4 Results

This section highlights key results of the analyses in this report. Complete results can be found in Appendices 3A and 3B. Appendix 3C describes how we have summarized the results generated by the simulation using tables and figures.

Section 4.1 discusses the modeled impact of importing ten BSE-infected animals into the U.S. under present-day conditions (*i.e.*, the base case as described in Section 3.1). The model predicts that such an introduction would be unlikely to result in new cases of BSE, that little infectivity would be likely to reach the U.S. human food supply, and that BSE would likely be cleared from U.S. in less than 20 years.

Section 4.2 describes the results of the sensitivity analyses outlined in Section 3.2. In particular, we describe how altering these assumptions influenced the predicted number of new BSE cases and the amount of infectivity potentially available for human consumption following introduction of ten infected animals. Key model parameters identified include the rate of misfeeding on the farm, the proportion of prohibited feed that is mislabeled, the proportion of clinical BSE cases detected during *ante-mortem* inspection, and the number of ID_{50}s in a symptomatic animal.

Section 4.3 describes the predicted impact of different sources of infectivity and evaluates both their plausibility and potential for BSE infectivty to spread to cattle or to be available for potential human exposure. The simulation model predicts that under current conditions (i.e., base case assumptions) cross species transmission of scrapie or spontaneous BSE, if they can occur, would produce one or two new cases of BSE per year in the U.S. and little infectivity to humans. Further evaluation of the effect of importing infected animals reveals that even if 500 infected animals were imported, the disease would eventually be eliminated from the U.S.

Finally, Section 4.4 describes the model's predictions for the scenarios outlined in Section 3.4. The predictions made by the model for the Switzerland scenario are sufficiently similar to those observed to lend the model credibility. Our analysis of potential imports of BSE-infected animals from the UK into the U.S. during the 1980s shows that it is unlikely although not impossible that these imports introduced BSE into the U.S. cattle population. Finally, the

simulation's predictions suggest that two risk management measures (a specified risk material ban or a ban on the rendering of cattle that die on the farm) would each further improve defenses against BSE in this country.

Section 4.5 concludes our report with a summary of the main findings and the implications of BSE for both animal and public health in the U.S.

Before proceeding, we note that many of the simulation results are "right skewed," meaning that the average value often exceeds the median (50^{th}) percentile and can sometimes even exceed the 95^{th} percentile. A right-skewed distribution arises when rare events can result in very large outcome values. For example, the probability that the brain of a BSE-infected animal will be selected for potential human consumption is very low because there are few sick animals and few brains harvested for human consumption. However, if this event does occur, it makes a substantial quantity of infectivity available for potential human consumption. If this event only occurs one time out of 1,000 simulation runs, the arithmetic mean for the number of cattle oral ID_{50}s available for human consumption from brain would exceed this outcome's value for 999 of the 1,000 runs (*i.e.,* zero). For this reason, we report key percentile values for each outcome, in addition to the arithmetic mean. Appendix 3C further describes how we have reported the simulation results. The results discussion focuses on mean and median values to characterize the central tendency for each quantity, and the 95^{th} percentile to characterize a quantity's extreme (although not worst possible) case value.

4.1 Base Case

The assumptions in the base case correspond to contemporary conditions in the U.S., including all risk management actions taken by government and industry. Appendix 1, Section 2 details the corresponding parameter values. Because BSE has not been found in the U.S., the base case is evaluated by assuming the import of ten BSE-infected animals. Such an introduction is considered unlikely because of the ban on importing ruminants from countries known to have BSE. However, this approach allows characterization of the way in which infectivity could spread to animals or humans should the disease be introduced.

Introduction of ten animals demonstrates the robustness of U.S. regulations and practices in preventing the establishment of BSE (full results can be found in Appendix 3A, Section 1). On

average, there are fewer than three new cases of BSE, with a 75 to 95% chance that there will be no new cases at all. The extreme case (the 95th percentile of the distribution) predicts 11 new cases. The simulation predicts an average of 35 cattle oral ID_{50}s potentially available for human consumption during the 20-year period following the import of the infected animals, with a 95th percentile value of 170 cattle oral ID_{50}s. In all cases, the disease is quickly cleared from the U.S., with virtually no chance that there are any infected animals 20 years following the import of infected animals.

