No Change in Risk for Antibiotic-Resistant Salmonellosis from Beef, United States, 2002–2010

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Restricting antibiotic use in food production animals is a target for reducing antimicrobial drug–resistant infections in humans. We used US surveillance data to estimate the probability of antibiotic-resistant nontyphoidal salmonellosis per meal made with beef during 2002–2010. Applying data for nontyphoidal *Salmonella* in raised-without-antibiotics cattle, we tested the effect of removing antibiotic use from all beef cattle production. We found an average of 1.2 (95% credible interval 0.6–4.2) antibiotic-resistant nontyphoidal salmonellosis cases per 1 million beef meals made with beef initially contaminated with antibiotic-resistant nontyphoidal *Salmonella* at slaughter or retail and 0.031 (95% credible interval 0.00018–0.14) cases per 1 million meals irrespective of beef contamination status. Neither outcome showed sustained change except for increases in 2003 and 2009 (>98% confidence) when larger or more outbreaks occurred. Switching all beef production to a raised-without-antibiotics system may not have a significant effect on antibiotic-resistant nontyphoidal salmonellosis (94.3% confidence).

Increased antimicrobial resistance (AMR), or antibiotic resistance, has resulted in initiatives to reduce the use of antibiotics in food production animals (*1*,*2*), but quantification of the public health effects of decreasing antibiotic use in livestock remains limited (*3*,*4*). Reduction of antibiotic use in livestock can lower resistance prevalence (i.e., proportion of pathogens with resistance) in animals (*4*), but some studies show that pathogen prevalence may be higher in livestock raised without antibiotics (*5*). Because transmission of foodborne pathogens is proportional to the prevalence of pathogens in the food source (*6*), quantifying the change in human antibiotic-resistant foodborne illnesses resulting from reduced antibiotic use in livestock is vital.

In the United States, the most common bacterial cause of foodborne illness is nontyphoidal *Salmonella* (NTS), which leads to >1 million foodborne illnesses and 20,000 hospitalizations per year (*7*). Antibiotic-resistant NTS is among the top 18 AMR threats in the United States (*8*), causing 100,000 infections annually. The Centers for Disease Control and Prevention National Antimicrobial Resistance Monitoring System (NARMS) tracks resistance to 25 antibiotics in patient samples positive for isolates such as NTS (*9*), including the clinically relevant antibiotics ciprofloxacin and ceftriaxone.

Multiple assessments of human AMR risk from meats have been performed (*10*–*14*). However, most focused on only 1 class of antibiotic (*10*,*11*), had limited or no longitudinal data (*14*), or were not based on nationwide surveillance at the animal source (*11*). Quantitative assessments of AMR risk with a more comprehensive resistance definition (*15*), such as resistance to any class, or to ≥3 classes, that use representative, longitudinal data, are critical to defining the risks and benefits from policy with regard to antibiotic use in livestock (*3*). Surveillance studies of antibiotic use and AMR in humans and livestock can be used to generate estimates of risk based on empirical data and can show the results of long-term conditions or systematic changes over time.

Our objective with this study was to use beef as a model to quantify trends in the longitudinal relationship between human NTS infections and antibiotic-resistant NTS in meats. We also used the estimates to predict change in antibiotic-resistant salmonellosis resulting from hypothetical scenarios of antibiotic restriction in beef cattle.

Methods

We developed a stochastic model to quantify the risk for antibiotic-resistant nontyphoidal salmonellosis

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per meal made with beef during 2002–2010. Our model follows the method of previously published AMR risk assessments (*6*,*16*) but uniquely addresses temporal changes and relies solely on nationwide surveillance data (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/26/9/19-0922-App1.pdf).We used this model for 3 objectives: 1) estimate the risk for antibiotic-resistant nontyphoidal salmonellosis per meal made with beef, using the yearly cases of illnesses (Ill_{res}) and the number of meals made with beef that year ($Meal_{res}$) (Figure 1); 2) evaluate change over time in all model outcomes; and 3) assess the effect that potential future restrictions on antibiotic use in beef cattle would have on antibiotic-resistant nontyphoidal salmonellosis disease burden (Appendix).

Risk for Antibiotic-Resistant Nontyphoidal Salmonellosis Attributable to Beef

Annual Incidence of Beef-Attributable Antibiotic-Resistant Nontyphoidal Salmonellosis (Ill_{res} Incidence) per 100,000 Persons

We obtained the annual total nontyphoidal salmonellosis cases in the United States for 1998–2015 from FoodNet (https://www.cdc.gov/foodnet), an active foodborne disease surveillance system, after adjusting for the proportion of the US population included in FoodNet surveillance sites. To correct for underdiagnosis and restrict case estimates to domestically acquired foodborne cases, we also included adjustment factors constant for the study period. By using annual food attribution estimates derived from the National Outbreak Reporting System (NORS; https://www.cdc.gov/nors/index.html), cases of nontyphoidal salmonellosis were further restricted to foodborne cases attributed to ground beef and intact beef. To ensure that the resistance fraction is specific to nontyphoidal salmonellosis attributed to consumption of beef, we estimated the fraction of beef-attributed nontyphoidal salmonellosis cases with AMR by matching cases in the Centers for Disease Control and Prevention data collected from clinical patient samples as part of NARMS (*17*) with beef-attributable outbreak data from NORS by using sample metadata, (Appendix Table 1). We calculated incidence of Ill_{res} by using the population of the United States in the relevant year.

Annual Meals Prepared with Beef Initially Contaminated with Antibiotic-Resistant NTS ($Meals_{res}$)

We calculated the number of beef meals consumed annually in the United States by using beef disappearance data from the US Department of Agriculture (USDA) (*18*) and the mean grams of beef consumed per beef meal from the National Health and Nutrition Examination Survey (*19*). We estimated the prevalence of NTS in beef by using USDA Food Safety and Inspection Service surveillance data, and we derived the fraction of isolates with AMR from USDA NARMS and US Food and Drug Administration NARMS data (*9*). $Meals_{res}$ were stratified by beef cut (ground beef data for 2002–2015 vs. intact beef for 1998–2010). By using $Meals_{res}$, we assumed that the beef used to prepare a meal was initially contaminated (as measured at the slaughter plant or retail) with the pathogen. This assumption does not necessarily mean that the actual meal consumed was contaminated because safe cooking and handling practices would reduce or completely inactivate the bacterial load.

Risk for Antibiotic-Resistant Nontyphoidal Salmonellosis per Beef Meal

Dividing Ill_{res} by $Meals_{res}$ resulted in the probability of antibiotic-resistant nontyphoidal salmonellosis per meal made with beef initially contaminated with antibiotic-resistant NTS (P_{ill}). Also, by using all meals in the denominator, we calculated the probability of antibiotic-resistant nontyphoidal salmonellosis per meal made with beef, regardless of contamination status (P_{meal}) (Figure 1). We report both risk outcomes per 1 million meals, on a per-year basis (P_{ill} and P_{meal}) and as the mean of each for all years combined ($P_{ill,overall}$ and $P_{meal,overall}$). We repeated the analyses for NTS with multidrug resistance (NTS_{MDR}) (i.e., resistance to ≥3 antimicrobial classes) and for clinically relevant resistance (NTS_{CRR}), also known as resistance of concern (i.e., resistance to ≥5 drugs or quinolones [ciprofloxacin] or third-generation cephalosporins [ceftriaxone]) (*8*).

Testing for Temporal Changes

To identify the confidence of a consistent increase (or decrease) in each outcome over the study period, we used Mann-Kendall trend test bootstrapping (*20*). In addition, we used numerical integration to compute the confidence in pairwise year-to-year Bayesian posterior differences (*21*) and the difference between the mean of each outcome in the last years of the study period versus the remaining previous years. Unlike the Mann-Kendall tests, the year-to-year test identified short-term changes, and the comparison of the first versus the last 5 years of the study period provided an assessment of nonlinear changes during the study period.

Scenario Analysis: Effects of Hypothetical Antibiotic Restriction in Beef Production

Relationship between Antibiotic Use and Antibiotic-Resistant NTS in Beef

To model the relationship between antibiotic use and antibiotic-resistant NTS, we used nationwide data (C.P. Fossler, USDA, pers. comm., 2018 Jul 16) from the National Animal Health Monitoring System feedlot survey (*22*). The feedlot survey is based on a nationwide representative sample of farms and thus captures the effect of long-term and current antibiotic practices on AMR. In the survey, individual fecal pats from raised-without-antibiotics cattle and conventionally raised cattle were collected to estimate the prevalence of NTS isolates and the fraction of these with AMR. These 2 parameters were combined to measure the overall prevalence of antibiotic-resistant NTS in raised-without-antibiotics cattle and conventionally raised cattle and to derive the relative risk (RR) of antibiotic-resistant NTS prevalence in raised-without-antibiotics versus conventionally raised cattle.

Prediction of Changes in Beef-Attributable Antibiotic-Resistant Nontyphoidal Salmonellosis

We constructed 2 scenarios to evaluate Ill_{res} changes from hypothetical antibiotic restriction in beef production. We assumed no changes in slaughtering, processing, consumer habits, and food preparation.

For scenario 1, we estimated the change in antibiotic-resistant nontyphoidal salmonellosis if all beef production were switched to raised-without-antibiotics by using the annual estimated Ill_{res} for 2002–2010 and the RR of antibiotic-resistant NTS prevalence in raised-without-antibiotics versus conventionally raised cattle. By doing so, we assumed that the animal-level prevalence of antibiotic-resistant NTS is proportional (but not equal to) its prevalence in meals prepared with beef and that RR has a direct linear effect on the change in Ill_{res}. This relationship is documented for food pathogens (*6*,*23*), including NTS (*24*), so here we assumed that it extends to antibiotic-resistant isolates.

