and it is currently difficult to envisage plausible routes by which a re-emergence of classical BSE could occur in Europe.

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### 1. Introduction

The first bovine spongiform encephalopathy (BSE) case was diagnosed in November 1986 in Great Britain and the disease was subsequently spread by infected feedstuff and cattle to other European member states (MS) and countries worldwide. Epidemiological studies subsequently identified the vehicle of infection to be meat and bone meal (MBM), incorporated as a protein source in concentrated feedstuffs (Wilesmith et al., 1988). A number of

stringent control measures were introduced to eliminate the risk of recycling of the infectious agent, both at a national and European Union (EU) level to protect animal and human health. High risk bovine tissues were removed from the food, animal by-product and waste chains as 'Specified Risk Materials' to be incinerated, inactivating any prions present. There was also a ban on the use of proteins of animal origin in feed for farmed animals (with certain exemptions) enforced. These control measures were introduced in different years in EU member states with varying effects on the transmission potential of the disease (de Koeijer et al., 2004; Ducrot et al., 2010). The impact of European control measures was monitored by the surveillance regime involving active surveillance, in addition to the observation of clinical suspects. Active

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surveillance was based on the systematic post-mortem testing of the healthy slaughtered cattle, after animals reach certain age, and of “at risk cattle”, which included: (i) animals showing any clinical abnormality during ante-mortem inspection prior to slaughter, (ii) emergency slaughtered animals and (iii) fallen stock. Passive surveillance was carried out by testing all animals that are clinically suspected of BSE (European Commission, 2001). From this surveillance data three strains of BSE have been identified with different neuropathological and molecular phenotypes: the classical strain, that caused the widespread epidemic originating in the UK, and atypical strains (L and H type), which have been suggested to be distinct strains of prion disease arising spontaneously (Biacabe et al., 2008; Ducrot et al., 2008). Post implementation of controls, with the aid of active surveillance results, an exponential decline in BSE cases was observed in most MSs (Ducrot et al., 2010). In view of the continuing steady decline in the number of BSE infected cattle the EU surveillance program has been successively modified, with increases in the minimum age at testing, to make testing more risk-based. Such reductions in testing are not without losses in the information subsequently collected when considering a theoretical re-emergence of BSE in cattle, e.g. if younger animals are not tested then it will take longer to detect changes in the epidemiological situation, which may impact on the time to first detection of a change in the prevalence trend.

To aid the design of future EU BSE surveillance schemes the Cattle TSE Monitoring Model (C-TSEMM) was commissioned by the European Food Safety Authority (EFSA) and developed to estimate the sensitivity of surveillance to detect BSE in cattle (Adkin et al., 2012; Adkin et al., 2016). C-TSEMM determined the number of healthy slaughter cattle that needed to be tested in order to observe a BSE detectable prevalence of 1 in 100,000 in the standing population at the current time. Here we report on a cohort-based approach to estimate the time taken for different EU surveillance schemes to observe a theoretical future re-emergence of BSE in cattle, with particular focus on 1) the number of years until the re-emergence of BSE was observed by surveillance scheme (based on the threshold number of detected cases per year in a given age bracket); 2) the number of infected cattle between the start of the re-emergence and the time of detection entering the slaughter population and 3) the number of animals tested by different hypothetical surveillance scenarios.

## 2. Materials & methods

### 2.1. Model overview

It was assumed that in a given historical year,  $y_0$ , a re-emergence of BSE in cattle began. The model described here estimated how long it would take for this re-emergence to be detected by surveillance activities. The overall approach of estimating the time to detection involved estimating the current trend of BSE infection prevalence and then predicting the trend of the BSE infection prevalence in successive forecasted annual birth cohorts, simulating forecasted cases and determining when an observed threshold was exceeded. This framework is described in Fig. 1. The forecasting model was based on those exit streams provided by the EU legislation: healthy slaughter (HS), emergency slaughter (ES), fallen stock (FS) and clinical suspects (CS). In this paper we present the results for a merged dataset consisting of data from 25 EU MSs (EU25); Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

The demographic data used to populate the model were centrally collected and maintained by the European Commission (EC) and European Food Safety Authority (EFSA) and contained the details of over 91 million cattle tested within the EU25 surveillance scheme from 2002 to 2011 and have been used to inform a previous EFSA scientific opinion (EFSA, 2012).

The forecasting model used this demographic information based on year 0 to forecast for each future year the standing population and the number of cattle exiting that population via the different exit streams, their age (in months), BSE status (not infected or infected and stage of incubation period), whether an animal was tested under the surveillance scheme being evaluated and the test result. Here we present the key results based on an assumed re-emergence which started in 2012.

The baseline monitoring regime considered the testing of ES and FS animals between 48 and 72 months of age, no testing of HS animals and testing of all CS animals. Alternative scenarios, varying the start and end ages of testing and including testing of HS, were also investigated.

The model was developed using the R programming language (R Foundation for Statistical Computing, 2008) with all analysis and simulations carried out in R.

### 2.2. Current BSE infection prevalence

The current BSE infection prevalence in birth cohort,  $c$ , in the absence of a re-emergence,  $r_0(c)$ , was estimated using the cohort based back calculation part of the C-TSEMM model for the EU25 dataset. This model is described in detail elsewhere (Adkin et al., 2012, 2016; EFSA, 2012). Briefly, the back calculation model used historical demographic and test data to estimate the best fitting values,  $A_1$  and  $A_2$ , for an exponential model,  $r_0(c) = A_1 \exp(A_2 * c)$ , along with one constant,  $B$ , determining the differential slaughter of infected cattle between the combined exit streams (CSFS = CS and FS, HSES = HS and ES), by using a solver routine to minimise the negative log likelihood function

$$L = - \sum_{c=1}^C \sum_{y=1}^Y (L_{CSFS}(c, y) + L_{HSES}(c, y)),$$

where  $y$  denotes the testing year and  $Y$  the total number of testing years in the model. The variables  $L_{CSFS}$  and  $L_{HSES}$  took the form

$$L_k = \sum_{c=1}^C \sum_{y=1}^Y (N_k(c, y) - D_k(c, y)) \ln(1 - \hat{\Lambda}_k(c, y)) + D_k(c, y) \ln(\hat{\Lambda}_k(c, y)),$$

where  $k$  denotes the exit streams,  $N_k$  the number of animals tested and  $D_k$  the number of test positives. The probability of being detected as a case,  $\hat{\Lambda}_k(c, y)$ , differed between exit streams and depended on the age of clinical onset at age  $a$ ,  $O(a)$ , the probability of being detected by the post-mortem test at  $t$  days before clinical onset,  $\psi(t)$ , and the BSE infection prevalence,  $r_0(c)$

$$\hat{\Lambda}_{HSES}(c, y) = B * \left[ \int_{x=a}^{x=\infty} O(x) \psi(x-a) dx \right] * r_0(c),$$

$$\hat{\Lambda}_{CSFS}(c, y) = (1 - B) * \psi(0) * O(a) * r_0(c).$$

For this paper, the back calculation model was run for the EU25 dataset with parameter values provided in Table 1.

### 2.3. Forecasting model

The BSE infection prevalence in birth cohorts born in year zero as a result of the original outbreak,  $r(y_0)$ , was estimated from the back calculation model in Section 2.2, i.e.  $r(y_0) = r_0(y_0)$ . For each subsequent year there was a  $\omega\%$  increase applied to the BSE prevalence per year. Thus, the assumed prevalence of infection in each

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