Potential human exposure routes include consumption of brain (26% of the total on average), contaminated AMR product (67%), beef on bone (11%), intestine (2 %), and spinal cord (5 %). Even these estimates are likely to overstate true human exposure because they represent the amount of infectivity *presented* for human consumption but do not take into account waste or actual consumption rates. For example, the reported quantity for potential exposure of ID_{50}s in beef on bone potential reflects the presence of spinal cord and dorsal root ganglia in a fraction of cuts like T-bone steaks. The spinal cord may never be consumed but is still available for potential human exposure. Similarly, not all bovine brain removed for human consumption is actually eaten by humans. Some is not purchased at the retail level and some is not consumed even when purchased. These issues are also relevant to the other tissue categories. For these reasons, our estimates of potential human exposure are likely to overestimate true exposure to infected BSE tissues.

To further characterize the resilience of the U.S. agriculture system, we simulated the impact of introducing 1, 5, 20, 50, 100, 200 or 500 infected cattle (see Section 4.3.3).

4.2 Sensitivity Analyses and Alternative Assumptions

There exist considerable data gaps for many important model assumptions, and as a result, the assumptions used reflect the judgment of professionals in the field, as well as published data. The incompleteness o the data introduces uncertainty. We evaluate the influence of uncertainty for several key parameters as a means to identify research or data collection needs. A formal uncertainty analysis is impossible because a probability distribution of plausible values cannot be specified for the uncertain parameters. Instead, we vary the values individually for each parameter analyzed, assigning it first its "worst case" value and then its "best case" value while holding all the other parameters equal to their base case values (Section 4.2.1). The

parameters and values analyzed as part of this sensitivity analysis are described in Section 3.2 of the report and in Section 2.2 ofAppendix 2. We also evaluate the effect of assuming that infectivity can be present in bovine blood at the level of detection of a standard test and that infectivity in the trigeminal ganglia can be harvested in the slaughter process (Section 4.2.2).

4.2.1 Sensitivity Analysis

Figures 4-1 and 4-2 summarize the sensitivity analysis results. These figures illustrate the influence of altering each parameter's value on each of two outcome quantities – the number of new BSE cases (Figure 4-1), and on human exposure to BSE (Figure 4-2). This section focuses on the predicted mean value for these outcomes. In Figures 4-1 and 4-2, the horizontal axis lists the individual parameters analyzed, while the vertical axis quantifies the associated range of outcome values. A horizontal line above the horizontal axis designates the arithmetic mean value for the outcome quantity computed when all parameters were set equal to their base case value. The range of values associated with each parameter's best and worst case values are represented by the small horizontal lines at the extreme ends of a vertical line above the label for each parameter. Because some of the parameters influence only very rare events, the output value ranges associated with some parameters do not encompass the output value computed by setting all parameters to their base case value.

Figure 4-1 indicates that the parameters that have the greatest influence on the mean number of new BSE cases are directly associated with feed ban compliance. The most influential parameter is the misfeeding rate, which represents the proportion of feed formulated for other species and containing prohibited MBM illegally administer to cattle. The second-most influential parameter is the probability that prohibited feed will be mislabeled (*i.e.,* lack the required warning labels). Other parameters evaluated had only a very small influence on the total number of new BSE cases.

Figure 4-2 illustrates the impact of parameter uncertainty on the mean number of cattle oral ID_{50}s potentially available for human consumption. Both the misfeeding and mislabeling rates are again prominent, but two other parameters are influential as well. First, the proportion of animals with clinical BSE signs identified and eliminated by the AM (*antemortem*) inspector is clearly important. Second, the assumed number of cattle oral ID_{50}s in a full-blown clinical BSE case is clearly influential. These results are also sensitive to assumptions about contamination

during the carcass splitting process ("splitter"). Note that in virtually all these cases, even the worst case values result in little infectivity being available for human consumption over a 20-year period following the introduction of ten sick animals.