To relax this assumption, for scenario 2, we empirically estimated the relationship between antibiotic-resistant NTS prevalence in beef and Ill_{res} via Poisson

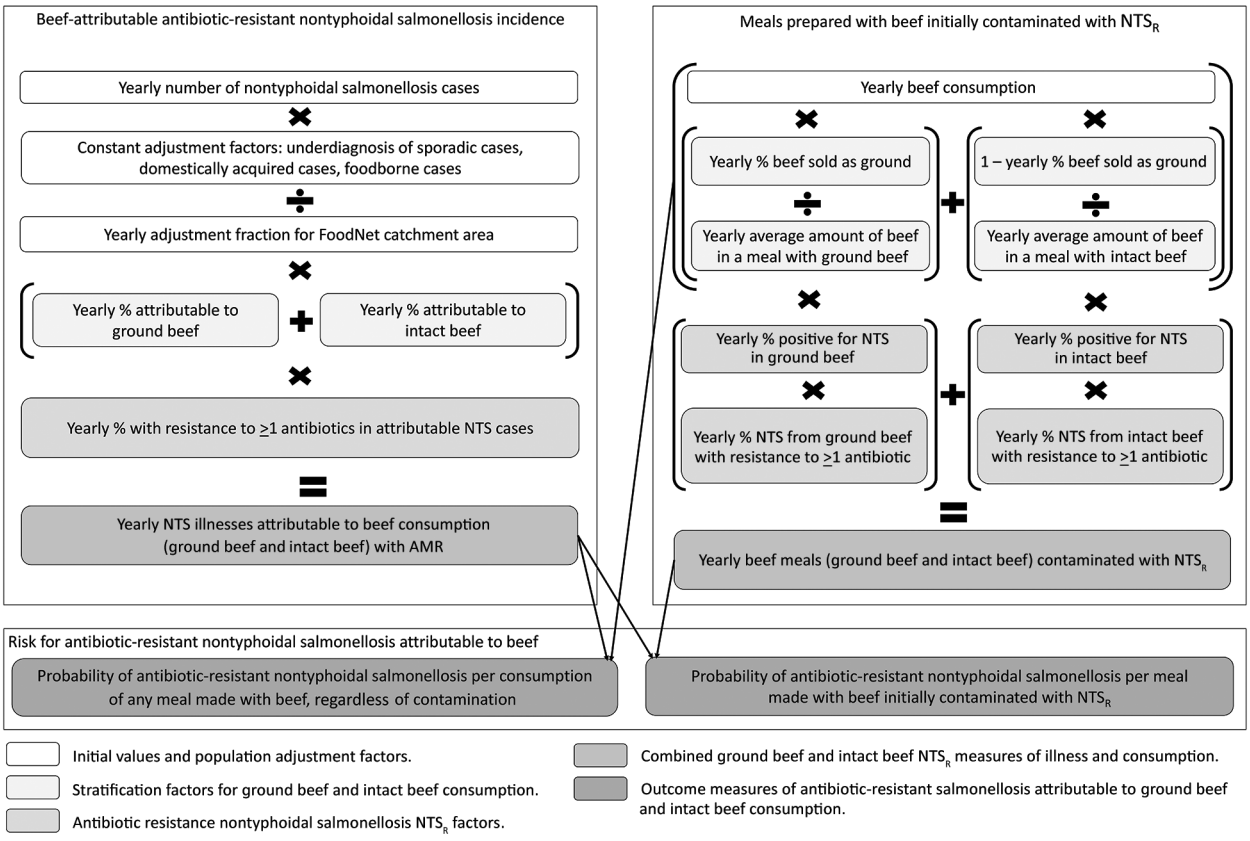

Figure 1. Conceptual model and data sources for calculation of risk for beef-attributable antibiotic-resistant nontyphoidal salmonellosis per 1 million beef meals (P_{ill}) for study of risk for antimicrobial-resistant salmonellosis from beef, United States, 2002–2010. NTS, nontyphoidal *Salmonella*; NTS$_R$, antibiotic-resistant NTS.

regression and used the Poisson regression to create an adjustment factor to the calculations done for scenario 1. For each scenario, we reported the posterior confidence in the change in Ill_{res} being <0 (i.e., reduction of antibiotic-resistant nontyphoidal salmonellosis) for each year of the study and for all years combined.

Model Implementation

We used R version 3.4.1 (https://www.R-project.org) to perform all analyses. We used Monte Carlo simulation to calculate the posterior uncertainty in all outcomes. Statistical significance was assessed at the 95% confidence level. We performed a sensitivity analysis of the key drivers of P_{ill} and $P_{ill,overall}$ by calculating the effect that extreme values of each input had on the output means (Appendix).

Results

Descriptive Statistics of Main Parameters and Risk Measures

During 2002–2010, approximately 554 billion beef meals were consumed, 59% as ground beef. Of these meals, 4% came from beef at slaughter or retail with NTS, half of which were antibiotic-resistant (11.23 billion, 95% CrI 9.08–13.54 billion). Approximately 93% of meals with beef initially contaminated with antibiotic-resistant NTS were made with ground beef (10.4 billion meals, 95% CrI 8.3–12.73 billion) (Figure 2), resulting from higher prevalence of both NTS and antibiotic-resistant NTS in ground than intact beef (Table 1). Yet, the attribution of nontyphoidal salmonellosis, regardless of antibiotic resistance, was relatively even between ground and intact beef (Figure 2). The total incidence of Ill_{res} was 0.64 (0.0036–2.75)/100,000 persons.

During 2002–2010, the mean risk for antibiotic-resistant nontyphoidal salmonellosis was 0.031 cases (95% CrI 0.00018–0.14)/1 million beef meals; intact and ground beef contributed equally to the rate (Table 1; Figure 2). The risk per million beef meals initially contaminated with NTS was 1.8 (95% CrI 0.007–8.5) overall, 1.16 (95% CrI 0.0015–5.2) for ground beef and 9.5 (95% CrI 0.03–50) for intact beef (Figure 2). The higher $P_{ill,overall}$ for intact beef possibly indicates a higher risk from consumption of intact beef carrying antibiotic-resistant NTS.

Tests for Temporal Changes in Main Parameters and Risk Measures

None of the tested parameters or outcomes based on a resistance definition of ≥1 antibiotic (i.e., $Meals_{res}$ or Ill_{res} per 100,000 population [Figure 2], or P_{ill} or P_{meal} [Figure 3]) showed a sustained change (Table 2). We also observed no change when we used multidrug resistance (MDR) and clinically relevant resistance (CRR) as the definition of resistance (Table 2; Appendix Figures 5–8), except that meals made with ground beef contaminated with NTS_{CRR} declined during 2002–2015. More differences based on the last 5 years of the study period were found. The risk for NTS_{MDR} per 1 million meals made with ground beef initially contaminated with NTS_{MDR} increased during 2010–2015, while the number of these meals made with NTS_{MDR}-contaminated ground

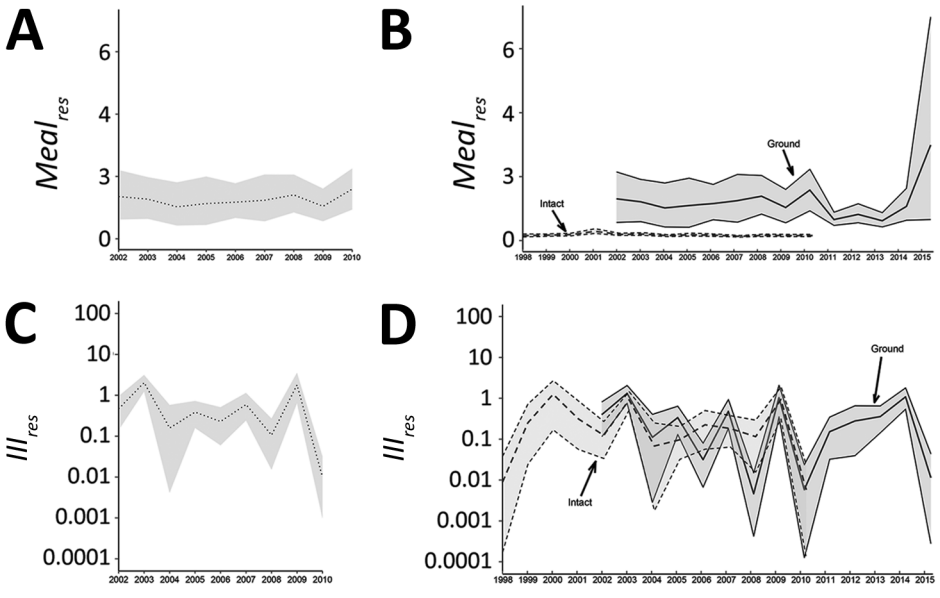

Figure 2. Estimates of the number of annual beef meals (in millions) prepared with beef initially contaminated with NTS resistant to >1 antibiotic ($Meal_{res}$) and of the incidence of salmonellosis with resistance to >1 antibiotic and attributable to beef (Ill_{res}) per 100,000 persons, United States, 2002–2010. A) $Meal_{res}$ for total beef, 2002–2010. B) $Meal_{res}$ stratified as ground (2002–2014) or intact (1998–2010) cuts. C) Ill_{res}, 2002–2010. D) Ill_{res} attributable to beef stratified as ground (2002–2014) or intact (1998–2010) cuts. Center lines represent means; gray shading represents 95% credible intervals; for panels B and D, light gray shading represents intact beef and dark gray shading indicates ground beef.

Table 1. Calculations of beef consumption, NTS, and risk for antimicrobial-resistant salmonellosis from beef, United States*

Input	Mean (95% CrI)	
	2002–2010†	Any years with data
Meals prepared with beef		
Total	554B (527B–581B)	554B (527B–581B)
Ground	326B (306B–345B)	497B (473B–521B)
Intact	228B (219B–238B)	329B (319B–339B)
Meals prepared with beef carrying NTS		
Total	24.9B (22.5B–27.0B)	24.9B (22.5B–27.0B)
Ground	22.5B (20.3B–24.9B)	36.3B (31.1B–42.7B)
Intact	2.4B (2.1B–2.7B)	4.2B (3.7B–4.6B)
Meals prepared with beef carrying NTS_R ($Meal_{res}$)		
Total	11.2B (9.08B–13.54B)	11.2B (9.08B–13.54B)
Ground	10.4B (8.3B–12.71B)	16.22B (12.69B–20.90B)
Intact	811M (708M–925M)	1.30B (1.16B–1.46B)
Nontyphoidal salmonellosis attributable to beef, no. cases/100,000 US population		
Total	15.10 (0.096–44.44)	15.10 (0.096–44.44)
Ground	8.27 (0.028–25.99)	8.99 (0.028–26.94)
Intact	6.83 (0.028–20.07)	6.75 (0.043–19.72)
Ill_{res}/100,000 US population		
Total	0.64 (0.0036,2.75)	0.64 (0.0036–2.75)
Ground	0.39 (0.0007,1.54)	0.36 (0.0008–1.46)
Intact	0.25 (0.001,1.25)	0.31 (0.00084–1.54)
Nontyphoidal salmonellosis attributable to beef/1 million beef meals		
Total	0.74 (0.0046–2.20)	0.74 (0.0046–2.20)
Ground	0.70 (0.0022–2.25)	0.78 (0.0024–2.35)
Intact	0.81 (0.0034–2.38)	0.78 (0.0051–2.29)
Nontyphoidal salmonellosis attributable to beef/1 million NTS beef meals		
Total	17.1 (11.4–24.0)	17.1 (11.4–24.0)
Ground	10.2 (6.73–14,4)	12.9 (8.6–18.2)
Intact	82.1 (53.8–118.1)	70.4 (46.7–100)
P_{meal}		
Total	0.031 (0.00018–0.14)	0.031 (0.00018–0.14)
Ground	0.031(0.000056–0.13)	0.031 (0.000067–0.13)
Intact	0.032 (0.0001–0.15)	0.036 (0.00013–0.18)
P_{ill}		
Total	1.78 (0.007–8.56)	1.78 (0.007–8.56)
Ground	1.15 (0.001–5.38)	1.25 (0.001–5.21)
Intact	9.10 (0.039–47.21)	9.48 (0.032–50.19)

*Years included are 2002–2015 for ground beef, 1998–2010 for intact beef, and 2002–2010 for total beef. Calculations include measures of exposure (meals prepared from beef with various states of microbiological contamination), disease incidence (no. illness cases/100,000 US population), and different measures of disease risk per meals consumed. B, billion; Ill_{res}, antibiotic-resistant nontyphoidal salmonellosis attributable to beef; M, million; NTS, nontyphoidal *Salmonella*; NTS_R, antibiotic-resistant NTS; P_{meal}, antibiotic-resistant nontyphoidal salmonellosis/1 million beef meals; P_{ill}, antibiotic-resistant nontyphoidal salmonellosis/1 million NTS_R beef meals.
†Years 2002–2010 summary statistics reflect the data used to create the combined totals.

beef decreased (Table 2). In contrast, for CRR, the beef-attributable risk for CRR nontyphoidal salmonellosis was significantly lower for all beef meals initially contaminated—and ground beef specifically—in the last 5 years of data, as were both the incidence of CRR nontyphoidal salmonellosis and its risk per 1 million beef meals, overall and for intact beef (Table 2).

