Simulating the bovine spongiform encephalopathy situation in Japan

K. Sugiura(1)*, N. Murray(2), T. Tsutsui(3), E. Kikuchi(4) & T. Onodera(5)

(1) Food and Agricultural Materials Inspection Center, 2-1 Shintoshin, Chuo-ku, Saitama-shi, Saitama 330-9731, Japan
(2) Canadian Food Inspection Agency, 59 Camelot Drive, Ottawa, Ontario, Canada
(3) National Institute of Animal Health, Epidemiological Research Team, 3-1-5, Kannondai, Tsukuba 305-0856, Japan
(4) Animal Health Division, Ministry of Agriculture, Forestry and Fisheries, 1-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100-8950, Japan
(5) Department of Molecular Immunology, University of Tokyo, Bunkyo-ku, Tokyo 113-8657, Japan

*Corresponding author: katsuaki_sugiura@nm.famic.go.jp

Summary
Despite various measures taken by the Japanese government to protect the cattle population from exposure to the bovine spongiform encephalopathy (BSE) agent, the first case of BSE was detected in September 2001. Subsequently, BSE surveillance was enhanced, involving mandatory reporting and investigation of all clinical BSE suspects, and testing of fallen stock and all cattle slaughtered for human consumption. Tests on over nine million cattle led to the detection of 35 additional cases by the end of May 2009. Using the surveillance data and other information as input variables, models were developed to explore the possible source of introduction of BSE into Japan, evaluate the effectiveness of control measures, estimate the prevalence of BSE in different birth cohorts, predict a future BSE epidemic, and simulate the impact of changes in surveillance strategies. Despite difficulties associated with the availability and uncertainty of some of the input variables, these models provided an objective insight into the BSE situation in Japan.

Keywords
Bovine spongiform encephalopathy – Epidemiology – Japan – Simulation model.

Introduction
The first case of bovine spongiform encephalopathy (BSE) reported in Japan was detected on 10 September 2001, in a five-year-old dairy cow born in Hokkaido and raised in Chiba prefecture. Before detection of the first case, the Japanese government had taken various measures to protect the cattle population from exposure to contaminated feed:

– in July 1990, importation of live cattle and meat-and-bone meal (MBM) had been prohibited from the United Kingdom (UK) and other countries with a BSE incident (except for MBM heat treated at 133°C/3 bar/30 min)
– in March 1996, importation of MBM from the UK had been totally prohibited
– in April 1996, administrative guidance had been issued to prohibit the use of ruminant MBM for ruminant feed
– in January 2001, importation of MBM had been prohibited from Member States of the European Union (EU), Switzerland and Liechtenstein.

After detection of the first case, the Japanese government introduced the following measures:

– the mandatory removal and incineration of specified risk material from all cattle slaughtered for human consumption after 27 September 2001. Specified risk material was defined initially as the brain, the spinal cord, eyes and the distal ileum, and this was expanded on 16 February 2004 to include the vertebral column;
– a legal ban on the domestic use of ruminant protein for ruminant feed was implemented on 18 September 2001,
followed by a ban on the domestic use and importation of all processed animal protein for the production of feed for ruminants, pigs, and chickens and as a fertiliser, effective from 4 October 2001;  
– enhanced BSE surveillance, involving mandatory reporting and investigation of all clinical BSE suspects (passive surveillance), together with testing of fallen stock and all cattle slaughtered for human consumption (active surveillance);  
– the introduction, in December 2003, of an animal identification system that enables trace-back to the farm of origin and access to other relevant information, including the date of birth.

As a result of the enhanced BSE surveillance, 35 additional cases had been detected by the end of March 2009, with between two and ten cases being detected each year up to the end of 2007. The epidemic appeared to peak in 2006. Cases were detected mostly in dairy cattle; in cattle born in 1996 and 2000; and in cattle born in Hokkaido. Two were atypical cases of BSE and the remainder were classical cases.

Using the surveillance and other data, and simulation models, attempts have been made to simulate the BSE situation in Japan. This paper describes and discusses the simulation models used in these attempts.

