Estimating the BSE infection and detectable prevalence in cattle born after 2000 in Japan

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ABSTRACT

We estimated the infection prevalence of BSE in Japanese cattle born in the period 2000–2012, using maximum likelihood methods and BSE surveillance data of these birth cohorts. From this, we predicted the number of infected cattle and test positives in years 2004–2020. Assuming that the infection prevalence decayed exponentially over time from 2000, the infection prevalence of the 2000 birth cohort was estimated to be 0.00058 which declined exponentially by 0.115 times per year in the following years. The number of infected cattle was calculated to have peaked in 2005 and would be zero by 2020. The number of test positives was calculated to have peaked in 2005 and would be zero by 2012. The number of BSE cases actually detected was within the 95% confidence interval of the predicted numbers. The detectable prevalence (predicted number of test positives/number of cattle tested) was predicted to be highest in 2005. In this year it was predicted that one animal out of 160,000 tested would test positive. The detectable prevalence would decline exponentially to zero in the subsequent years.

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1. Introduction

The first case of BSE in Japan was confirmed in September 2001. As a result the Japanese Government immediately introduced a compulsory ban on the use of processed animal protein in feed for ruminant animals and in fertilizers. The purpose was to stop the exposure of these food animals to transmissible spongiform encephalopathy (TSE) agents (including the BSE agent) via the oral route since processing methods to convert animal-derived raw materials to edible protein could not be guaranteed to destroy TSE agents. In 2001 surveillance for BSE was enhanced in two main ways. First, reporting of fallen-stock ≥24 months of age and all clinical BSE suspects from all herds irrespective of type became mandatory so that brain testing (for PrP BSE) could be used to confirm or exclude BSE. Secondly, BSE testing was introduced for cattle of all ages slaughtered for human consumption. Positive cases were destroyed and did not enter food or feed chains. As a result, by the end of 2012, 35 additional BSE cases had been detected, with the last case being detected in January 2009. Japan obtained the negligible BSE risk status at the World Assembly of the World Organisation for Animal Health (OIE) in May 2013 (OIE, 2013a). Since 1 July 2013, the target age for BSE testing of slaughter-cattle has been raised so that all slaughter-cattle ≥48 months are tested. Although

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Japan is a net importer of cattle and beef and exports no cattle and only a small amount of beef; it is important for Japan to ensure an effective BSE surveillance that demonstrates a continuing negligible risk from BSE to maintain the confidence of consumers and trading partners.

Sugiura and Murray (2007) and Sugiura et al. (2009a) previously estimated the prevalence of BSE-infected animals within birth cohorts of dairy cattle born between 1992 and 2001 using Bayesian inference and the surveillance data. In the present study, we estimated the infection and detectable prevalence in the birth cohorts of beef and dairy cattle from 2000 to 2012, using an exponential decay model similar to the C-TSEMM developed by Adkin et al. (2012) and the surveillance data of these birth cohorts, and predicted the number of infected and test positive animals that would occur until 2020. We also predicted the detectable prevalence until 2020 to provide data to enable the design of a future surveillance program.

2. Materials and methods

2.1. Assumptions

Our previous studies indicated that there were two peaks of BSE infection in Japan, the first in the 1996 birth cohort and the second in the 2000 birth cohort (Sugiura and Murray, 2007; Sugiura et al., 2009a, 2009b, 2011). The source of infection was likely to have been BSE-infected concentrate feed consumed in these years. Based on the results of these studies and with the knowledge that a strictly enforced ban on the use of ruminant protein in feed has been in place since 2001, we focused on the birth cohorts born in 2000–2012. We assumed that the infection prevalence decayed exponentially over time from the 2000 birth cohort through 2012 birth cohort. This seems reasonable because, with no source of infection in the feed produced from 2001, the only significant source of BSE infection would be from infected feed produced before 2001 that remained in the delivery chain such as transport, feed stores, and the like.

We assumed that when cattle leave the population they are either slaughtered for human consumption, or reported as fallen stock. In Japan, no distinction is made between clinical suspects that are killed and fallen-stock that have died on farm. We also assumed that the number of spontaneous cases is so low that it would not affect the model outputs.