We found some year-to-year variations in Ill_{res}, P_{ill}, and P_{meal} but generally no yearly changes in meals made with beef initially contaminated with antibiotic-resistant NTS ($Meal_{res}$). For all beef and for ground beef and intact beef individually, defining resistance as resistance to ≥1 antibiotic, Ill_{res}, P_{ill}, and P_{meal} were higher in 2003 and 2009 and a peak for ground beef also occurred in 2014. $Meals_{res}$ showed no significant year-to-year changes for all beef cuts combined. Intact beef $Meals_{res}$ had 1 peak in 2001 (100% confidence). When MDR and CRR were used as the resistance definition, only the peaks in 2003 and in 2014 remained significant. A peak in some intact beef risks and illnesses was also observed in 2000 (Table 2).

Scenario Analysis of Changes in Antibiotic-Resistant Nontyphoidal Salmonellosis Resulting from Antibiotic Restriction in Beef Production

In the first scenario analysis, we found no significant changes (≤94.3% confidence) in antibiotic-resistant salmonellosis for any year when switching from current antibiotic practices to hypothetical 100% raised-without-antibiotics production. The mean change in the number of antibiotic-resistant nontyphoidal salmonellosis cases across the study period was –5,218 (Figure 4), ranging from an additional 1,441 resistant

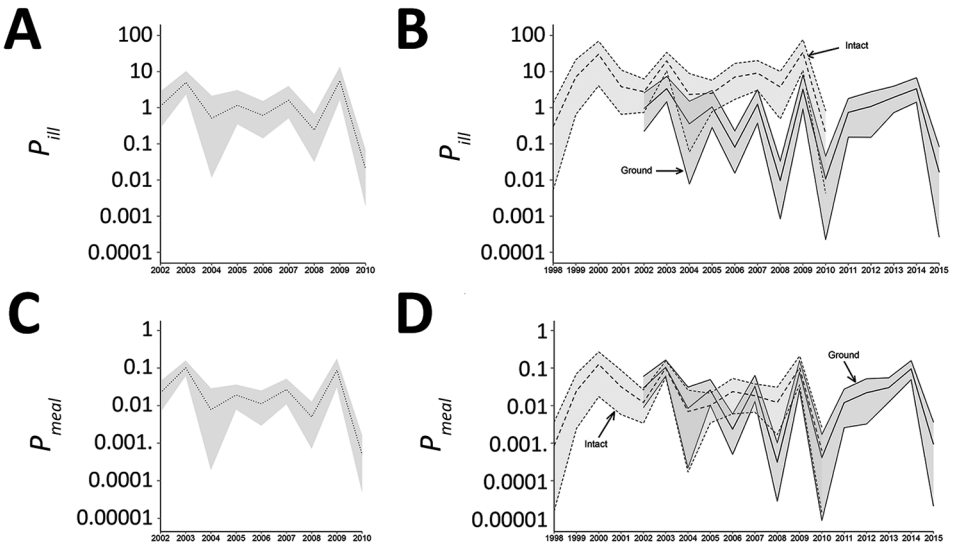

Figure 3. Estimates of the risk of antibiotic-resistant nontyphoidal salmonellosis per 1 million beef meals initially contaminated with antibiotic-resistant nontyphoidal Salmonella (P_{ill}) and per 1 million beef meals (P_{meal}) regardless of contamination status, United States, 2002–2010. Center lines represent means and gray shading represents the 95% credible intervals. A) P_{ill} for total beef, 2002–2010. B) P_{ill} stratified by intact (1998–2010) or ground beef (2002–2014). C) P_{meal} for total beef, 2002-2010. D) P_{meal} stratified by by intact (1998–2010) or ground beef (2002–2014). For panels B and D, light gray shading represents intact beef; dark gray shading indicates ground beef.

nontyphoidal salmonellosis cases to a reduction of 14,350 cases.

The second scenario (Figure 4), in which the direct linear assumption was relaxed, predicted significant decreases (>98% confidence) in cases for 2003 (–5,152) and 2009 (–4,763) and a significant increase of 1,098 cases (99.9% confidence) in 2010. However, switching to 100% raised-without-antibiotics production did not significantly change the number of antibiotic-resistant nontyphoidal salmonellosis cases over the full study period combining all 9 years (–8,588, 95% CrI –27,842 to 16,317, 60% confidence).

Discussion

Our risk analysis uses nationwide surveillance data on animal production and human illnesses to longitudinally estimate antibiotic-resistant nontyphoidal salmonellosis in the United States and assess how it might be affected by antibiotic restriction in livestock. Our approach is grounded in empirical data and minimizes assumptions while modeling parameter uncertainty and its effect on the results. Although farm-to-fork AMR risk analyses have been published (*10*), recent work has followed more parsimonious approaches like ours (*11*–*14*). However, direct comparison with other published risk analyses is difficult because most focus on the association between antibiotic use and AMR for a single drug and rarely include longitudinal data.

In our 2002–2010 analysis, the risks were stable over time; on average, a case of antibiotic-resistant salmonellosis occurred <1 time per 32 million meals made with beef or <1 time per 500,000 meals made with beef initially contaminated with antibiotic-resistant NTS. Likewise, prevalence of the antibiotic-resistant pathogen in beef available at retail in the United States and in the food production chain remained stable. Exceptions were 2 years in which more beef-attributable illnesses occurred than was typical for other years: 5 average-sized outbreaks (8% of attributable outbreaks) in 2003 and 2 *Salmonella* Montevideo outbreaks with high total case numbers in 2009.

The proportion of MDR and CRR was higher in NTS isolates from NARMS matched to outbreaks in 2003 and 2009 than in other years: 80% of matched samples in 2003 had CRR, and all 2009 *Salmonella* Montevideo matched samples to (71% of all matched 2009 cases) had MDR. This increase remained after we adjusted for exposure to infection in the form of meals prepared with beef with NTS and the fraction of these with AMR, which were stable. The association between MDR and CRR and larger/more frequent outbreaks may suggest a link between MDR/CRR and pathogenicity or infectivity, as described by Guillard et al. (*25*). Yet, in vitro phenotypic resistance does not fully capture actual clinical outcomes. Current foodborne surveillance programs do not record outcomes of AMR illnesses such as treatment failures and their consequences (e.g., extra hospitalizations). Estimating treatment failures resulting from resistant infections and the relative contribution of different sources of AMR—including antibiotic use in livestock—would better quantify the

societal cost benefit of curtailing resistant illnesses from livestock.

In our analysis, we had to estimate AMR specific to beef-attributable cases because the NARMS database contains salmonellosis cases of any source and yet resistance of salmonella varies by source (*9*). Lacking direct links between the NORS outbreak data used in source attribution and the outbreaks in NARMS, we used timing of the infection, state, and serotype to match cases. Although this method enabled us to approximate resistance in beef-attributable cases (5% vs. 22% AMR across human NARMS samples for NTS over the study period), use of this method probably resulted in some misclassification of the NARMS samples. This issue would be easily alleviated if a unique outbreak identifier were available in both datasets.

Of note, the per-portion risk for susceptible or resistant salmonellosis from beef initially contaminated was ≈8 times higher for intact cuts of beef than for ground beef. Because the prevalence of susceptible and resistant pathogens is greater for ground beef, the total illnesses are evenly split between types of beef, as are attributed illnesses, a result also noted by Laufer et al. (*26*). Intact cuts include some high-risk foods such as delicatessen

Table 2. Confidence in a significant monotonic trend in the data (bootstrapped Mann-Kendall test) and in the difference between posteriors estimates of the last 5 years versus the previous years for measures of beef consumption, NTS illnesses, and risk for antimicrobial resistant salmonellosis from beef, United States*

Variable	Monotonic (confidence trend exists), %	Last 5 vs. previous years (confidence difference exists), %	Years found significantly higher based on all pairwise comparisons†
$Meals_{res}$	38.2	68.7	None
Ground	66.6	44.7	None
Intact	88.0	93.8	None
$Meals_{res,MDR}$	87.0	86.3	None
Ground	94.5 (D)	85.8	None
Intact	53.0	98.4 (D)	2001
$Meals_{res,CRR}$	82.0	85.7	None
Ground	96.7 (D)	94.5	None
Intact	34.2	91.4	None
Ill_{res}	82.0	67.2	2003, 2009
Ground	66.8	55.3	2003, 2009, 2014
Intact	57.3	69.0	2003, 2009
$Ill_{res,MDR}$	86.6	87.2	2003
Ground	67.0	57.6	2003, 2014
Intact	61.9	84.5	2000, 2003
$Ill_{res,CRR}$	90.6	100 (D)	2003
Ground	70.1	54.7	2003
Intact	66.2	98.6 (D)	2000, 2003
P_{meal}	82.1	84.7	2003, 2009
Ground	62.9	54.7	2003, 2009, 2014
Intact	56.8	70.5	2003, 2009
$P_{meal, MDR}$	86.7	97.7 (D)	2003
Ground	66.9	50.8	2003, 2014
Intact	61.9	85.0	2000, 2003
$P_{meal, CRR}$	91.0	99.9 (D)	2003
Ground	67.2	49.9	2003
Intact	70.4	98.7(D)	2003
P_{ill}	87.3	84.1	2003, 2009
Ground	54.4	75.2	2003, 2009, 2014
Intact	42.6	49.9	2003, 2009
$P_{ill,MDR}$	82.2	86.0	2003
Ground	46.5	97.6 (I)	2003, 2014
Intact	53.2	66.1	2003
$P_{ill,CRR}$	87.0	99.6 (D)	2003
Ground	36.8	99.9 (D)	2003, 2014
Intact	70.5	91.7	2000, 2003

*D indicates that a significant decrease was found; I indicates that a significant increase was found, based on a 95% limit. CRR, clinically relevant resistance; Ill_{res}, human cases of beef-attributable antibiotic-resistant NTS; $Ill_{res,MDR}$, human cases of beef-attributable MDR NTS; $Ill_{res,CRR}$, human cases of beef-attributable CRR NTS; $Meals_{res}$, meals prepared with beef initially contaminated with antibiotic-resistant NTS resistant to ≥1 antibiotic; $Meals_{res,MDR}$, meals prepared with beef initially contaminated with NTS resistant to ≥2 antibiotics; $Meals_{res,CRR}$, meals prepared with beef initially contaminated with NTS with CRR; MDR, multidrug-resistant; NTS, nontyphoidal *Salmonella*; P_{meal}, probability of antibiotic-resistant NTS per meal made with beef of any kind; $P_{meal,MDR}$, probability of MDR NTS per meal made with beef of any kind; $P_{meal,CRR}$, probability of clinically relevant antibiotic-resistant NTS per meal made of beef of any kind; P_{ill}, probability of antibiotic-resistant NTS per meal made with beef initially contaminated with antibiotic-resistant NTS; $P_{ill,MDR}$, probability of MDR NTS per meal made with beef initially contaminated with MDR NTS; $P_{ill,CRR}$, probability of CRR NTS per meal made with beef initially contaminated with CRR NTS.
†Based on pairwise posterior comparisons between all years.

