Harvard Risk Assessment of Bovine Spongiform Encephalopathy (BSE)

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Background

- Work conducted by Harvard Center for Risk Analysis (HCRA) using the Harvard BSE simulation model
- History of the Harvard BSE simulation model
  - Delivered to USDA in November 2001
  - Underwent a technical review by scientists outside of USDA*
  - Finalized in October 2003*
- USDA Food Safety Inspection Service (FSIS) asked HCRA to
  - Update the Harvard BSE model*
    - To assess risks associated with introduction of BSE into the U.S.
    - To assess the impact of risk management measures
  - Analysis underwent formal independent peer review in Fall 2005 according to OMB information quality guidelines*

*Reports, peer review comments, and response to comments available on the USDA/FSIS website

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Overview

- Model structure and enhancements
- Scenarios considered
  - Base case
  - Measures either taken or proposed to mitigate BSE risks
    - Measures adopted by USDA after December, 2003
    - Regulations considered by the Food and Drug Administration (FDA)
    - Proposals advanced by the International Review Subcommittee
  - Sensitivity analyses
- Results
- Conclusions

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1. Model Structure and Enhancements

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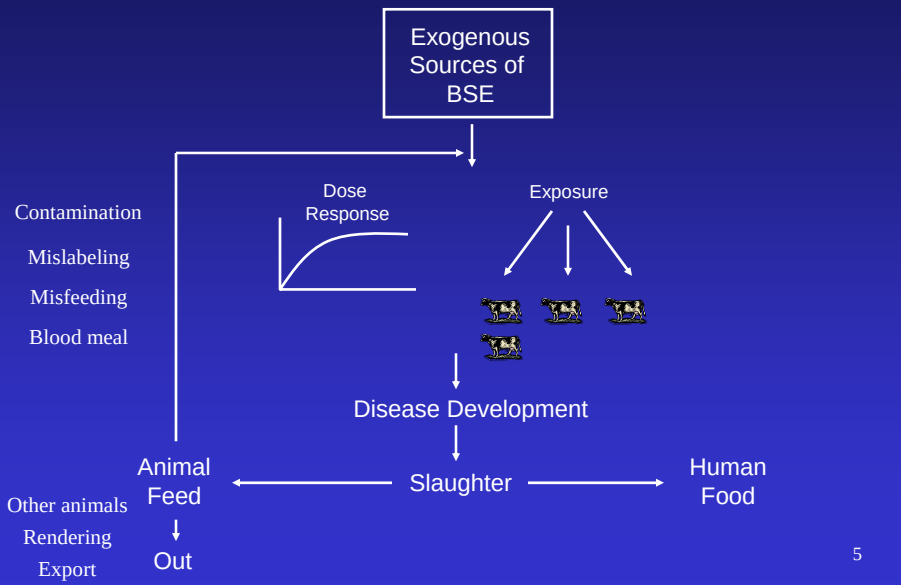
Harvard Model – October 2003 Risk Assessment



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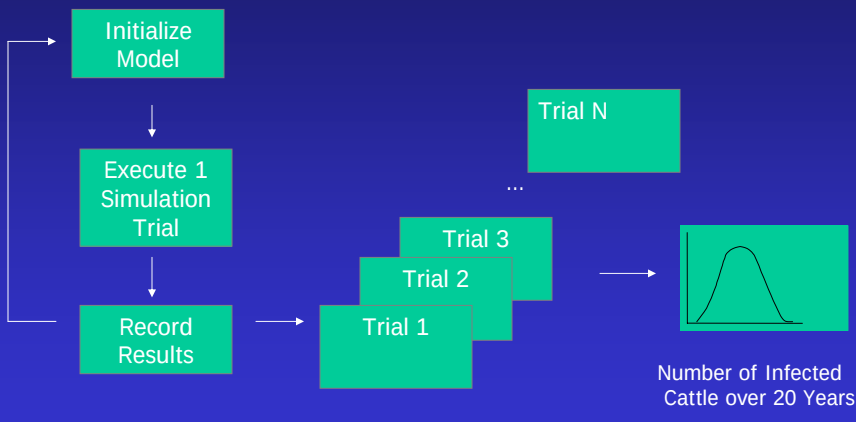
Model is Probabilistic



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Model Revisions - Motivation

- Update assumptions to represent conditions in the U.S. in December 2003, just prior to the discovery of the BSE-positive animal in Washington State
- Accommodate evaluation of additional risk mitigation measures
- Account for data on the presence of the BSE agent in cattle tonsils