4.2.2 Inherent Infectivity in Blood

Although blood infectivity has not been found in BSE-infected cattle, we test the implications of assuming that the disease inherently results in infectivity in blood. Our assumptions reflect the judgment of the SSC that one kg of any cattle tissue negative for infectivity in the mouse bioassay could contain as much as ten oral cattle ID_{50}s (SSC 2000). Hence, we assume that the 3.8 kg of blood dried blood that can be recovered from an average steer (Romans and Ziegler 1974) could contain 38 cattle oral ID_{50}s.

Assuming that blood recovered from cattle contains 38 cattle oral ID_{50}s has a minimal impact on animal health and human exposure to BSE infectivity following the import of ten BSE-infected cattle into the U.S. The model predicts an average of four new cases of BSE over the 20-year period following this introduction. The 95th percentile value for the number of new BSE cases is 14. Blood infectivity on average contributes 0.11 new cases over the 20-year period (95th percentile value of 1.0) There is no effect on potential exposure of humans to infectivity (mean of 34 ID_{50}s for the 20-year period). Section 2.6 in Appendix 3A and 3B detail the simulation results for this analysis.

4.2.3 Harvesting of Trigeminal Ganglia

Assuming that some fraction of trigeminal ganglia would be harvested along with cheek meat has little impact on human exposure. Nor do the simulation results indicate that this assumption influences the predicted spread of BSE among cattle. On average, the model predicts that trigeminal ganglia would contribute less than 0.00001% of the total infectivity that would be available for potential human consumption. Section 2.7 in Appendix 3A and 3B detail the simulation results for this analysis.

4.3 Alternative Sources of Infectivity

We evaluate two potential sources of BSE in the U.S., cross-species transmission of scrapie from sheep (Section 3.3.3) and spontaneous development of the disease and its spread

through cattle feed (Section 3.3.1). In both cases we use base case assumptions. To further characterize the US system we evaluate the effect of importation of infected animals, modeling the results of bringing 1, 5, 20, 50, 100, 200 or 500 infected cattle into the US.]

4.3.1 Spontaneous

For this scenario, the model predicts an average of 27 infected animals over a 20-year period (95th percentile value of 37). It is predicted that only 2.6 animals, on average, would reach the advanced stages of the disease (95th percentile of six). Virtually all of the animals that become infected develop the disease spontaneously, although maternal transmission and tranmission from contaminated protein both make a small contribution. A mean of 77 cattle oral ID_{50}s are predicted to reach humans (95th percentile value of 220).

These results suggest that if this hypothesis is true the disease is essentially endemic, with one-to-two cases occurring each year. Current agricultural practices and regulations (the feed ban) effectively check the spread of disease to other cattle but the disease cannot be eliminated because it of its sporadic occurrence. The very low number of animals developing clinical signs would make detection through any method of surveillance very difficult.

4.3.2 Imports

Figure 4-3 illustrates the relationship between the number of infected cattle imported and the mean number of new cases (*i.e.*,, the number of cases in addition to the imported animals) during the 20 year period following the arrival in the U.S. of these imports. Even with the introduction of 100 BSE-infected cattle, there are fewer than 100 new cases of BSE in the subsequent 20 years.

Figure 4-4 illustrates the relationship between the number of infected cattle imported and human exposure to BSE infectivity (mean number of cattle oral ID_{50}s potentially available for human consumption) during the 20 year period following the arrival in the U.S. of these imports. The contribution of the different exposure routes is roughly the same as in the base case. The mean number of cattle oral ID_{50}s potentially available for human consumption over 20 years is estimated to be approximately 2,000 following the introduction of 500 infected animals. These ID_{50}s result from the consumption of both the introduced cases and the new cases that follow.

Finally, Figure 4-6. illustrates the relationship between the number of infected cattle imported and the probability that BSE will still be present in the U.S. 20 years following these imports. The results indicate that after 20 years, BSE is eliminated with 90% probability even following the introduction of 500 infected cattle. The probability of cases remaining 20 years after the introduction of one sick animal is zero. The tendency for BSE to be eliminated is also implied by the predicted number of new infected animals following the import of infected animals. Unless the number of new cases exceeds the number of challenge cases (*i.e.*, unless each case gives rise to more than one case on average), the disease will tend to die out. The time it takes to die out depends on the number of infected animals introduced initially.