Models used to explore the possible source of introduction of the bovine spongiform encephalopathy agent

In the 1990s, live cattle were imported from Germany and France and substantial amounts of bone-in beef and MBM

Fig. 1
A scenario tree outlining the events and pathways leading to the release of infected meat-and-bone meal following the importation of live cattle (5)
SRM: specified risk materials
MBM: meat-and-bone meal
were imported from some EU Member States. Using data on these imports, Sugiura et al. (5) quantitatively assessed the risk of the introduction of BSE in terms of the weight of infected MBM released into Japan. They constructed a simulation model by identifying three scenario trees with pathways leading to the release of infected MBM following importation of live cattle, MBM and bone-in bovine meat, respectively. The scenario tree used to estimate the amount of infected MBM released into Japan following importation of live cattle is shown in Figure 1. A stochastic simulation model was used, with key input variables in the form of probability distributions that accounted for the uncertainty associated with the input variables. The authors estimated that between 23.4 kg and 53.8 kg of infected MBM was released into Japan between 1993 and 2000. The simulation result also indicated that imported MBM represented the most important risk factor for the release of the BSE agent into Japan during that period (Table I).

In the 1980s, 33 live cattle were imported into Japan from the UK. Using these data and a simulation model, Sugiura estimated that at least one of these cattle developed BSE (reached the end of the incubation period) and entered the animal feed chain, most probably in 1991, 1992 or 1993, with a cumulated probability of 16% (3). In another study, Sugiura et al. extended this simulation model to calculate the number of infected animals and the amount of BSE infectivity that may have entered the animal feed chains in Japan (7). They estimated that, of the 33 cattle imported from the UK into Japan, probably seven or eight were infected and entered the animal feed chain. They also estimated that 400 to 550 cattle oral median infectious dose (ID$_{50}$) of the BSE agent entered the animal feed chain in each of 1992 and 1993. The amounts of infectivity that entered the feed chain in 1989, 1991, 1994 and 1995 were all smaller but still substantial, suggesting that the BSE agent might have entered the feed chain in any of these years (7) (Table II).

The fact that the earliest born indigenous case in Japan was born in July 1992, together with the above simulation result, indicates that the BSE agent entered the animal feed chain in Japan around 1992.

### Table I

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Amount of infected MBM released into Japan (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Importation of live cattle (kg)</td>
<td>0.014 (0.008-0.019)</td>
</tr>
<tr>
<td>Importation of bone-in meat (kg)</td>
<td>0.051 (0.038-0.069)</td>
</tr>
<tr>
<td>Importation of MBM (kg)</td>
<td>36.2 (23.3-53.7)</td>
</tr>
<tr>
<td>Total</td>
<td>36.3 (23.4-53.8)</td>
</tr>
</tbody>
</table>

MBM: meat-and-bone meal

### Table II

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of infected animals that entered the animal feed chain (95% confidence interval)</th>
<th>Amount of BSE infectivity that entered the animal feed chain in cattle oral ID$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>1.0 (0.3)</td>
<td>34-66</td>
</tr>
<tr>
<td>1990</td>
<td>0.2 (0.1)</td>
<td>12-21</td>
</tr>
<tr>
<td>1991</td>
<td>0.5 (0.2)</td>
<td>69-87</td>
</tr>
<tr>
<td>1992</td>
<td>2.4 (0.5)</td>
<td>399-544</td>
</tr>
<tr>
<td>1993</td>
<td>1.9 (0.5)</td>
<td>411-526</td>
</tr>
<tr>
<td>1994</td>
<td>0.3 (0.1)</td>
<td>59-78</td>
</tr>
<tr>
<td>1995</td>
<td>0.3 (0.2)</td>
<td>94-118</td>
</tr>
</tbody>
</table>

BSE: bovine spongiform encephalopathy
ID: infectious dose

Models used to evaluate the effectiveness of control measures for bovine spongiform encephalopathy taken in the past

The Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) issued administrative guidance in April 1996 calling for feed producers to stop the use of MBM in the production of compound feed for ruminants from April 1996 to protect the cattle population from exposure to BSE. Following detection of the first case of BSE in 2001, MAFF was severely criticised for only issuing administrative guidance instead of implementing a legal ban in 1996.