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Updates

1. How *Antemortem* (AM) inspection works
2. Addition of tonsils as a tissue that can harbor the BSE agent
3. Specified risk material (SRM) inspection allows for removal of tissues from dead animals, not just those that go to slaughter
4. Feed control compliance estimates updated
5. Contamination of bone-in-beef revised

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Update #1
Antemortem Inspection

Clinical Status

Animal Age

October 2003 Model

Detect BSE Signs	AM Condemn	Human Food	Animal Feed
None Identified	Pass	OK	OK
	Condemn	No	OK
Detected	Pass	No	No
	Condemn	No	No

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Antemortem Inspection
Revised Model

Clinical Status

Animal Age

Detect BSE Signs	AM Condemn	Ambulatory Status	Human Food	Animal Feed
None Identified	Pass	Normal	OK	OK
		Non-Amb	OK	OK
	Condemn	Normal	No	OK
		Non-Amb	No	OK
Detected	Pass	Normal	No	No
		Non-Amb	No	No
	Condemn	Normal	No	No
		Non-Amb	No	No

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Detection of BSE Clinical Signs

- BSE clinical signs more likely to be detected among ambulatory animals
  - Ambulatory – AM inspection detects 95% of animals with BSE clinical signs
  - Non-ambulatory – AM inspection detects 85% of animals with BSE clinical signs
- Fraction of animals that are non-ambulatory
  - For animals that have not reached clinical status: 0.5%
  - For animals that have reached clinical status: 8%

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Update #2
BSE Infectivity in Tonsils

- October 2003 model
  - No infectivity in tonsils
- Revised model
  - Assumes 0.2% of total carcass infectivity is in cattle tonsils

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Update #3
SRM Inspection

- October 2003 Model
  - SRM inspection removes tissues only from animals that are sent to slaughter
- 2005 revised model for FSIS
  - Revised model assumes SRM tissues are also removed from animals that die prior to slaughter

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Update #4
Ruminant Feed Control Compliance Rates

- Mislabeling of meat and bone meal (MBM) or feed known to have ruminant protein as “non-prohibited”
- Cross-contamination of non-prohibited production lines in plants that process both prohibited and non-prohibited materials

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FDA Compliance Data

	Inspected	Cited for Mislabeling		Cited for Comingling	
Facility Type	(N)	(N)	%	(N)	%
Renderers	171	4	2.3%	3	1.8%
Feed mills					
Licensed mills	370	8	2.2%	2	0.5%
Non-licensed mills	1224	55	4.5%	28	2.3%
Total mills	1594	63	4.0%	30	1.9%

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Assumptions for Mislabeling and Cross-Contamination

	MBM Production		Feed Production	
	Base Case 2003	Base Case Revised	Base Case 2003	Base Case Revised
Contamination probability	14%	1.8%	16%	1.9%
Proportion of prohibited material transferred to non-prohibited per contamination event	0.1%	0.1%	0.1%	0.1%
Mislabeling probability	5%	2.3%	5%	4%

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FDA Compliance Data May Overstate Non-Compliance

- Data indicate proportion of facilities with at least 1 rule violation, which can be greater than proportion of material processed in violation of rules
- Data from September 2003 and earlier are likely to overstate feed control non-compliance rates after identification of the BSE positive animal in Washington State in December 2003

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Update #5
Bone-in-Beef Contamination

- Both models
  - For animals 12 months and older
    - 30% of infectivity in spinal cord ends up in bone-in beef if the spinal cord is not removed prior to splitting
- October 2003 Model
  - Bone-in beef cuts (like T-bone steaks) are restricted to animals under the age of 24 months
  - Hence, model effectively assumed 30% of spinal cord infectivity deposited in bone-in-beef for animals of age 12-23 months
- Revised model
  - When spinal cord not removed, 30% of spinal cord infectivity deposited in bone-in-beef for animals extended to animals 24 months and older

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2. Scenarios Considered

- Base case
- "What-if" scenarios
- Sensitivity analyses

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Base Case

- October 2003 assessment
  - Introduction of 10 infected animals
  - Simulate 20 years post introduction
  - 5,000 simulation trials
- Current assessment
  - Same base case with 750,000 simulation trials
  - Run time: 4 weeks

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Achieving Precision in Less Time

- Introduce 500 infected animals at the beginning of each trial and conduct 50,000 trials
- Arithmetic mean for original base case results can be estimated
  - Divide inflated base case results by 50
- Why it works
  - The introduction of each infected animal is an independent event
  - Total events scale linearly with the number of infected animals introduced