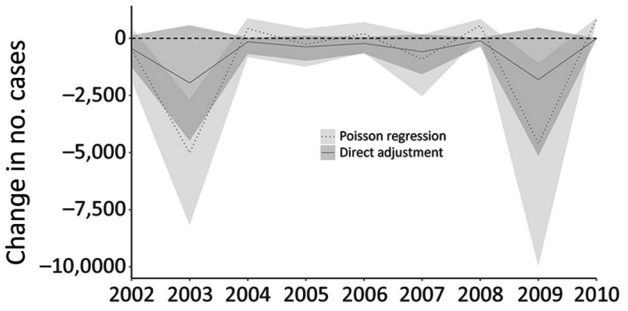

Figure 4. Predicted changes in each year's cases of antimicrobial-resistant salmonellosis from beef, United States, 2002–2010. Mean and 95% credible intervals of the predicted change are shown for the hypothetical scenario of 100% raised-without-antibiotics beef consumption, assuming a direct linear relationship between prevalence of antimicrobial-resistant *Salmonella* in beef and antimicrobial-resistant salmonellosis cases (solid line and dark grey shading), contrasted with the result from adjusting the relationship of beef resistance and prevalence with human cases based on the Poisson regression between the 2 variables (dotted line and light grey shading).

roast beef and ready-to-eat products (*27*). Doneness might also partly explain this finding. A survey found that 61% of US consumers preferred their steak medium or rarer (*28*), and another study found that 21% of restaurant customers requested medium or rarer hamburgers (*29*).

Using NTS in beef, beef-attributable salmonellosis cases, and resistance to ≥1 antibiotic provided a case definition that maximizes the chances of finding a statistical signal in this dataset, should a trend exist in the outcomes. Consequently, the lack of sustained change suggests that the modeled risks were indeed stable nationwide. Assuming that, as often described, antibiotic use in beef production is a key driver of AMR illnesses in humans, we consider 2 alternative explanations for this stability: either antibiotic use was stable during the study period or sustained use in beef resulted in a plateau in AMR salmonellosis so that changes in use can no longer affect the outcome. Although nationwide data on antibiotic use is unavailable for the study period, antibiotic use in beef is unlikely to have remained stable. For example, the fraction of beef cattle treated with tylosin in feed or water increased from 42.3% in 1999 to 71.2% in 2010 (*30*,*31*), whereas in Canada, where beef production practices are equivalent to those in the United States, overall use in beef decreased during 2008–2012 (*32*). A hypothetical resistance plateau cannot be empirically answered without detailed use data, but its implication is that changes such as the recent US Food and Drug Administration feed directive should eventually reduce beef-attributable antibiotic-resistant nontyphoidal salmonellosis. This hypothesis warrants a re-estimation of our model in the future.

An alternative hypothesis for the lack of change is that antibiotic use in beef does not significantly affect incidence of human AMR salmonellosis. This hypothesis does not necessarily imply a lack of risk but a risk that is too small or confounded to be measured. Empirical data for this effect are scarce because field studies typically link antibiotic use to AMR in animals or animal products, not in human illnesses. Benedict et al. (*33*) described how exposure to antibiotics in feedlot cattle did not affect AMR presence in non–type-specific *Escherichia coli*. Others have described a lower prevalence of resistance resulting from decreased use (*4*), although pathogen prevalence among raised-without-antibiotics livestock may be higher than that among conventionally raised animals (*5*). Although our study cannot confirm or refute this hypothesis, it provides new empirical evidence based on nationwide estimates and can be further updated as antibiotic practices in livestock are documented.

The scenarios with all raised-without-antibiotics beef cattle enabled us to model a hypothetical upper limit of the human health effect of antibiotic reduction and resulted in nonsignificant changes in resistant illnesses overall. This finding held true even under an unrealistic assumption of a direct decrease in resistant illnesses resulting from decreased pathogen prevalence and resistance after complete withdrawal of antibiotics. Being based solely on nationwide estimates—resistant illnesses based on surveillance data and the effect of antibiotic use on antibiotic-resistant NTS based on a nationwide survey (*22*)—these findings suggest that, according to collected surveillance data, reducing antibiotic use in cattle may not significantly reduce antibiotic-resistant nontyphoidal salmonellosis by a measurable level. Although external validation is not feasible because no other study, to our knowledge, has directly tested human and animal resistance at a national level, these results are consistent with those of recent studies of cecal contents of fed cattle (*5*) and ground beef (*34*) that found few AMR differences between raised-without-antibiotics and conventionally raised cattle production. Our findings also demonstrate that a direct relationship between prevalence of antibiotic-resistant NTS in beef and resulting AMR salmonellosis is not supported by current surveillance data.

This analysis suggests that the risk of contracting antibiotic-resistant nontyphoidal salmonellosis from beef consumption is <1 time/32 million beef meals and remained stable during 2002–2010. Despite

assessing salmonellosis only, our work highlights improvements needed to better quantify the effect that antibiotic use in livestock has on human health: monitoring of clinical outcomes in foodborne surveillance programs, better connection between surveillance for foodborne pathogen resistance and outbreak sourcing, and detailed studies exploring the effect of raised-without-antibiotics production practices on pathogen prevalence and resistance throughout the farm-to-fork production chain. Elucidating not only consumers' exposure to resistant pathogens but also how exposure translates into resistant illnesses and, ultimately, treatment failures, is required for the development of optimal AMR reduction strategies.

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No Change in Risk for Antibiotic-Resistant Salmonellosis from Beef, 2002–2010

Appendix

Supplemental Description of Methods

We developed a stochastic model to 1) estimate the risk of human antibiotic-resistant non-typhoidal salmonellosis per meal made with beef using the yearly incidence of antibiotic-resistant non-typhoidal salmonellosis illness and number of meals made with beef that year, 2) evaluate temporal trends in all model outcomes over the period 2002-2010, and 3) assess the effect that potential future antibiotic use (AMU) restrictions in beef cattle would have on this antibiotic-resistant non-typhoidal salmonella disease burden, using national surveillance data.

The Appendix Table provides a detailed summary of the variables and sources of data used to estimate each of the outcomes described below.

1. Risk of human antibiotic-resistant non-typhoidal salmonellosis illness attributable to beef

a. Annual incidence of beef-attributable antibiotic-resistant non-typhoidal salmonellosis illness per 100,000 people (Ill_{res})

We estimated the number of nontyphoidal salmonellosis illnesses attributable to beef consumption per year (*Ill*), and the number of these with AMR (Ill_{res}):

$$Ill = NTSc \times FB \times UD \times (GBA + IBA) \times DA \div USFN \text{ [Equation 1]}$$

$$Ill_{res} = Ill \times AMR_{perc} \text{ [Equation 2]}$$

The annual total NTS_c illnesses in the USA from years 1998-2015 were obtained from the FoodNet active surveillance system, and adjusted for the FoodNet catchment area (*USFN*), domestically-acquired fraction (*DA*), underdiagnosis (*UD*), attribution to food (*FB*), and attribution of foodborne cases to ground beef (GBA) or Intact beef (IBA). The adjustment factors *UD*, *FB* and *DA* were constant for the study period.

To derive the AMR fraction specific to beef-attributable cases of human illness, AMR_{perc}, we used metadata available in both datasets (serotype, date, and location) to match cases in the NARMS data collected by the CDC from clinical patient samples (*1*) with outbreaks from NORS attributed to beef consumption (*2*). The NORS data includes information on identified food source, and these variables were used to identify ground vs intact beef-attributable outbreaks among all salmonella outbreaks.

b. Annual meals prepared with beef initially contaminated with antibiotic-resistant non-typhoidal salmonellosis ($Meals_{res}$)

$Meals_{res}$ quantifies the meals initially contaminated (as measured at the slaughter plant or retail) with the pathogen. This doesn't necessarily mean that the actual meal consumed was contaminated, as safe cooking and handling practices would reduce or completely inactivate the bacterial load. $Meals_{res}$ was calculated as the sum of meals prepared with either ground or intact beef initially contaminated with antibiotic-resistant non-typhoidal salmonellosis and consumed annually in the US:

$$Meals_{res} = \frac{(1-GBF)\times Beef_{dtot}}{MS_{IB}} \times Pp_{IB} \times AMR_{IB} + \frac{GBF\times Beef_{dtot}}{MS_{GB}} \times Pp_{GB} \times AMR_{GB}$$ [Equation 3]

To estimate the annual number of meals, we combined beef disappearance data from USDA Economic Research Service to estimate total beef available for consumption ($Beef_{dtot}$) with the mean amount of beef consumed per meal containing beef stratified by beef cut (MS_{GB} and MS_{IB}) estimated using NHANES data (GB, years 2002-2015 vs IB, years 1998-2010) using the proportion of beef sold as ground beef (National Cattlemen's Beef Association, pers. com., 2018).