2.2. Exit model

The exit model uses the power of simulation to estimate both the probability that a BSE-infected animal leaves (exits) the cattle population as a result of death or being culled for slaughter at a certain age in relation to the stage of its incubation period.

2.2.1. Input parameters

The input parameters used for the exit model are: the age that an animal is infected; the age at which an infected animal dies or is slaughtered; the incubation period; and the duration of clinical signs. The age that an animal becomes infected was modeled as a uniform distribution over its first year of life, because cattle are mostly likely exposed and infected during this time (Wilesmith et al., 1988; Arnold and Wilesmith, 2004). The age at slaughter or death was estimated using statistics derived from data on the number of cattle slaughtered and the number of fallen stock in Japan, provided by the Cattle Identification Scheme Database in 2011 (Anonymous, 2012). A distribution of the incubation period was modeled as a gamma distribution with mean 5 and variance 1.6, as estimated by Anderson et al. (1996). The duration of clinical signs was modeled as a uniform distribution between 2 and 6 months.

2.2.2. Output variables

The output variables, which are used as inputs in the BSE epidemic model described in Section 2.3, are as follows:

- $P_{FS_0}$ is the probability that an infected animal dies at age $a$ during the clinical onset or within 6 months before the clinical onset.
- $P_{SC_0}$ is the probability that an infected animal is culled for slaughter within 6 months before the clinical onset or during clinical stage at age $a$.
- $I_{FS_0}$ is the probability that an infected animal dies at age $a$ irrespective of the reason.
- $I_{SC_0}$ is the probability that an infected animal is slaughtered for human consumption at age $a$.

The input parameters are combined using a series of IF statements to determine whether or not an animal leaves (exits) the cattle population at a certain age as a result of death or being culled for slaughter relative to the stage of its incubation period. The probability estimates are derived as point values, which represent the proportion of successful iterations. A probability distribution can then be defined by combining the estimates for each age and exit pathway. The simulation was undertaken with the software @Risk 6.0 (Palisade) added into the spreadsheet software Excel 14.0 (Microsoft Corporation). To account for rare events in the model, for example the likelihood of an animal not being slaughtered or dying from BSE before reaching 12 years of age, 100,000 iterations were undertaken. This ensured that a sufficient number of successful iterations were obtained for such rare events from which reliable estimates could be obtained. The obtained probability distributions for $P_{FS_0}$ and $P_{SC_0}$ and $I_{FS_0}$ and $I_{SC_0}$ are shown in Fig. 1.

2.3. BSE epidemic model

Maximum likelihood methods based on those used by Adkin et al. (2012), but adjusted to incorporate the input parameters estimated in Section 2.2, were used to estimate the infection prevalence (proportion of infected animals) in birth cohorts born in 2000 through to 2012.

2.3.1. The infection prevalence of birth cohort $c$ ($p_c$)

We assumed that the infection prevalence decayed over time and gave the equation of the curve by:

$$p_c = A \cdot \exp(K \cdot c)$$

(1)
infected months (b, data infected data where \(L\))

2.3.2. Cohort model for birth cohort. The joint log-likelihood function for the number of test positive birth cohort is given by:

\[
L_{BC} = \sum_{c=0}^{12} \sum_{y=0}^{12} (H_c - D_{BC,y}) \ln(1 - E_{BC,y}) + D_{BC,y} \ln(E_{BC,y})
\]

where \(H_c\) is the size of the birth cohort \(c\), \(D_{BC,y}\) is the number of test positives in birth cohort \(c\) in year \(y\), and \(E_{BC,y}\) is the probability of an animal in cohort \(c\) exiting the population and being detected as birth cohort in year \(y\).

2.3.2.1. Log-likelihood model for fallen-stock. The joint log-likelihood function for the number of test positive fallen-stock is given by:

\[
L_{FS} = \sum_{c=0}^{12} \sum_{y=0}^{12} (H_c - D_{FS,c,y}) \ln(1 - E_{FS,c,y}) + D_{FS,c,y} \ln(E_{FS,c,y})
\]

where \(H_c\) is the size of the birth cohort \(c\), \(D_{FS,c,y}\) is the number of test positives in birth cohort \(c\) in year \(y\), and \(E_{FS,c,y}\) is the probability of an animal in cohort \(c\) exiting the population and being detected as fallen-stock in year \(y\).