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Empirical Evidence of Linear Scaling

Statistic	10 Animals	500 Animals	Ratio
Epidemic statistics			
Total infected	14	680	49
Total infected w/o imports	3.5	180	51
Total clinical	4.3	210	49
Mode of infection			
Maternal	0.54	27	50
Protein	3.0	150	50
Blood	0.010	0.53	53
ID_{50} Sources			
From slaughter	7,400	370,000	50
From death on farm	34,000	1,800,000	53
Disposition of ID_{50}s			
Total to cattle	65	3,400	52
Total potential humans	75	3,800	51
Human exposure			
Brain	14	710	51
Advanced meat recovery	32	1,600	50
Tonsils	0.028	1.5	54

Note: Reported statistics are rounded to 2 sig. figures

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Rationale for the Inflated Base Case

- Precision and speed
  - Precision depends on total number of infected animals introduced
  - Execution time depends mostly on number of trials

Infected Animals Introduced	Trials	Total Infected Animals Introduced	Execution Time on a 2.8 GHz PC
10	750,000	7.5 million	~ 28 days
500	50,000	25 million	~ 3 days

Note – Percentiles do not scale.

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"What-if" Scenarios

- USDA/FSIS
- FDA
- The International Review Subcommittee

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USDA/FSIS Scenarios

- Prohibit for use as human food of all non-ambulatory cattle
- Prohibit the use of SRMs for human consumption
  - Brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column, dorsal root ganglia from cattle 30 months and older
  - Small intestines and tonsils from all cattle
- Prohibit the use for human food of
  - Meat collected from vertebral column using advanced meat recovery (AMR) from cattle 30 months of age or older
  - Mechanically separated meat from all cattle

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FDA Scenarios

- Prohibit the use of ruminant blood in ruminant feed
- Requirement of dedicated lines for production of animal feeds or meat and bone meal in facilities that also produce materials designated for non-prohibited uses

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International Review Subcommittee Scenarios

- Prohibit the use of SRMs for human consumption or animal feed
  - Cattle 12 months of age or older: brain, spinal cord, vertebral column
  - All cattle: Intestine
  - Assume applicability of rule to both slaughtered and animals that die prior to slaughter
  - Assume perfect compliance
    - Results provide an upper bound on impact of strategy
- Prohibit the use of any MBM in ruminant feed

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Sensitivity Analyses

Scenario	Parameter	Base Case	Sensitivity Analysis
1	Renderer – contamination probability Renderer – mislabel probability Feed producer – contamination probability Feed producer – mislabel probability	1.8% 2.3% 1.9% 4%	14% 5% 16% 5%
2	Proportion of correctly labeled prohibited feed administered to cattle (misfeeding)	1.6%	15%
3	Rendering technology - % Batch (3.1 log reduction) Continuous – fat added (2 log reduction) Continuous – no fat added (1 log reduction) Vacuum (no reduction)	 5% 45% 45% 5%	 5% 20% 70% 5%

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Sensitivity Analyses

Scenario	Parameter	Base Case	Sensitivity Analysis
4	Proportion of bone-in-beef consumed		
	Cattle 0 to 23 months	70%	100%
	Cattle 24 to 29 months	50%	90%
	Cattle 30 months and older	25%	45%
5	Probability of detecting BSE clinical signs at *antemortem* inspection		
	Normal ambulatory status	95%	50%
	Nonambulatory	85%	25%
6	BSE incubation period		
	Median incubation period (months)	~ 50	~ 100

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Sensitivity Analyses

Scenario	Parameter	Base Case	Sensitivity Analysis
7	Proportion of cattle that are non-ambulatory		
	Pre-clinical cattle	0.5%	0%
	Clinical cattle	~ 8%	~ 8%
8	Proportion of cattle that are non-ambulatory		
	Pre-clinical cattle	0.5%	0.5%
	Clinical cattle	~ 8%	100%

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3. Results

- Key output statistics
- Base case
- Measures to mitigate BSE risks
- Sensitivity analyses

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Key Output Statistics

- Question 1 – To what extent are humans potentially exposed to the BSE agent?
  - Simulation output: Potential human exposure to the BSE agent, quantified in terms of cattle oral ID_{50}s
  - Value represents potential human exposure
- Question 2 – To what extent does BSE spread among cattle in the U.S.?
  - Number of cattle that become infected with BSE after the initial introduction
  - The disease reproductive constant, designated "R_0."