We estimated the prevalence *Pp* of nontyphoidal salmonella in beef using samples collected by USDA Food Safety and Inspection Service (FSIS). We then calculated the prevalence of the pathogen with AMR in IB (AMR_{IB} and AMR_{GB}) nontyphoidal salmonella using a combination of USDA-NARMS data from meat samples collected during IB and GB production for the years available and FDA-NARMS retail studies from GB (*3*) for years 2002-2010. Although these datasets are based on a national catchment area and are the most comprehensive sampling efforts to date, the evolution of the FSIS program targets over time and the small sample size of the FDA-NARMS study in particular may limit the ability to calculate true prevalence from these data.

c. Risk of antibiotic-resistant non-typhoidal salmonellosis per meal with beef

We estimated the probability of human antibiotic-resistant non-typhoidal salmonellosis illness per meal made with beef initially contaminated with antibiotic-resistant non-typhoidal salmonellosis (P_{ill}) by dividing the estimated number of antibiotic-resistant non-typhoidal salmonellosis illnesses for a given year (Ill_{res}) by the number of meals made with beef with antibiotic-resistant non-typhoidal salmonellosis that year ($Meals_{res}$).

$$P_{ill} = \frac{Ill_{res}}{Meals_{res}}$$ [Equation 4]

As explained earlier, we derive $Meals_{res}$ considering the initial contamination of the intact beef carcass (IB) and through the production of ground beef (GB), not the contamination of the meal as consumed. Food preparation will likely modify pathogen prevalence and load, but such practices are unlikely to change as result of AMU changes, so by using $Meals_{res}$ to calculate P_{ill} we avoid the issue of modeling the risk per prepared meal since surveillance data focuses on production and slaughter.

To provide context, we also calculated P_{meal}, the Ill_{res} per consumption of any meal of beef $Beef_{dtot}$, irrespective of contamination:

$$P_{meal} = \frac{Ill_{res}}{Beef_{dtot}}$$ [Equation 5]

See Appendix Figure 1.

2. Testing for temporal changes

We tested for monotonic yearly change for all outcomes via Mann-Kendall test for the overall study period, and bootstrapped the test statistic to calculate a of a consistent increase (*4*).

Using numerical integration (*5*), we computed the posterior confidence in pairwise year-to-year differences and in the difference between the mean of the parameter in the last five years versus the remaining years.

3. Scenario analysis: Effect of hypothetical restriction on AMU in beef production

a. Relationship between AMU and antibiotic-resistant non-typhoidal salmonellosis in beef

We used unpublished nationwide data (C.P. Fossler, pers. comm., 2018). from the NAHMS feedlot survey (*6*) to model nontyphoidal salmonella prevalence in cattle RWA vs raised under conventional (CONV) AMU practices: we estimated the sample-positive prevalence

of nontyphoidal salmonella ($Prev_{NTS,CONV}$ and $Prev_{NTS,RWA}$), and the fraction of nontyphoidal salmonella isolates with AMR ($Prev_{AMR,CONV}$ and $Prev_{AMR,RWA}$).

The relative risk (ΔRR) of antibiotic-resistant non-typhoidal salmonellosis prevalence in cattle RWA versus CONV was estimated as:

$$\Delta RR = \left(\frac{Prev_{NTS,RWA}}{Prev_{NTS,CONV}}\right) \times \left(\frac{Prev_{AMR,RWA}}{Prev_{AMR,CONV}}\right) \text{ [Equation 6]}$$

b. Prediction of changes in Ill_{res}

We constructed two scenarios to evaluate Ill_{res} changes from a hypothetical AMU restriction in beef production, assuming no changes in consumer habits and food preparation.

We modified the methods described by Williams et al. (*7*) to model the change in Ill_{res} if switching all production to RWA, as follows:

$$\Delta Ill_{res} = Ill_{res} \times (1 - \Delta\, RR) \text{ [Equation 7]}$$

where ΔRR is estimated in Equation 6.

In scenario 1, by using ΔRRs rather than prevalence of antibiotic-resistant non-typhoidal salmonellosis, we assumed that animal-level prevalence is proportional (but not equal to) prevalence in meals and ΔRR has a direct linear (i.e. 1:1) effect on ΔIll_{res}.

To relax this assumption, in a second scenario we empirically estimated the relationship between antibiotic-resistant non-typhoidal salmonellosis prevalence in beef and Ill_{res} via Poisson regression, and used it to create an adjustment factor to the calculations done for scenario 1.

In scenario 2, we empirically estimated the relationship between antibiotic-resistant non-typhoidal salmonellosis prevalence in beef and Ill_{res} via Poisson regression (see section i. below). Then, to relax the assumption of scenario 1, we used the slope of this Poisson regression to create an adjustment factor to Equation 7 (Appendix Figures 2- 5).

We tested the confidence in ΔIll_{res} being less than zero (i.e. reduction of human antibiotic-resistant non-typhoidal salmonellosis illnesses) using numerical integration.

i. Regression between Beef nontyphoidal *Salmonella* and -resistant non-typhoidal salmonellosis human illnesses

To adjust the estimated AMR illnesses associated with antibiotic-resistant non-typhoidal salmonellosis prevalence in beef under a 100% raised-without-antibiotic production system, the relationship between prevalence in beef and illnesses may either be assumed to be 1:1 or may be adjusted by an empirically estimated adjustment factor. The adjustment factor was calculated using a Poisson regression of illnesses with beef-attributed antibiotic-resistant non-typhoidal salmonellosis predicted by the centered and transformed product of the prevalence of salmonella and percentage of resistance in beef salmonella as the predictor of case count in one year.

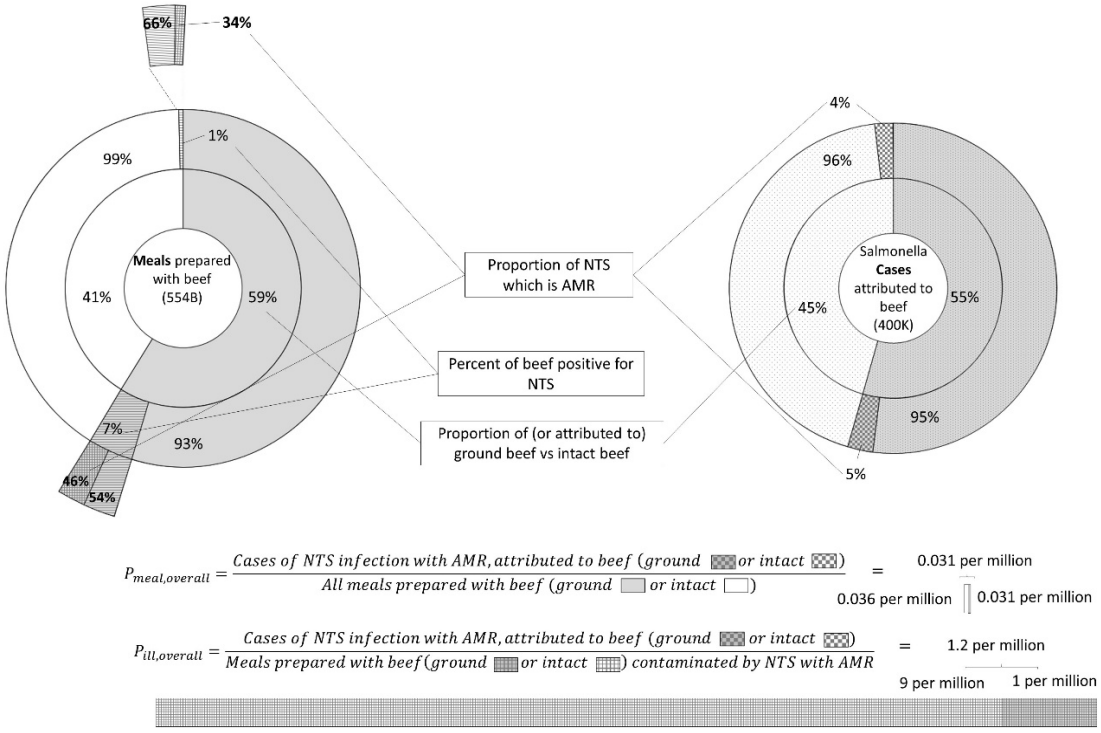
$$\mathrm{Pred}_{trans} = \sin^{-1}\sqrt{Prevalence \times Resistant\ \%} - mean(\sin^{-1}\sqrt{Prevalence \times Resistant\ \%})$$

This regression was carried out omitting the years 2003 and 2009, as these years with abnormally large case counts (Appendix Figure 2) impact prevalence (Appendix Figure 3) rather than resistance (Appendix Figure 4). This is because the relationship between human resistant cases and % resistance is improved by the inclusion of these years, but the regression of prevalence vs human resistant cases is worsened (Appendix Figure 5). The coefficient of the transformed predictor was estimated to be 59.36 (SE 42.3, p=0.233), and the intercept was 6.68 (SE 0.34).

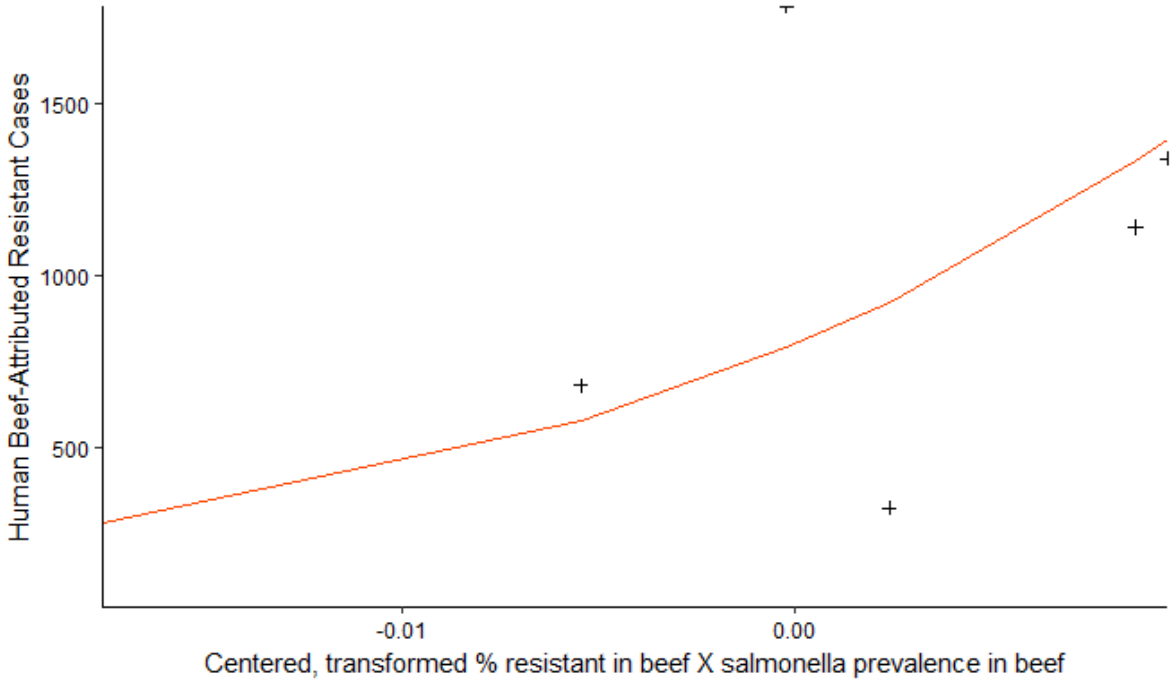
Appendix Table. Variable distributions and parameters used in the computation of the probability of beef-attributable resistant illness per meal made with beef contaminated with resistant nontyphoidal Salmonella