2.3.2.2. Log-likelihood model for slaughter-cattle. The joint log-likelihood function for the number of test positive slaughter-cattle is given by:

\[
L_{SC} = \sum_{c=0}^{12} \sum_{y=0}^{12} (H_c - D_{SC,c,y}) \ln(1 - E_{SC,c,y}) + D_{SC,c,y} \ln(E_{SC,c,y})
\]

where \(H_c\) is the size of the birth cohort \(c\), \(D_{SC,c,y}\) is the number of test positives in birth cohort \(c\) in year \(y\), and \(E_{SC,c,y}\) is the probability of an animal in cohort \(c\) exiting the population and being detected as slaughter-cattle in year \(y\).

2.3.2.3. Overall joint log-likelihood function. From joint log-likelihood functions 2 and 3, the overall joint log-likelihood function for the number of test positive fallen-stock and slaughter-cattle animals of birth cohorts born in 2000 through 2012 is given:

\[
L = L_{FS} + L_{SC}
\]

2.3.3. Input variables

2.3.3.1. The size of the birth cohort \(c\) \((H_c)\). The numbers of cattle born in year from 2004 through 2012 were 1,419,977, 1,432,766, 1,413,234, 1,421,145, 1,411,683, 1,389,139, 1,377,578, 1,331,785 and 1,282,505, respectively, obtained from the National Cattle Identification Scheme Database (Anonymous, 2013). As there is no data available for 2000–2003 birth cohorts, we assumed that the size of 2000–2003 cohorts is the same as the 2004 birth cohort. The deviation of this assumed size of 2000–2003 birth cohorts from the actual size would be small considering the stable milk and beef production observed in the following years.

2.3.3.2. The proportion of slaughter-cattle tested in year \(y\) \((T_{FS,y}\ and \ T_{SC,y})\). The proportion of fallen-stock and slaughter-cattle tested in 2000–2012 is shown in Table 1.

The probability that fallen-stock \(\geq 24\) months of age are tested for BSE was determined by dividing the number of fallen-stock \(\geq 24\) months tested each year from 2000 to 2005 by the number tested in 2005. Since all fallen-stock \(\geq 24\) months have been tested for BSE since 1 April 2004,
the number tested in 2005 is assumed to be the same as
the number of fallen stock reported in that year under
the National Cattle Traceability Scheme (Anonymous, 2012).
Likewise, the probability that a slaughter animal was tested
determined by dividing the number of slaughter-cattle
tested each year from 2000 to 2002 by the number of
slaughter-cattle tested in 2002, since all slaughter cattle
were tested since 18 October 2001. The number of
slaughter animals tested in 2002 was obtained from
the Ministry of Health, Labour and Welfare’s database

### 2.3.3. The number of fallen-stock and slaughter-cattle test
positives in birth cohort in year \( y \) \((D_{FS_{y},y} \text{ and } D_{SC_{y},y})\).
The number of BSE cases detected in 2003–2009 by year of
detection and exit-streams is shown in Table 2. No case
had been detected in animals born in 2002 and subse-
quent years, except for one case born in 2001 and another
born in 2002, both detected in 2003. We did not con-
sider these cases in estimating the infection prevalence,
because the confirmatory diagnosis for these cases was
made by Western blot only, which detected an accumu-
lation of unusually small amounts of core fragments of
\( \text{PrP}^{\text{Sc}} \) (PrPcore) and the transmission study conducted later
by inoculating bovine PrP-overexpressing transgenic mice
(TgBoPrP) with brain material from these cases resulted in
none of these mice developing evidence of BSE infection
(Yamakawa et al., 2003; Yokoyama et al., 2007; Ono et al.,
2011).