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Key Output Statistics
R_0: Disease Reproductive Constant

- R_0 is the average number of new BSE cases resulting from each incident BSE case
- For $R_0 = 2$
  - Initial condition – Introduce 1 case
  - Generation 1 – 2 more cases
  - Generation 2 – 4 more cases
  - Generation 3 – 8 more cases
  - …

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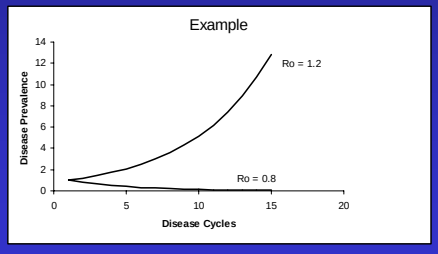
R_0: Disease Reproductive Constant

- Whether $R_0 > 1$ is critical

$R_0 = 1.2$ vs. $R_0 = 0.8$



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R_0 - Continued

- R_0 is estimated as "N" divided by "D" where
  - N = Number of newly infected BSE cases over the course of the simulation (i.e., excluding cases introduced)
  - D = Number of BSE cases that die during the course of the simulation

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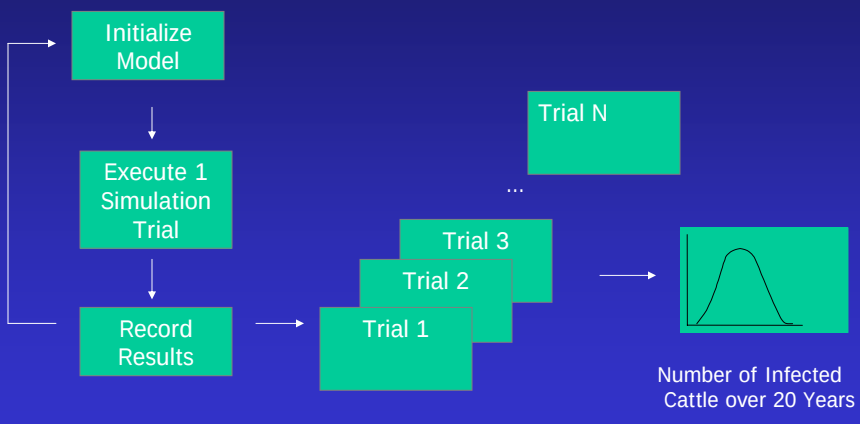
Model is Probabilistic



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Other Statistics Reported by Simulation

Label	Mean	5th	25th	50th	75th	95th
Epidemic Statistics						
Total Infected	14	10	10	10	11	21
Total Infected w/o Imports	3.5	0	0	0	1	11
Total Clinical	4.3	1	3	4	5	8
Probability Infected > 0 at End	0.0027	0	0	0	0	0
R_0 Parameter	0.087	0	0	0	0.091	0.52
Mode of Infection						
Maternal	0.54	0	0	0	1	2
Spontaneous	0	0	0	0	0	0
Protein	3	0	0	0	0	11
Blood	0.01	0	0	0	0	0
Exogenous	0	0	0	0	0	0
Mode of Death						
Slaughter	8.3	4	5	6	8	14
Die on Farm - Render	4.4	1	3	4	5	8
Die on Farm - No Render	0.78	0	0	1	1	2
ID50 Sources						
From Slaughter	7,400	500	1,000	3,500	11,000	22,000
From Death on Farm	34,000	10,000	20,000	30,000	40,000	61,000
Disposition of ID50s						
1 To Prohibited MBM	3,600	160	1,100	1,800	3,200	12,000
2 Eliminated by SRM ban	0	0	0	0	0	0
3 Eliminated by Rendering	33,000	9,700	20,000	29,000	39,000	61,000
4 To NP MBM - Contamination	0.0032	0	0	0	0	0
5 To NP MBM - Mislabeling	84	0	0	0	0	110
6 Out After Rendering	1,200	0.08	28	200	1,100	10,000
7 To Prohibited Feed	2,400	34	250	1,100	2,100	11,000
8 To NP Feed - Misdirected	7.7	0	0	0	0	0
9 To NP Feed - Contamination	0.003	0	0	0	0	0
10 To NP Feed - Mislabeling	100	0	0	0	0	240
11 To Blood	0.63	0	5.4E-6	0.0037	0.21	3.6
12 Out After Feed Production	2,400	41	270	1,100	2,100	11,000
13 Misfed to Cattle	38	0	0	0	0	23
14 Total to Cattle	65	0	0	0	0.00058	100
15 Total Potential to Humans	75	3.7E-6	0.07	2.6	46	320
16 Eliminated by AM Inspector	4,100	0	0	0	10,000	20,000
Human Exposure						
Brain	14	0	0	0	0	0
Spinal Cord	5.2	0	0	0	0	0
Blood	0.033	0	0	0	0	0.00025
Distal Ileum	7.5	0	0	0	0	0.044
Contaminated Organ Meat	0	0	0	0	0	0
Eyes	0.00086	0	0	0	0	0
Contaminated Muscle Meat	0.15	8.3E-6	0.000089	0.003	0.028	1
AMR	32	0	0.0044	0.54	22	200
Beef on Bone	17	0	0	0.00036	0.66	84
Trigeminal Ganglia	0	0	0	0	0	0
Tonsils	0.028	0	0	0	0	0