Variable	Definition	Distribution type	2010 Distribution Parameters	2010 Distribution Summary Statistics	Source
NTS_c	Cases per state per year in FoodNet States of Non-Typhoidal Salmonella by Serotype	Discrete	580, 686, 479, 2785, 468, 451, 343, 295, 989, 1063	total cases=8483 national est = 53404	CDC FoodNet
USFN	Multiplier per state per year to scale the catchment area of FoodNet states to the US population	Discrete	0.017, 0.011, 0.031, 0.014, 0.012, 0.007, 0.009, 0.019, 0.021	total % of US population = 14.1%	CDC FoodNet
FB	Fraction of cases of nontyphoidal salmonellosis which are attributed to food	Pert	min=0.91, mode=0.94, max=0.96	mean=0.94, sd=0.01	Scallan et.al 2011.
UD	Underdiagnosis multiplier	Gamma	shape=32.83, scale=0.74	mean=24.3, sd=4.2	Ebel et al., 2016
GBA	Proportion of Foodborne cases attributed to ground beef	Beta	α=1, β=3260	mean=0.0003, sd=0.0003	CDC NORS
WBA	Proportion of Foodborne cases attributed to intact beef	Beta	α=1, β=3260	mean=0.0003, sd=0.0003	CDC NORS
DA	Proportion of cases acquired in the United States	Pert	min=0.07, mode=0.11, max=0.15	mean=0.89, sd=0.015	Scallan et.al 2011.

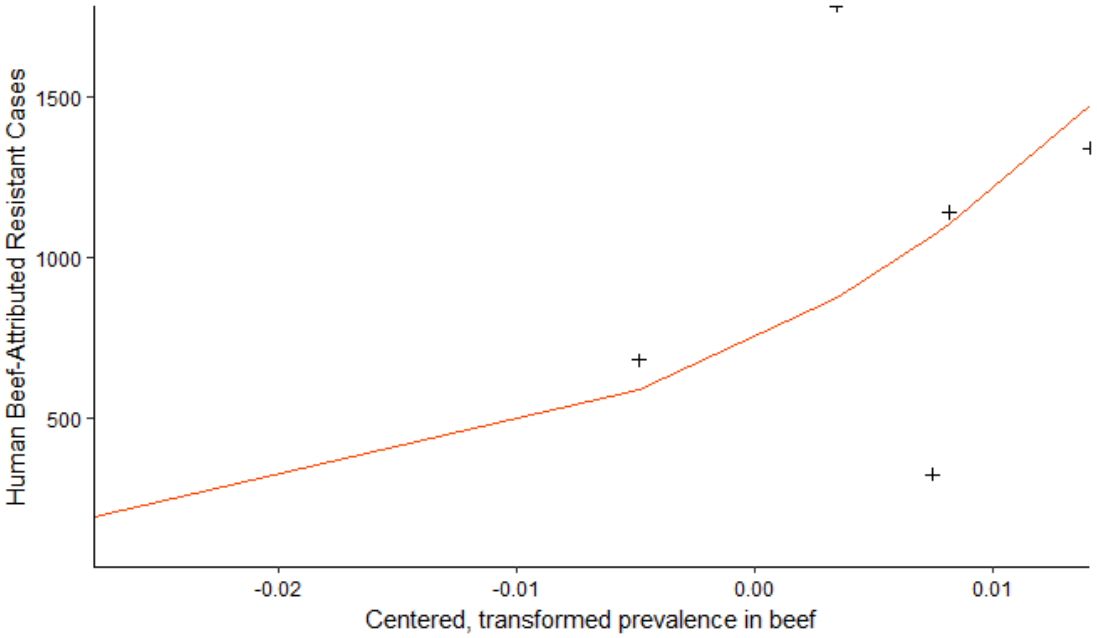
Variable	Definition	Distribution type	2010 Distribution Parameters	2010 Distribution Summary Statistics	Source
AMR_{perc}	Fraction of nontyphoidal *Salmonella* samples in the NARMS CDC data (matched to NORS outbreaks attributable to beef) with resistance to 1 or more AMD	Beta	α=2, β=1; α=1, β=5; α=0, β=13; α=2, β=1	mean=0.046, sd=0.014	CDC NARMS
GBF	Proportion of beef production sold as ground beef	Discrete	0.58	0.58	NCBA
$Beef_{dtot}$	Total beef disappearance annually, adjusted for food waste in lbs	Discrete	3.91×10^{12}	3.91×10^{12}	USDA ERS
MS_{IB}	Meal Size of beef consumed, not ground, in lbs	Normal	mean = 67.2 grams, sd=3.9	mean = 67.2 grams, sd=3.9	NHANES
Pp_{IB}	Percent Positive for nontyphoidal *Salmonella* from carcass sampling per establishment per year	Beta	for establishment 187, α=5, β=82	mean=0.057. sd=0.025	USDA FSIS
AMR_{IB}	Proportion of nontyphoidal *Salmonella* resistant to AMR from NARMS USDA carcass samples	Beta	α=97, β=152	mean=0.39, sd=0.031	USDA NARMS
MS_{GB}	Meal Size of beef consumed, ground, in lbs	Normal	mean = 61.0 grams, sd=4.8	mean = 61.0 grams, sd=4.8	NHANES
Pp_{GB}	Proportion Positive for nontyphoidal *Salmonella* from ground beef sampling, per establishment per year	Beta	α=34, β=54	mean=0.61, sd=0.05	USDA FSIS
AMR_{GB}	Proportion of nontyphoidal *Salmonella* resistant to AMR from NARMS FDA retail ground beef samples, and by establishment for USDA FSIS samples	Beta	for establishment 795, α=4, β=2	mean=0.67, sd=0.18	FDA NARMS, USDA FSIS
$Prev_{NTS,CONV}$	Prevalence of nontyphoidal *Salmonella* in the NAHMS study among conventionally-raised cattle.	Beta	α=678, β=4940	mean=0.12, sd=0.005	Unpublished data
$Prev_{NTS,RWA}$	Prevalence of nontyphoidal *Salmonella* in the NAHMS study among raised-without-antibiotic cattle.	Beta	α=54, β=679	mean=0.09, sd=0.01	Unpublished data
$Prev_{AMR,CONV}$	Proportion of nontyphoidal *Salmonella* with AMR in the NAHMS study among conventionally-raised cattle.	Beta	α=134, β=650	mean=0.26, sd=0.02.	Unpublished data
$Prev_{AMR,RWA}$	Proportion of nontyphoidal *Salmonella* with AMR in the NAHMS study among raised-without-antibiotic cattle.	Beta	α=11, β=66	mean=0.23, sd=0.06	Unpublished data



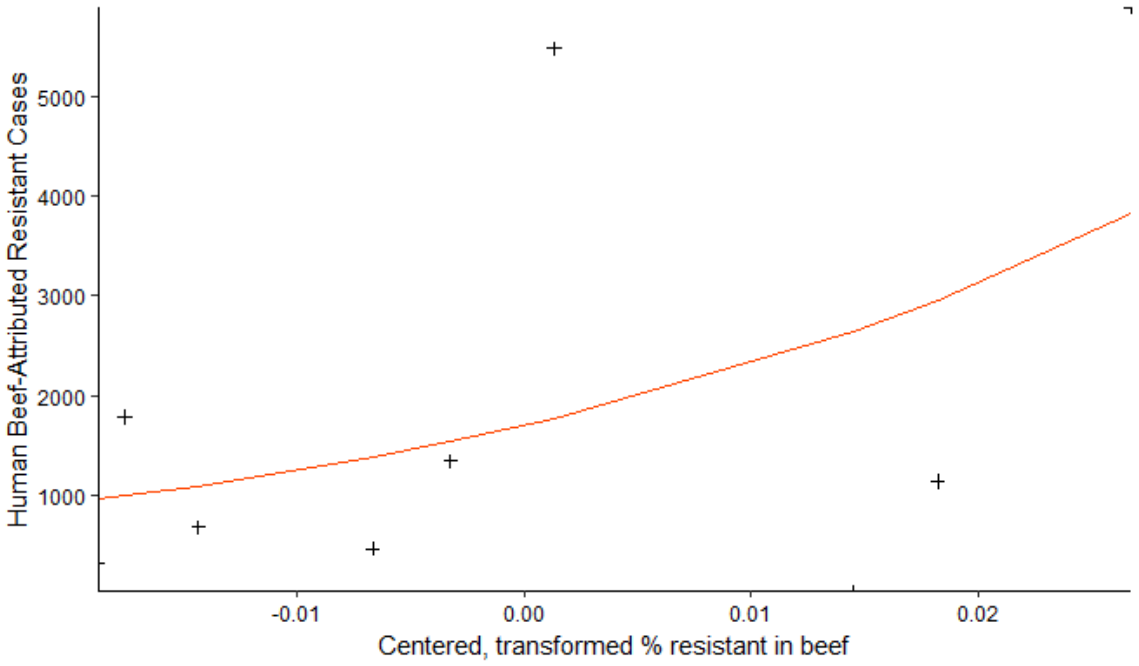
Appendix Figure 1. Probability of non-typhoidal salmonellosis with resistance to one or more antibiotic (antibiotic-resistant non-typhoidal salmonellosis) per million meals made with beef ($P_{meal,overall}$), and per million meals made with beef initially contaminated with antibiotic-resistant non-typhoidal salmonellosis ($P_{ill,overall}$) in 2002-2010. The sunburst diagrams represent the data used for parameterization, stratified by beef type – ground and intact: meals prepared with beef (approximately 554 billion), and human cases of non-typhoidal salmonellosis attributed to beef (over 400,000). The diagrams indicate, from center to periphery: the relative proportions of ground (grey) and intact (white) beef, the proportion of meals contaminated with nontyphoidal Salmonella (stripes), and the proportion of antibiotic-resistant nontyphoidal Salmonella (grid). The symbols in the equations for $P_{meal,overall}$ and $P_{ill,overall}$ refer to the data used for parameterization and represented in the sunburst diagrams, and the bar sizes represent the relative magnitude of these probability means.