### 2.3.4. Estimating the infection prevalence of birth cohort
\( c \) \((p_{c})\)

As discussed in Section 2.2 (input parameters), values
for all the parameters in overall joint log-likelihood
function in Section 2.3.2.3, apart from model parameters
\( A \) and \( K \) in Section 2.3.1, can be obtained from existing
sources of information. In this situation, \( A \) and \( K \) were
estimated by maximizing the overall joint log-likelihood in
Section 2.3.2.3 using RiskOptimizer (Palisade). RiskOpti-
mizer is software added into the spreadsheet software
Excel 14.0 (Microsoft Corporation) that enables estimation
of two or more unknown variables by genetic algorithm.
We obtained the values of \( A \) and \( K \) that maximize the joint
log-likelihood by undertaking 10,000 simulations of 1000
iterations each. The infection prevalence of birth cohort \( c \)
\((p_{c})\) was estimated by inserting the values of \( A \) and \( K \) into
the model in Section 2.3.1.

### 2.4. Predicting the number of BSE infected animals and
test positives

The number of BSE infected animals originating from
birth cohort \( c \) that left the population in year \( y \) \( \geq 24 \) months after
birth is calculated as the number of cattle deaths in year
\( y \) \( \geq 24 \) months after birth (Yamakawa et al., 2003).
these born after 2013, we assumed that $\tilde{p}_c$ declines after 2013 with the same trend as up to 2013.

The number of test positives of fallen-stock and slaughter-cattle originating from birth cohort $c$ in year $y$ was estimated respectively by:

$$\text{Pos}_{FS,c,y} = H_c \ast T_{FS,y} \ast P_{FS} \ast \tilde{p}_c$$  \hfill (7)
$$\text{Pos}_{SC,c,y} = H_c \ast T_{SC,y} \ast P_{SCa} \ast \tilde{p}_c$$  \hfill (8)

The number of BSE infected fallen-stock and slaughter-cattle and the number of test positives in fallen-stock and slaughter-cattle in a particular year was calculated by summing over the birth cohorts for the respective exit streams. The total number of BSE infected cattle culled and the total number of test positives in a particular year was computed by summing over the two exit streams and birth cohorts.

To incorporate the uncertainty of the model results arising from the binomial function, we put these estimates into a Poisson function as a mean number of events per year and used Monte Carlo simulation and ran 100,000 iterations. The simulations were performed using software @Risk 6.0 (Palisade) added into the spreadsheet software Excel 14.0 (Microsoft Corporation).

2.5. Predicting the detectable prevalence

The detectable prevalence in a particular year was calculated by dividing the total number of test positives by the total number of animals tested in that year. In calculating the number of cattle tested, we assumed that active surveillance composed of testing of all fallen-stock ≥24 months and all slaughter-cattle ≥0 month will continue until 2020.

3. Results and discussion

Fig. 2 shows the estimated infection prevalence for each of the 13 birth cohorts from 2000 to 2012. The infection prevalence of cattle born in 2000 was estimated to be 0.00058 and declined from 2001 birth cohort exponentially by $e^{-2.2}$ (=0.115) times per year. This infection prevalence in the 2000 birth cohort is higher than the infection prevalence of slaughter-cattle in the 2000 birth cohort of dairy cattle that we estimated previously, namely 0.00016 (95% CI: 0.00008–0.00028) (Sugiura et al., 2009a). This is because the infection prevalence that we estimated in the current study is the average of fallen-stock and slaughter-cattle and takes account of dairy and beef cattle, and that the infection prevalence ratio of fallen-stock over slaughter-cattle is higher in the current study. This reflects the surveillance result that in cattle born after 2000, most of the BSE cases are in fallen-stock (Table 2).

Fig. 3 shows the predicted total number of infected fallen-stock and infected cattle slaughtered for human consumption during the years 2004–2020. It is predicted that there will be no infected animals culled after 2020. The results show that the presence of infected animals would last longer in the current study than in our previous studies (Sugiura and Murray, 2007; Sugiura et al., 2009a). This is because in the previous study we assumed that cattle born after 2002 are not infected, while in the current study we assumed that the infection prevalence decays exponentially over time from 2002.
Fig. 4. Predicted number of bovine spongiform encephalopathy test positives in total (a), fallen-stock (b) and slaughter-cattle (c) in years from 2004 to 2020. Solid lines indicate the mean estimates, and dashed lines the 95% confidence intervals, assuming a surveillance program composed of BSE testing of all fallen-stock ≥24 months and all slaughter-cattle ≥0 month was in effect until 2020 and is rigidly enforced. Dotted lines indicate the number of BSE cases actually detected.