The effect of this administrative guidance was quantitatively assessed in two studies. Yamamoto et al. (15) modelled three routes of exposure to BSE via MBM, i.e. feeding cattle concentrates containing MBM as an ingredient; feeding cattle concentrates contaminated with MBM from non-ruminant feed at feed plants; and directly feeding MBM in supplemental form to cattle on farms. They estimated the total infectivity to cattle via MBM from an infected animal to be 0.49 ID$_{50}$ and 0.22 ID$_{50}$ in 1995 and 1997 respectively. Thus, the feed ban in 1996 had the effect of reducing the exposure risk by 55% (15).
Sugiura et al. (10), using a simulation model, and assuming that the number of secondary infections that a BSE-infected animal can produce once it has reached the last stage of its incubation period is between 200 and 600, estimated that the administrative guidance issued in 1996 reduced the probability that the MBM derived from cattle was fed back to cattle by a factor of between 104 and 141 (10). Thus, different results were produced by the use of different models. Nevertheless, both simulation results indicated that the administrative guidance had the effect of reducing the MBM fed to cattle, although it did not eliminate the feeding of MBM completely.

Models used to estimate the prevalence of infection and to predict a future epidemic

Sugiura and Murray (8) estimated the number of infected animals in each dairy birth cohort born from 1992 to 2001, using a Bayesian model and the surveillance data up to the end of 2004. From the number of infected animals, they predicted historical and future trends in the number of infected animals culled from each cohort and whether or not they could be detected with a rapid test. Assuming that BSE infectivity entered Japan in 1995, 225 infected animals (95% confidence interval [CI]: 111 to 418) were predicted to have been culled from 1995 to 2001, of which 116 (CI: 56 to 219) would have been slaughtered for human consumption, and 33 (CI: 12 to 65) cases would have been detected during this period if a BSE surveillance programme as comprehensive as the one in place as of April 2004 had been applied. Assuming that BSE infectivity entered Japan in 1992, these numbers would be 905 (CI: 366 to 4,633), 694 (CI: 190 to 2,473) and 201 (CI: 53 to 693), respectively. They predicted that 18 (CI: 3 to 111) were likely to be detected in 2004 and beyond and that the BSE epidemic in Japan should be eradicated around 2012 (8). Sugiura et al., using the same model but using data obtained from surveillance until the end of 2008, updated these estimates and predictions (6) (Figure 2).

Yamamoto et al. (14) estimated the number of infected cattle in each birth year by maximum likelihood estimation using data on the number of cases detected from 2002 to 2006. They also estimated the number of infected cattle that died or were slaughtered each year by Monte Carlo simulation. They estimated that the number of infected animals born in 1996 was 155 (95% CI: 90-275); this represented the majority of infected cattle that could have been sources of infection before 2001. They also estimated that, of these 155 infected animals, 56 died or were slaughtered before October 2001 and after the accumulation of infectious agent in their bodies, and that five of these 56 animals entered the food chain. Based on this estimation, they concluded that the
number of infected animals that could have served as a source of human infection would appear to have been a limited subset of the BSE-infected cattle in Japan (14). Hamasaki and Yamamoto, using the BSurvE method, estimated that the BSE-infected cattle born in 1996 numbered 288 (1). Table III shows the estimated number of infected animals in the 1996 dairy birth cohort reported in these studies.

### Models used to simulate the impact of changes to the surveillance strategies

As of 18 October 2001, all cattle slaughtered in abattoirs for human consumption have been subjected to BSE testing, under the Abattoir Law. All cattle for slaughter are subjected to ante-mortem inspection before they are slaughtered in abattoirs. Meat inspectors, who are veterinarians, collect brain stem samples from all cattle slaughtered, which are then sent to prefecture meat-inspection laboratories for the BSE screening test. The carcass of any animal testing positive for BSE is incinerated.