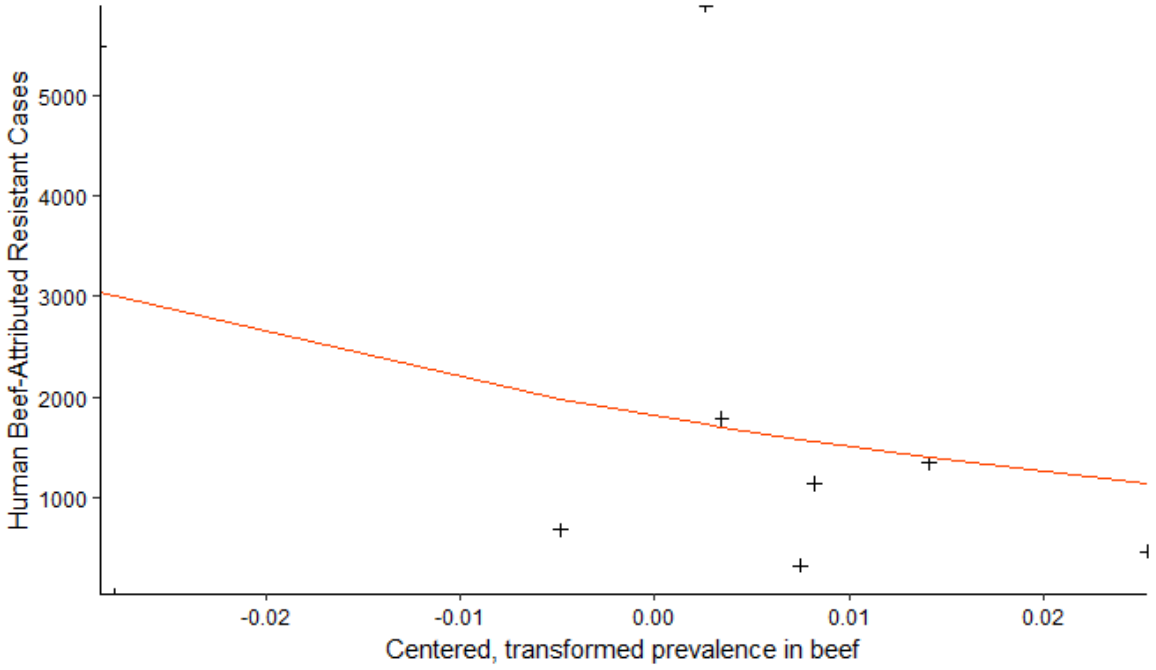
Appendix Figure 2. Poisson regression estimated cases (line) plotted over the human resistant cases and transformed resistance-prevalence in beef.



Appendix Figure 3. The centered, transformed prevalence of salmonella in beef as a predictor for human cases with resistance, omitting years 2003 and 2009.



Appendix Figure 4. The centered, transformed percent of beef with resistance as a predictor for human cases with resistance, including all years 2002-2010.



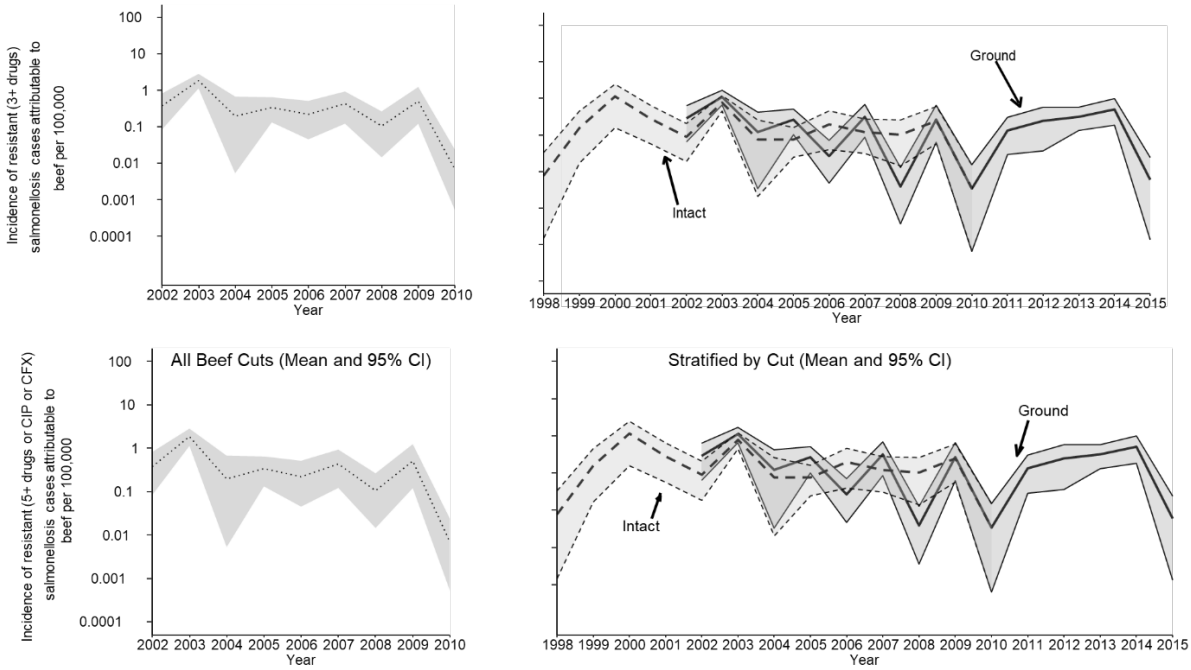
Appendix Figure 5. The centered, transformed prevalence of salmonella in beef as a predictor for human cases with resistance, including all years 2002-2010.

Supplemental Text on Multidrug (MDR) and Clinically relevant resistances (CRR)

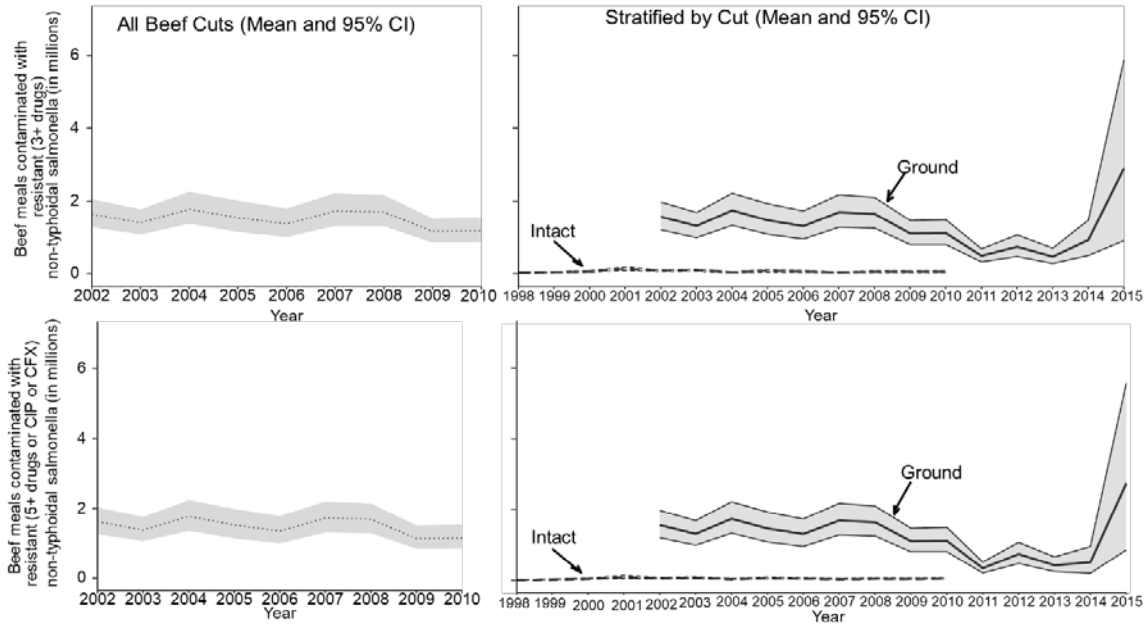
The mean $P_{ill,overall}$ for nontyphoidal *Salmonella* $_{MDR}$ was 0.023 per million meals made with beef with nontyphoidal *Salmonella* $_{MDR}$ (95%CrI: 0.011 - 0.1), and beef-attributable nontyphoidal *Salmonella* $_{MDR}$ did not increase over time. The mean $P_{ill,overall}$ for nontyphoidal *Salmonella* $_{CRR}$ was 2.66 per million (95% CrI: 0.006 - 18 per million), and $P_{meal,overall}$ was 0.0268 (0.00011 - 0.12 per million). The mean population incidence of these beef-attributed CRR cases across all years was 0.54 per 100,000 (0.002 - 2.45).

Of the 24 beef-attributable outbreaks in the NORS dataset that were matched to NARMS samples with resistance to any drug, only 6 of those were resistant to just one class. Eleven of the 24 were resistant to 5 or more classes, and most CRR outbreaks fit that part of the definition rather than resistance to fluoroquinolones or third generation cephalosporins specifically. Interestingly, the NARMS samples with Fluoroquinolone resistance which were matched to two beef outbreaks were not resistant to any other antibiotics in the panel. In contrast, the third-generation cephalosporin-resistant outbreaks were also resistant to more than five other antibiotic classes in all but one case – which was resistant to four classes.

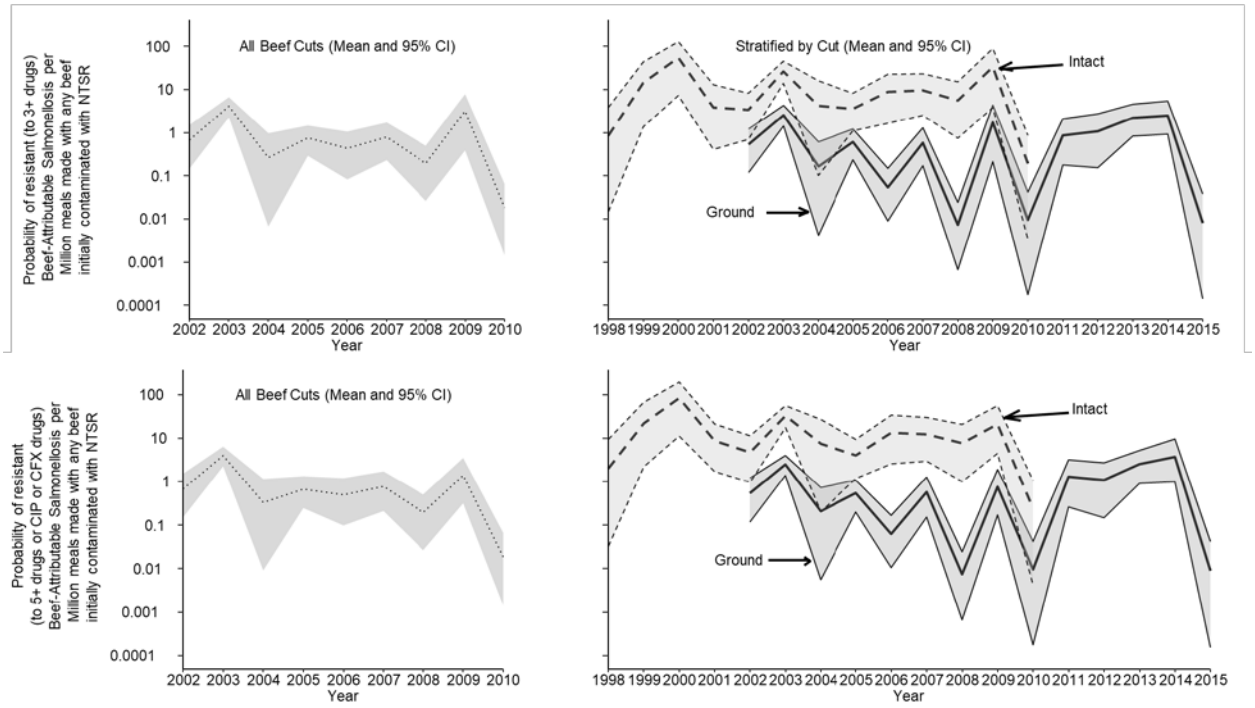
The trends in MDR and CRR P_{ill}, $Meals_{res}$, Ill_{res}, and P_{meal} for all cuts of beef combined are shown in Appendix figures 5-8.