- Epidemic statistics – Cattle infected, clinical cases, R_0
- Mode of infection – maternal, spontaneous protein, blood, imports
- Mode of death – Slaughter, on farm
- ID_{50} sources – from slaughter or from animals that die on the farm
- Disposition of ID_{50}s – How they are processed and whether they are administered to cattle or are potentially available for human consumption
- BSE agent in human food by tissue

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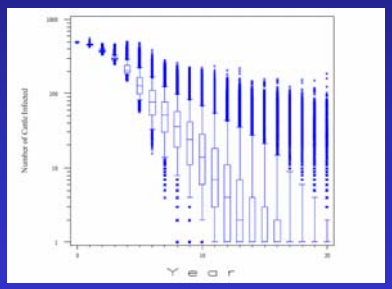
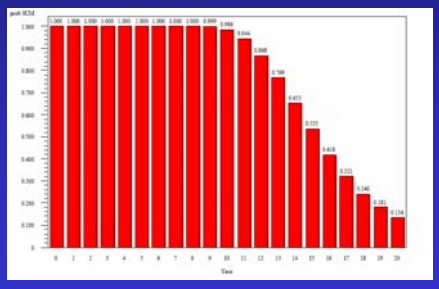
Other Statistics Reported by Simulation: Evolution of Agricultural System Over Time

Example – BSE Prevalence





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Base Case Results**

Introduce 10 infected animals – 750,000 simulation trials

	Mean	5th Pctl	25th Pctl	Median	75th Pctl	95th Pctl
New Cattle Infected	3.5	0	0	0	1	11
Potential Human Exposure*	75	< 0.01	0.07	2.6	46	320
R_0	0.087	0	0	0	0.091	0.52

Introduce 500 infected animals – 50,000 simulation trials

	Mean	5th Pctl	25th Pctl	Median	75th Pctl	95th Pctl
New Cattle Infected	180	33	98	160	240	400
Potential Human Exposure*	3,800	1,600	2,400	3,200	4,400	8,700
R_0	0.24	0.062	0.16	0.24	0.33	0.45

* Potential human exposure expressed as cattle oral ID_{50}s over 20 years
** Results rounded to 2 significant digits

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Precision
500 Animals Introduced – 50,000 Trials*

95% Confidence Interval – Number of New BSE Infections

	Mean	5th Pctl	25th Pctl	Median	75th Pctl	95th Pctl
Lower 2.5% Bound	178	33	97	154	241	396
Central Estimate	179	33	98	156	243	400
Upper 97.5% Bound	180	34	99	158	246	403

95% Confidence Interval – Potential Human Exposure

	Mean	5th Pctl	25th Pctl	Median	75th Pctl	95th Pctl
Lower 2.5% Bound	3,760	1,580	2,390	3,180	4,410	8,580
Central Estimate	3,780	1,590	2,400	3,190	4,440	8,660
Upper 97.5% Bound	3,800	1,610	2,410	3,210	4,470	8,770

*Results rounded to 3 significant digits to make evident distinction between central and bounding estimates

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Measures to Mitigate BSE Risks: New BSE Cases

	Mean	5th Pctl	25th Pctl	Median	75th Pctl	95th Pctl
BASE CASE	180	33	98	160	240	400
USDA/FSIS						
No non-ambulatory to food	180	33	98	160	240	400
No SRMs (30 mo+) to food	180	33	98	160	250	400
No AMR (30 mo+) to food	180	33	97	160	240	400
FDA						
No cattle blood to cattle feed	180	33	98	160	240	400
Dedicated prohibited prod. lines	180	33	97	160	240	400
Int. Review Subcomm.						
No SRMs (12 mo+) to food/feed	35	19	25	30	38	71
No MBM to cattle feed	170	32	92	150	230	390