In September 2004, on the basis of the results of risk assessment by the Food Safety Commission (FSC), the Ministry of Health, Labour and Welfare (MHLW) decided to exempt cattle younger than 21 months old from BSE testing. The MHLW amended the regulations so that all cattle 21 months old or older were tested from 1 August 2005. However, reflecting the concerns of consumers, all cattle slaughtered for human consumption continue to be tested voluntarily by the prefecture governments, with financial support from the MHLW (the financial support ceased on 1 August 2008).

In addition to the risk assessment by the FSC, a couple of attempts have been made to assess the impact of potential changes to the surveillance strategies quantitatively, using simulation models.

Tsutsui and Kasuga (12) constructed a stochastic model using Monte Carlo simulation to estimate the BSE infectivity destined for the food chain from a single BSE-infected animal at slaughter, and then compared the impact of different testing strategies and removal of risk material. The expected fraction of BSE-infected cattle presented for slaughter that would be detected by screening tests was 20%, even if all slaughtered cattle were tested. The reduction in infectivity obtained through cattle screening tests was greater than that obtained through the removal of specified risk materials, but reduction efficacy did not differ among the various testing strategies. The study suggested that the impact on beef safety of changing the age limit for testing cattle is small, provided that the removal of risk materials is conducted properly (12).

Sugiura et al. evaluated the impact of potential changes to the current BSE surveillance programmes for slaughter cattle and fallen stock using a stochastic model (9). They calculated the probability that a BSE-infected animal slaughtered for human consumption or occurring as fallen stock would be tested and detected. (The animals included in the model were: dairy cows, Wagyu beef cattle [Japanese indigenous breeds including the Japanese Black, Brown, Shorthorn, and Polled], Wagyu-Holstein cross steers or heifers, and Holstein steers.) They found that increasing the minimum age of testing from 0 to 21 months for both dairy cattle and Wagyu beef cattle had very little impact on the probability that a BSE-infected animal slaughtered for human consumption would be detected. They also found that, although increasing the minimum age at testing from 21 to 31 or 41 months would lead to fewer slaughtered animals being tested, the impact on the probability of detecting infected animals would be insignificant (9).

### Other models of bovine spongiform encephalopathy

Using maximum-likelihood methods, Sugiura (4) calculated the ‘adjusted incidence risk’ of BSE by different ages and risk subpopulations (clinical suspects, fallen

<table>
<thead>
<tr>
<th>Model used</th>
<th>Surveillance data used</th>
<th>Number of infected animals in the 1996 cohort</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayesian inference</td>
<td>Up to the end of 2004</td>
<td>230 (95% CI: 120-490)</td>
<td>Sugiura and Murray (2007) (8)</td>
</tr>
<tr>
<td>Maximum likelihood estimation</td>
<td>Up to the end of 2006</td>
<td>175 (90% CI: 95-285)</td>
<td>Yamamoto et al. (2008) (14)</td>
</tr>
<tr>
<td>BSurvE method</td>
<td>Up to the end of 2006</td>
<td>288</td>
<td>Hamasaki et al. (2008) (1)</td>
</tr>
<tr>
<td>Bayesian inference</td>
<td>Up to the end of 2008</td>
<td>461 (95% CI: 262-802)</td>
<td>Sugiura et al. (2009) (6)</td>
</tr>
</tbody>
</table>

CI: confidence interval
stock, sick slaughtered and healthy slaughtered animals). Based on this indicator, which is comparable with incidence risks in Europe, he noted that the ratio of incidence risk in slaughter cattle to that in fallen stock is higher in Japan than in the EU and Switzerland (4). The author concluded that the relatively high incidence of BSE in slaughter cattle in Japan might have occurred because sick or moribund cattle are more likely to be sent to abattoirs for human consumption in Japan than in Europe, and are less likely to become either clinical suspects or fallen stock (4).

Yamamoto et al. evaluated the BSE infection risk of cattle from sewage sludge from wastewater treatment facilities in slaughterhouses in Japan (13). They estimated an infectious dose ingested by cattle in Japan from an infected animal to be $5.5 \times 10^{-3}$ bovine oral ID$_{50}$, assuming that the total infectivity attributed to specified risk materials from a BSE-infected animal is 7,500 bovine oral ID$_{50}$. They concluded that the prevention of scattering of specified risk materials during the slaughter process, installing filters to remove tissue residues from the drain water and preventing the application of sludge-derived fertilizer on pasturelands would be effective in reducing the risk of BSE infectivity being ingested by cattle (13).