4.3.3 Scrapie

This simulation evaluates the impact of assuming that scrapie contributes one cattle oral ID_{50} to feed consumed by cattle each month. The simulation predicts that this contamination results in an average of 38 infected cattle over a period of 20 years (95^{th} percentile estimate of 63). The simulation also predicts that an average of about six animals would develop clinical symptoms during that period (95^{th} percentile of 13). Current surveillance would be unlikely to detect this number of clinical cases. On average, approximately 90 cattle oral ID_{50}s are predicted to be available for potential human exposure during the 20 y ear period (95^{th} percentile estimate of 260).

Because scrapie is assumed to contaminate cattle feed continually, the disease would essentially be endemic. Note that the simulation predicts that most new cases of BSE would arise directly from exposure to scrapie infectivity, although a small number would result from exposure to contaminated ruminant protein that slips through the feed ban. Maternal transmission makes a small contribution to the total.

We expect that the predictions made here are likely to overstate the true contribution of scrapie to BSE, as explained in Section 3.3.3. In brief, it is likely that the true species barrier is greater than the value of 1,000 used (it has proven impossible to transmit North American scrapie orally to cattle), and the prevalence of scrapie in the U.S. is probably less than the UK prevalence rates used in the calculation. Section 3.3 of Appendices 3A and 3B detail the simulation results.

4.4 Alternative Scenarios

This section details the results of several simulations designed to investigate further factors influencing spread of BSE infectivity. The first scenario described models the small BSE outbreak in Switzerland as check on the plausibility of our model (section 4.4.1). Next we examine the spontaneous hypothesis by looking at how spontaneous disease might have spread in the years before the FDA feed ban (section 4.4.2). Section 4.4.3 examines how importation of cattle from the UK during the 1980s may have affected the U.S. The last two sections evaluate specific risk management strategies, including a specified risk material (SRM) ban identical to that imposed in the UK (Section 4.4.4), and a prohibition on the rendering of animals that die on the farm (Section 4.4.5).

4.4.1 Switzerland

As discussed in Section 3.4.1, our model is not amenable to formal validation because there are no known controlled experiments in which the introduction and consequences of BSE introduction to a country has mean monitored and measured. However, as a test of the model's plausibility, we model the small BSE outbreak reported in Switzerland following the introduction of BSE infectivity from the UK. Our simulation took into account risk management actions taken by the Swiss during the ensuing period (*e.g.*, the introduction of a feed ban regulation).

The model predicts both the total number of infected animals in Switzerland and those that develop clinical disease. Only the latter can be detected using the standard surveillance methods in use early in the outbreak. Current surveillance practices can detect disease in animals several months before development of clinical signs. We also describe the predicted the time course of the BSE outbreak.

Our simulation of Switzerland predicts an average of approximately 480 infected animals, 170 of which develop clinical signs of the disease. It is impossible to know the true number of infected animals in Switzerland (because some may not have been identified), but the Swiss did report the identification of 324 animals with clinical signs between 1990 (when the first case was identified) and 2000. Our simulation follows a time course similar to that observed in Switzerland where risk management measures, including feed bans, have reduced the number of clinical cases found and the outbreak appears to be abating. Complete simulation results appear in Section 4.1 of Appendices 3A and 3B.

Our model's modest underprediction of clinical cases could be due to incorrect specification of the number of infected animals imported or amount of contaminated feed introduced, among other factors. At the same time, the similarity of our predictions and the observations from Switzerland provide some confidence that the model's structure and approach are reasonable. It is important to note that this is not a true validation and, in fact, the model's predictions could be close to reported observations for the wrong reasons. However, given the absence of data suitable for validating the model, the results of the Switzerland scenario are encouraging.