Fig. 4 shows the predicted total number of test positives (fallen-stock and slaughter-cattle) during the years 2004–2020, assuming that active surveillance composed of BSE testing of all fallen-stock animals ≥24 months and all slaughter-cattle ≥0 months is in place, enforced and effective. The number of BSE cases actually detected is within the 95% confidence interval of the predicted numbers. Also, the predicted mean number of test positives (BSE cases) will be zero in the years after 2010, which is consistent with the fact that no BSE case has been detected since the last case detected in January 2009. Fig. 4(a) indicates that the probability that a BSE case is detected will be practically zero after 2012.

Our model assumes that the infection prevalence delays exponentially over time through birth cohorts, as does the C-TSEMM model (Adkin et al., 2012). This assumption is reasonable because the only significant source of BSE infection after a rigidly enforced feed ban would be from infected feed produced prior to 2001 and which had contaminated feed vehicles, feed stores and the like. In fact, the number of BSE infected animals detected declined exponentially over time between different birth cohorts in the UK, France and other EU members after the feed ban in 1996 (European Commission, 2013), indicating the exponential decline in infection prevalence over time between birth cohorts. In Japan, although the number of BSE cases detected is too low to fit an exponential decay curve, the results of official on-site inspections conducted after 2002 indicated nearly full compliance with the feed ban by feed importers, manufacturers, distributors and end-users (farmers) (Kusama et al., 2009).

One advantage of our model, compared to the C-TSEMM model, is that our model does not have to use the differential slaughter parameter in the model, as the parameter is essentially incorporated into the probability estimates that an infected animal exits in the fallen-stock or slaughter streams (\(P_{FSa}\) and \(P_{SCa}\)), which were obtained using the exit model.

Our model can be used to simulate the effectiveness of different surveillance programs by changing the target age of BSE testing and predicting the number of test positives. For example, the predicted number of test positives will not change, even if we raise the target age of BSE testing from zero to 48 months for slaughter-cattle from 2013 (results not shown).

Fig. 5 shows the predicted detectable prevalence during 2004–2020. The detectable prevalence was predicted to be highest in 2005, with one BSE animal detected in 16,000 fallen-stock or in 0.9 million slaughter-cattle tested. On average one in 0.2 million cattle tested can be detected. From 2006, the detectable prevalence starts to decline exponentially as the infection prevalence declines and most of the cattle in 2000 and 2001 birth cohorts with relatively high infection prevalence had been culled.

The detectable prevalence in all cattle, fallen-stock and slaughter-cattle falls below one in one million animals after 2008, 2010 and 2006, respectively.

Countries recognized as negligible or controlled BSE risk by the OIE are required to conduct surveillance that is capable of detecting at least one BSE animal if there is
one detectable animal in 50,000 or 100,000 respectively if they want to maintain their respective status (OIE, 2013b). Adkin et al. (2012) evaluated the effectiveness of the current BSE monitoring schemes in the EU members using the C-TSEMM model, and concluded that no healthy slaughtered cattle need to be tested in order to meet a design prevalence of one detectable case in 100,000 adult cattle with a 95% confidence level. Our model can also be used to estimate the number of fallen-stock and slaughter-cattle required to be tested. For example, under the current BSE surveillance scheme in Japan, the number of fallen-stock and slaughter-cattle to be tested for BSE in 2014 is 90,000 and 220,000, respectively. However, using the detectable prevalence in fallen-stock and slaughter-cattle estimated in our study and the binomial formulae used by Cannon and Roe (1982), the number of animals required to be tested to detect one animal in 100,000 cattle is calculated to be 56,000 fallen-stock and no slaughter-cattle need to be tested. Likewise, the number of cattle to be tested from 2015 onward to meet such a design prevalence can be calculated using the detectable prevalence in the respective years estimated in this study.

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