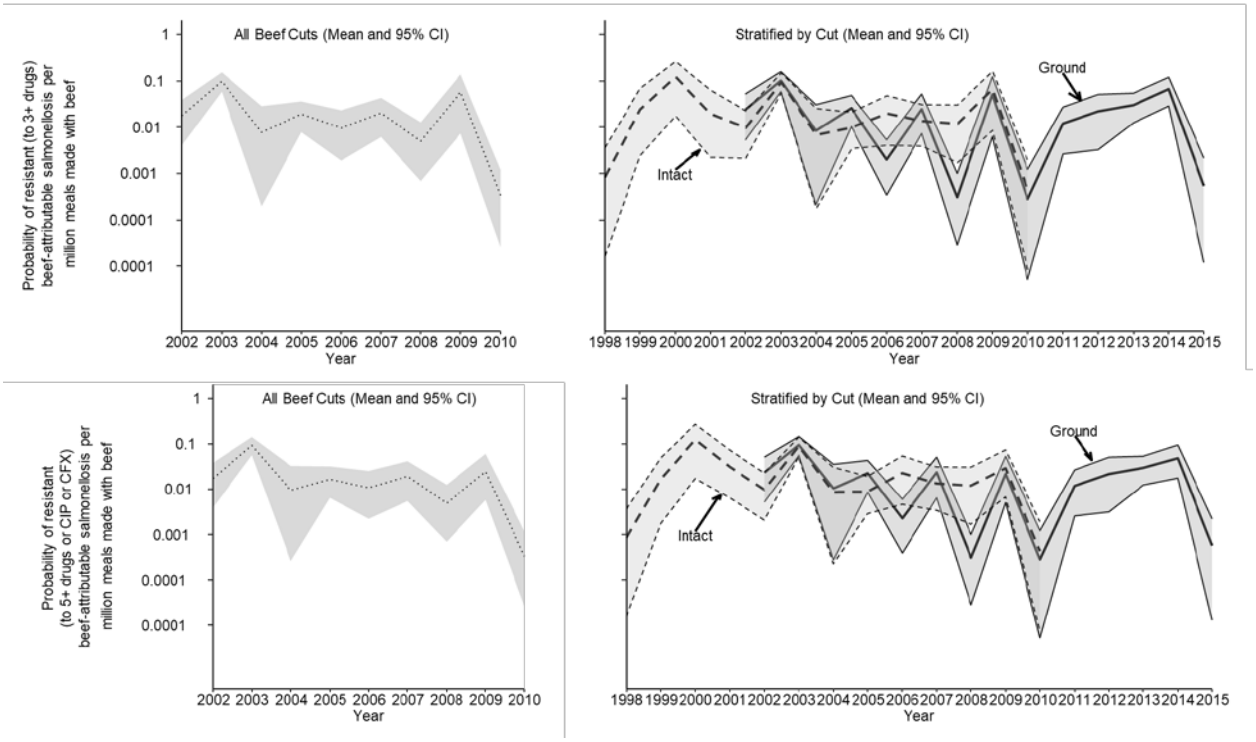
Appendix Figure 6. Mean and 95% Credible Interval of the incidence of salmonellosis cases with resistance to three or more AMD classes, or to more than 4 classes or 3rd Generation Cephalosporins or Fluoroquinolones, attributable to beef (intact, ground, or any) per 100,000 of the US population.



Appendix Figure 7. Mean average estimated consumed beef meals in the millions (ground, intact cuts, or both) with resistance to 3 or more classes (MDR), or to 4 or more classes or 3rd Generation Cephalosporins or Fluoroquinolones (CRR), for all years with available data, with 95% confidence limit.



Appendix Figure 8. Mean and 95% Credible Interval of the MDR and CRR P_{ill}, or the Probability of resistant salmonellosis per million meals consumed made with beef containing non-typhoidal salmonella resistant to more than 2 class of antibiotic (MDR) or to more than 4 classes, or specifically to 3rd Generation Cephalosporins and Fluoroquinolones (CRR).

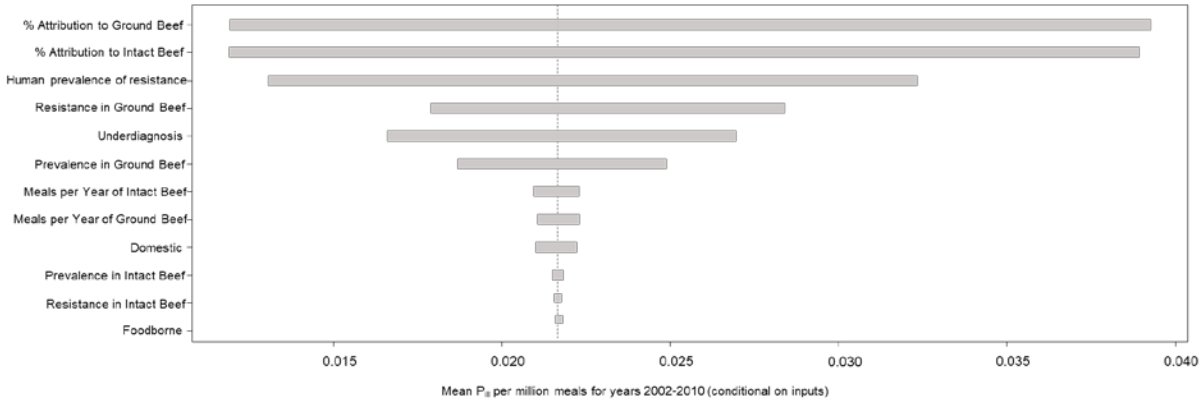


Appendix Figure 9. Mean and 95% Credible Interval of the MDR and CRR P_{meal}, or the Probability of (combined, ground, or intact) beef-attributable salmonellosis resistant to more than 2 class of antibiotic (MDR) or to more than 4 classes, or specifically to 3rd Generation Cephalosporins and Fluoroquinolones (CRR) per consumed meal made with beef per year (irrespective of nontyphoidal *Salmonella* contamination status).

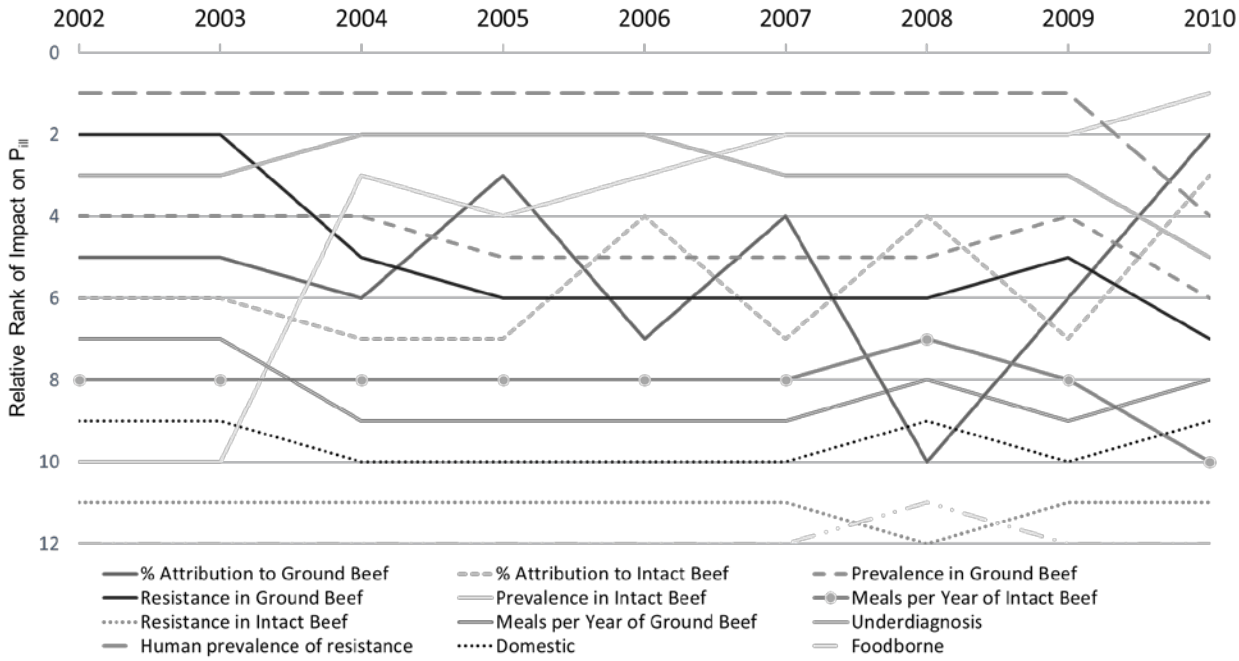
Supplemental Text on Sensitivity Analysis

The most influential drivers of Pill uncertainty were illness attributions for both IB and GB. The fraction of human nontyphoidal *Salmonella*cases which had AMR was third highest (Figure 9). Resistance prevalence in GB was the fourth most influential factor, followed by underdiagnosis and nontyphoidal *Salmonella* prevalence in GB. nontyphoidal *Salmonella* prevalence and resistance prevalence in IB, in contrast, were among the least influential of variables. When considering the change in influence over time, however, nontyphoidal *Salmonella* prevalence in IB steadily increased in importance over the period of the study to become the highest in 2010, (Figure 10). The fraction of nontyphoidal *Salmonella* attributable to IB was the most important factor for every year in the study except 2010, and attribution to GB had the greatest year-to-year change in rank of influence. Uncertainty of AMR prevalence among

human cases and uncertainty in GB nontyphoidal *Salmonella* prevalence remained relatively stable by comparison.



Appendix Figure 10. Tornado plot of conditional means analysis for the average $P_{ill,overall}$ across all 9 years of estimates for all types of beef. The broader the band, the more impact the input variable had in $P_{ill,overall}$.



Appendix Figure 11. Yearly rankings of the impact of uncertainty in predictors on the uncertainty of the outcome P_{ill}, where a rank of 1 shows the most impact on uncertainty.

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