4.4.2 Spontaneous With no Feed Ban

To further investigate the spontaneous hypothesis, we modeled a scenario in which spontaneous disease occurs using the rates described in Section 3.3.1, but no feed ban is present to mitigate the recycling of infectivity in ruminant feed. The scenario, described in Section 3.4.2 was run for 20 years.

The absence of a feed ban allows BSE infectivity to rapidly spread throughout the cattle population. The mean projection for this scenario suggests 42,000 animals infected over the 20 year period (95^{th} percentile of 190,000). The average number of clinical animals predicted is 1,500 (95^{th} percentile of 6,600).

It should be noted that the simulation often predicts that the BSE prevalence rapidly increases towards the end of the twenty year period (see Section 4.2 in Appendices 3A and 3B for complete results). This tendency suggests that if a longer time period were simulated, the model would predict a much greater burden of disease. Hence, while some simulation runs predict prevalence rates that are low enough to be compatible with the fact that BSE has not been detected in the U.S., the results suggests that even in these cases, the prevalence would climb much higher if a longer period were simulated. That is, in the absence of a feed ban, the prevalence would most likely reach a detectable level in any case in just over 20 years. The fact that BSE was not detected in the U.S. prior to the implementation of the feed ban therefore suggests that either spontaneous disease either does not occur, or that its incidence is less than we have assumed. Alternately, the imposition of the feed ban may have stopped an epidemic before

it could reach detectable levels. In that case, the base case results suggest that the feed ban will eliminate the disease shortly.

4.4.3 Cattle Imported from the UK in the 1980s

This scenario investigates the likelihood that BSE infectivity could have been introduced into the U.S. by the 173 cattle imported from the UK during the 1980s that may have contaminated either human food or animal feed (see Section 3.4.3). We also determine the amount of infectivity that may have been introduced. Using these findings, we characterize the likelihood that BSE could have been introduced into the U.S. and remained undetected.

As discussed in Section 3.4.3, some of the cattle imported into the U.S. from the UK between 1980 and 1989 may have been infected with BSE without showing clinical signs of the disease. As a result, diseased animals may have contaminated animal feed in this country. Figure 4-6 illustrates the cumulative distribution for the amount of infectivity (cattle oral ID_{50}s) that may have been in feed consumed by cattle in the U.S. (see methodology in Section 3.4.3 and Section 1.1 of Appendix 2). The distribution indicates it is likely (probability of 82%) that U.S. cattle were exposed to no infectivity from cattle imported from the UK. The probability that cattle were exposed to no more than 0.1 ID_{50}s is 84%, the probability that they were exposed to no more than one ID_{50} is 86%, the probability that they were exposed to no more than five ID_{50}s is 91%, the probability that they were exposed to no more than ten ID_{50}s is 93%, and the probability that they were exposed to no more than 50 ID_{50}s is 96%.

To characterize the impact of introducing infectivity into the U.S. during the 1980s, we have simulated the introduction of 0.1, 1.0, 5.0, 10.0, and 50.0 cattle oral ID_{50}s into cattle feed in 1980, and followed the evolution of the U.S. cattle population through 2010. The results of these simulations (see Section 4.3 in Appendices 3A and 3B) can be used to quantify the likely number of clinical BSE cases that would have occurred and hence to assess the plausibility of these scenarios in light of the fact that BSE has not been detected in the U.S. In particular, introductions that result in too large a number of clinical cases to be compatible with the fact that BSE has not been detected in the U.S. are not plausible.

Note that the distributions for the output quantities are highly skewed, indicating that under most circumstances the infectivity did not spread widely but that occasionally, there was a

combination of events leading to significant numbers of infected cattle. For example, when 0.1 cattle oral ID_{50} is introduced into feed, more than 950 of the 1,000 simulation runs for this scenario produced no new cases of disease. However, a few runs produced substantial numbers of diseased animals. Hence the mean number of infected animals (over all 1,000 simulations) is 45, and the mean number of animals with clinical signs is ten. Introducing larger quantities of infectivity also yields right-skewed results distributions.