Sugiura and Smith (11), using a simple stochastic model, simulated the time interval between slaughter and the predicted time of clinical onset of BSE in an infected animal, and thus compared the rise of BSE infectivity in beef from cattle younger than 21 months in Japan with that in beef from the United States, as assessed by the carcass maturity score (11).

**Discussion and conclusion**

Modelling has not been used widely in Japan for the management of animal diseases. Nevertheless, several attempts have been made to explore the possible source of introduction of the BSE agent into Japan, to evaluate the effectiveness of BSE control measures, to estimate the prevalence of BSE infection, to predict any future BSE epidemic, and to simulate the impact of changes in surveillance strategies.

Any model depends for its validity on the accuracy and completeness of the data underpinning it (2). In the models described above, surveillance data and other data available in Japan, as well as estimated input parameters based on the BSE epidemic in the UK, were used.

The detailed data were available for the 33 bovine animals imported from the UK in the 1980s, which made it possible to estimate when and with what probability the BSE agent entered the Japanese animal feed chain. However, there is little information on how the domestic cattle population was exposed to the infected MBM that may have been produced from infected animals. This, together with the fact that substantial amounts of MBM and animal fat were imported from Europe until the mid-1990s, makes it difficult to rule out the possibility of imported MBM or animal fat being a source of introduction of the BSE agent into Japan.

The surveillance data obtained by the end of 2008, which involved testing more than nine million animals with a rapid test, have enabled the estimation of the prevalence of infected animals in birth cohorts born in 1997 and later years with relative precision. However, it is not possible to estimate the prevalence of infection in birth cohorts born in 1996 and earlier years, because not many animals born in those years were alive when the comprehensive surveillance started in April 2004. Given that there were no accurate data on the amount of MBM mixed into cattle feed through cross-contamination after the administrative feed guidance was issued in 1996, the assessment of the effectiveness of this guidance was only possible retrospectively from the epidemic pattern, using the prevalence of infection estimated from these surveillance data.

The cattle identification system that was introduced in December 2003 has made available complete data on the demographic structure of cattle, i.e. survival curves for each type of cattle in Japan. This, together with the incubation period distribution and the information that a rapid test can only detect infected animals in the last stage of the incubation period, has made it possible to simulate the impact of changes in surveillance strategies.

Although not all of these results were used in policy-making, some proved to be useful in answering questions posed by policy-makers (some of the studies have been referred to in Food Safety Commission reports).
Simulation de la situation de l’encéphalopathie spongiforme bovine au Japon

K. Sugiura, N. Murray, T. Tsutsui, E. Kikuchi & T. Onodera

Résumé

Mots-clés

Simulación de la situación de la encefalopatía espongiforme bovina en Japón

K. Sugiura, N. Murray, T. Tsutsui, E. Kikuchi & T. Onodera

Resumen
Pese a las diversas medidas adoptadas por el Gobierno japonés para proteger a su cabaña bovina de la exposición al agente etiológico de la encefalopatía espongiforme bovina (EEB), en septiembre de 2001 se detectó el primer caso de esta enfermedad. A partir de ahí se reforzó la vigilancia de la EEB, imponiendo la obligatoriedad de notificar e investigar todos los casos clínicos sospechosos y de realizar pruebas en todo bovino que cayera muerto o fuera sacrificado con fines de consumo humano. Tras someter a prueba a más de nueve millones de ejemplares, a finales de mayo de 2009 se habían detectado otros 35 casos. Utilizando, entre otras variables iniciales, los datos de las actividades de vigilancia, se confeccionaron modelos para localizar eventuales fuentes de introducción de la EEB en el país, evaluar la eficacia de las medidas de lucha, estimar la prevalencia de la EEB en distintas cohortes de nacimiento, anticipar una futura epidemia de EEB y simular las consecuencias de hipotéticos cambios
References