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Measures to Mitigate BSE Risks: Potential Human Exposure (Cattle Oral ID_{50}s)*

	Mean	5th Pctl	25th Pctl	Median	75th Pctl	95th Pctl
BASE CASE	3,800	1,600	2,400	3,200	4,400	8,700
USDA/FSIS						
No non-ambulatory to food	3,700	1,600	2,400	3,100	4,400	8,500
No SRMs (30 mo+) to food	11	2.7	5.8	8.6	12	20
No AMR (30 mo+) to food	2,200	450	960	1,600	2,600	7,000
FDA						
No cattle blood to cattle feed	3,800	1,600	2,400	3,200	4,400	8,600
Dedicated prohibited prod. lines	3,800	1,600	2,400	3,200	4,400	8,600
Int. Review Subcomm.						
No SRMs (12 mo+) to food/feed	9.8	2.7	5.7	8.5	12	22
No MBM to cattle feed	3,800	1,600	2,400	3,200	4,400	8,600

*Over a 20 year period

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Sensitivity Analyses: New BSE Cases

	Mean	5th Pctl	25th Pctl	Median	75th Pctl	95th Pctl
BASE CASE	180	33	98	160	240	400
1. Cross contam. + mislabeling	200	38	110	180	270	440
2. Misfeeding	2,600	1,200	1,900	2,500	3,200	4,400
3. Render technology	240	38	130	210	330	530
4. Bone-in-beef consumption	180	33	97	160	240	400
5. Antemort. detect of clinicals	190	36	100	170	260	420
6. BSE incubation period	43	6	13	24	60	130
7. Non-amb. proportion (low)	180	33	97	160	240	400
8. Non-amb. proportion (high)	180	33	97	160	240	400

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Sensitivity Analyses: Potential Human Exposure (Cattle Oral ID_{50}s)*

	Mean	5th Pctl	25th Pctl	Median	75th Pctl	95th Pctl
BASE CASE	3,800	1,600	2,400	3,200	4,400	8,700
1. Cross contam. + mislabeling	3,800	1,600	2,400	3,300	4,500	8,700
2. Misfeeding	9,000	4,200	6,300	8,300	11,000	16,000
3. Render technology	4,000	1,700	2,500	3,400	4,700	8,800
4. Bone-in-beef consumption	4,500	2,000	3,000	3,900	5,300	9,400
5. Antemort. detect of clinicals	6,600	3,000	4,300	5,700	7,900	13,000
6. BSE incubation period	1,900	650	1,100	1,600	2,200	4,400
7. Non-amb. proportion (low)	3,800	1,600	2,400	3,200	4,400	8,700
8. Non-amb. proportion (high)	3,800	1,600	2,400	3,200	4,500	8,800

*Over a 20 year period

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Conclusions (1)

- Under the base case:
  - The model predicts that introduction of BSE into the U.S. will result in a minimal spread of disease
  - $R_0 << 1$
  - Human exposure over 20 years < 100 cattle oral ID_{50}s
  - Human exposure in the UK likely to have been millions of cattle oral ID_{50}s

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Conclusions (2)

- Risk mitigation measures
  - The USDA/FSIS ban on SRM use in food (mostly for animals 30 months of age and older) has a substantial impact on potential human exposure
  - Neither measure considered by FDA has a large impact on either human exposure or the spread of disease among cattle
  - The International Review Subcommittee's ban on the use of specified risk materials in either food or feed has a substantial impact on both potential human exposure and animal health

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Conclusions (3)

- Sensitivity analyses
  - The most influential assumption in this analysis is the misfeeding rate
    - R_0 can reach 1.0 or more with 5% probability if the most pessimistic value is used for this assumption
    - Even so, total human exposure remains relatively limited over the 20-year period
  - Other parameters have a much smaller influence on the model-predicted outcomes

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Conclusions (4)

- In the absence of adopting any additional measures
  - The U.S. agricultural system is able to limit the spread of BSE, if imperfectly
  - Human exposure is limited
- A ban on use of specified risk materials has the biggest impact on the spread of BSE among cattle and human exposure
- The assumed misfeeding rate is the most important source of uncertainty in this analysis.

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