The probability that BSE was introduced into the U.S. depends on two events – the introduction of contaminated material from imported animals into domestic cattle feed (probability of 18%), and the infection of exposed cattle and subsequent spread of BSE to other animals without the creation of so many cases that it would have been likely to have been discovered by surveillance. Figure 4-7 illustrates for the year 2000 (year 20 of the simulation) the predicted number of clinical (*i.e.*, detectable) cattle following introduction of 0.1, 1.0, 5.0, 10,0, or 50.0 cattle oral ID_{50}s from the imported UK animals. Also plotted is the USDA's estimate of the number of clinical cases surveillance would have detected in the year 2000 with 95% probability (Victoria Bridges, personal communication). For example, the curve in Figure 4-7 corresponding to the introduction of 10.0 ID_{50}s indicates that there is an 82% chance that this introduction caused no new BSE cases in the U.S.[4], and that it could have resulted in a maximum of approximately 1,100 clinical cases in the year 2000. However, all values exceeding the detection limit of 470 clinical cases in the year 2000 (*i.e.*, above the horizontal "detection limit" line) are incompatible with the fact that no BSE has been detected in the U.S. For the introduction of 10.0 ID_{50}s, there is a 6% chance that the number of clinical cases in 2000 exceed this limit (*i.e.*, a 94% chance that this number was below the detection limit). Hence, even if cattle in the U.S. did consume 10.0 ID_{50}s in 1980, there is only a 12% chance (94% minus 82%) that it resulted in BSE cases that have not been found. Corresponding probabilities can be computed for the other ID_{50} introductions considered.

Taken together, Figures 4-6 and 4-7 are useful for evaluating the likelihood that BSE cattle imports from the UK during the 1980s introduced BSE into the U.S. but the disease has not spread to enough animals to be detected. First, there is only an 18% chance that cattle in the U.S.

[4] Figure 4-7 illustrates the number of clinical cases in the year 2000, not the total number of BSE cases caused by the import of BSE-infected cattle from the UK. However, the scenario simulated assumes that action to mitigate the spread of BSE in the U.S. occurs only after implementation of the feed ban in 1997. Hence, as suggested by the figures in Section 4.3 of Appendix 3B, the number of clinical animals peaks

were exposed to any infectivity (see Figure 4-6). Second, if cattle were exposed to infectivity, there is only a limited probability that both 1) any cattle in the U.S. became infected, and 2) the number of clinical cases (in the year 2000) was less than the number that would have been likely to have been detected (see Figure 4-7).

Finally, the Figures in Section 4.3 of Appendix 3B illustrate how the disease spreads and contracts if it is introduced into the U.S. The figures suggest that the number of animals with detectable disease peaks in year 20 and declines thereafter. This prediction indicates that even if infectivity has been introduced from UK cattle imported before 1989, the disease rate has peaked and BSE will eventually be eradicated. The decline in the predicted disease prevalence in the U.S. is due primarily to the introduction of the FDA feed ban in 1997.

4.4.4 Specified Risk Material Ban

A risk management step that has been taken in many countries with BSE is the prohibition of certain tissues being used in either animal feed or human food. These specified risk material (SRM) bans focus on tissues carrying the greatest level of BSE infectivity. To evaluate the effects of this approach in the U.S. if BSE were to be introduced, we altered the base case scenario as described in section 3.4.4 to mimic the UK SRM ban.

The SRM ban has a dramatic effect on potential human exposure or the spread of BSE to cattle. Following the introduction of 10 infected cattle, as in the base case, the mean number of new BSE cases is reduced by 82% (from 2.9 to 0.51) and the mean number of cattle oral ID_{50}s potentially available for human exposure decreases by 95% (from 35 to 1.7). Results for this scenario appear in Section 4.4 of Appendices 3A and 3B.

4.4.5 Prohibition on Rendering Animals that Die on the Farm

The results for the base case simulation (section 4.2 and Section 1 in Appendices 3A and 3B) make clear that if the BSE is introduced into the U.S., the greatest potential source of infectivity in the feed system is animals that die on the farm and are rendered. The simulations in this report assume an animal lives for between two and six months following the development of

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around the year 2000. As a result, if there are zero clinical animals in the year 2000, it is almost certain that few if any animals were infected in the U.S.

clinical signs. If the animal is not sent to slaughter, it dies on the farm. Rendering an animal that has reached the clinical stage of disease introduces the maximum amount of infectivity into rendering and potentially into feed. Hence, a single breach of the feed ban can introduce expose cattle to a substantial amount of BSE infectivity. This scenario evaluates a risk management strategy that prohibits the rendering of animals that die on the farm.

The simulation results indicate that this risk management strategy would have a substantial effect on the spread of BSE to other cattle following introduction of ten infected cattle. Compared to the base case, the mean number of new cases decreases by 77% (from 2.9 to 0.68). Although this approach targets the spread of BSE to other animals, it still has an effect on potential human exposure to BSE infectivity, decreasing this quantity by 20% because it decreases the number of new BSE cases. Complete results appear in Section 4.5 of Appendices 3A and 3B.

4.5 Summary

This report is intended to address the potential for BSE to become a major animal health or public health threat in the U.S. Based on the simulation model and assumptions developed for this analysis, inferences can be drawn about the robustness of regulations and practices in the U.S., and data or research can be identified that would increase confidence in predictions. In addition, it is possible to characterize the potential impact that various sources of BSE may have had in the U.S., including cattle imported from the UK in the 1980s. Finally, the simulation can be used to characterize the effectiveness of additional risk management strategies.

We recognize that the identification of a single case of BSE in the U.S. would have important ramifications for public opinion, trade, and other areas. Yet this analysis demonstrates that even if BSE were somehow to arise in the U.S., few additional animals would be infected, little infectivity would be available for potential human exposure, and the disease would be eradicated. In short, the U.S. appears very resistant to a BSE challenge, primarily because of the FDA feed ban, which greatly reduces the chance that a sick animal will infect other animals. However, the effectiveness of the feed ban is somewhat uncertain because compliance rates are not precisely known.

Potential sources of human exposure to BSE infectivity can be divided into two categories: specific high-risk tissues and contamination of low-risk tissues. Although not widely popular in the U.S., both brain and spinal cord are consumed by some members of the population. If BSE were present in the U.S., these tissues would be an obvious source of exposure. Our analysis indicates that the most important means by which low risk tissue can become contaminated is the use of advanced meat recovery (AMR) technology, which can leave spinal cord or dorsal root ganglia (DRG) in the recovered meat. Our analysis further indicates mis-splitting of the spinal column and the resulting incomplete removal of the spinal cord is largely responsible for contamination of AMR meat. In addition, we assume that even in the absence of mis-splitting, some amount of DRG is extracted whenever vertabrae are processed by AMR. Contamination due to aerosolization of the spinal cord during splitting contributes substantially less contamination even though it occurs every time an infected animal is processed.

Despite the potential for the consumption of high risk-tissues and the contamination of low-risk tissues, our results indicate that only small amounts of infectivity are available for human consumption. The import of one infected animal yields in an average of 2.7 cattle oral ID_{50}s for potential human exposure over a 20 year period, while the import of ten infected cattle results in an average of 35 cattle oral ID_{50}s this period. These results can be put into context by comparing them to potential exposure in the UK where it is estimated almost one million cattle were infected over a 15 to 20 year period. If the UK population was potentially exposed to only one cattle oral ID_{50} from each of these animals, potential human exposure in the UK would dwarf our projections for the U.S. At this time, just over 100 cases of variant Creutzfeldt-Jakob disease (the human TSE linked to BSE) have been identified in the UK, although projections range from a few hundred to tens of thousands of eventual cases. If cattle oral ID_{50}s available for human consumption is a good indicator of possible disease risk, it is unlikely the UK experience would be duplicated in the U.S.

There are a number of model assumptions that cannot be verified with confidence, some of which influence the conclusions drawn. With regard to estimating the spread of BSE among cattle, the most influential sources of uncertainty are related to compliance with the FDA feed ban. Within this category, the most important source of uncertainty is the misfeeding rate on farms. Misfeeding prohibited feed (containing ruminant protein) to cattle on farms that raise both cattle and either pigs or chickens completely compromises the feed ban. This practice is the focus of efforts to understand how animals born after the implementation of feed bans in Europe

have become infected with BSE. Uncertainty with respect to compliance rates can be reduced with field work and data collection. A second source of uncertainty associated with the feed ban is the proportion of feed produced that is mislabeled (*i.e.*, lacks the proper labels identifying it as feed not to be administered to ruminants).

Improving estimates of compliance with the feed ban would also improve estimates of potential human exposure to BSE-contaminated meat. Other important sources of uncertainty influencing estimates of human exposure include: the number of ID_{50}s per clinical case of BSE, and the proportion of clinical animals that would be correctly identified by *ante mortem* inspectors. While the first of these two factors may be amenable to research, it is not clear how estimates for the second factor could be improved.

We have identified three important ways in which BSE could be introduced into the U.S: 1) cross-species transmission from a native TSE like sheep scrapie, 2) spontaneous development of the disease in a native animals, or 3) the import of an infected animal or animal product from a country with BSE. The analysis suggests that either cross-species transmission of a TSE (scrapie) or spontaneous disease, if they can occur, would lead to only a few cases of BSE each year and would result in relatively little potential human exposure. However, results from our evaluation of the impact of spontaneous BSE on the U.S. prior to the 1997 FDA feed ban casts doubt on the plausibility of this potential source of BSE. In particular, these results suggest there is a substantial probability that the number of animals with clinical signs would be sufficiently high to be inconsistent with the fact that surveillance has failed to detect BSE in the U.S. At the same time, the simulation results indicate that there is a non-trivial probability that spontaneous BSE would generate an insufficient number of animals to be detected by surveillance.

It is impossible to know if an infected animal was imported from the UK in the 1980s. Our analysis suggests it is highly unlikely. First, the imported animals whose disposition is not known came from farms where the disease was not found in any animal born the same year. Second, the beef breeding animals imported had little exposure to potentially infected protein supplements while in the UK. Finally, many of the animals are known to have lived beyond the average incubation period once they arrived in the US. Nonetheless, there is some small probability that at least one of these animals was infected and that infectivity from such an animal contaminated feed consumed by cattle in the U.S. Exposure to infectivity among U.S. cattle could not have been substantial because in the years prior to the 1997 FDA feed ban, such

exposure would have eventually resulted in a substantial number of clinical cases, a prediction that is inconsistent with the fact that BSE has not been identified in the U.S. to date. There is therefore a small chance that BSE could have been introduced into the U.S. and remained undetected. Even if BSE was introduced, actions by USDA and FDA have already arrested the spread of the disease and have begun to reduce its prevalence. If BSE is present in the U.S., these actions will ultimately lead to the disease's eradication.

Evaluation of potential risk management actions highlights an additional benefit of this type of analysis. The insights provided by the model demonstrated that steps very early in the rendering and feed production process can avoid the need for other, more obvious, measures. Specifically, removing most of the infectivity from rendered product can protect human and animal health even if the feed ban is not 100% effective. Prohibiting the rendering of dead animals, which may have died of BSE and hence have high levels of infectivity, or disposing of all specified risk materials both reduce potential new cases of BSE by more than 75%. The misfeeding rate, a key parameter identified in our sensitivity analysis, is not important if the infectivity in prohibited MBM is greatly reduced or eliminated. The SRM ban also reduces substantially the amount of infectivity available for potential human exposure. Of course, it must be recognized that even in the absence of these measures, animal health risks and human exposure are both small, with the import of ten infected cattle leading to an average of fewer than three new cases of BSE and potential human exposure to 35 cattle oral ID_{50}s.

As we strive to learn from BSE and limit the extent of the disease, the model developed for this analysis has many potential uses. It is flexible and can be changed easily. For example, if appropriate data are available, its parameters can be modified so that other countries or regions can be simulated. Specific scenarios of interest can be evaluated, including risk management actions under consideration. The model can also be used to evaluate hypotheses about sources and factors influencing the BSE's spread. We hope this model will find a place among the useful tools for understanding and controlling BSE.