11-2010

Quantitative Risk from Fluoroquinolone-Resistant Salmonella and Campylobacter Due to Treatment of Dairy Heifers with Enrofloxacin for Bovine Respiratory Disease

H. Scott Hurd
Iowa State University

Michael B. Vaughn
Veterinary Consulting Group, LLC

Derald J. Holtkamp
Iowa State University, holtkamp@iastate.edu

James S. Dickson
Iowa State University, jdickson@iastate.edu

Lorin Warnick
Cornell College

Quantitative Risk from Fluoroquinolone-Resistant Salmonella and Campylobacter Due to Treatment of Dairy Heifers with Enrofloxacin for Bovine Respiratory Disease

Abstract

The objective of this study was to evaluate the human health impact of using fluoroquinolones to treat bovine respiratory disease (BRD) in dairy heifers less than 20 months of age. Specifically, this study quantified the probability of persistent symptoms in humans treated with a fluoroquinolone, for a fluoroquinolone-resistant *Campylobacter*, *Salmonella*, or multidrug-resistant (MDR) *Salmonella* infection acquired following the consumption of ground beef. To comply with a Food and Drug Administration requirement for approval of enrofloxacin use in dairy heifers, a binomial event tree was constructed following Food and Drug Administration guidance 152. Release was estimated from the slaughter of dairy cattle carrying fluoroquinolone-resistant bacteria attributed to the proposed use in dairy heifers. For exposure, human foodborne exposure to *Campylobacter*, *Salmonella*, and MDR *Salmonella* after consumption of ground beef was estimated. The consequence assessment included illness, fluoroquinolone treatment, and persistent symptoms in patients treated with a fluoroquinolone. Using best available data to estimate the parameters and probabilities of each event, stochastic simulation was used to represent uncertainty and variability in many of the parameters. A scenario analysis was performed to evaluate the uncertainty of the following parameters: (1) probability of resistance development in treated animals, (2) portion of illnesses attributable to ground beef, and (3) probability of persistent symptoms in patients 18 years of age and over treated with a fluoroquinolone. The population at risk was restricted to people 18 years of age and over, as fluoroquinolones are not labeled for treatment of gastroenteritis in children. The mean annual increased risk of cases in the U.S. population (18 years of age and over) where compromised fluoroquinolone treatment resulted in persistent symptoms was estimated to be 1 in 61 billion (one case every 293 years) for *Salmonella*, 1 in 33 billion (one case every 158 years) for MDR *Salmonella*, and 1 in 2.8 billion (one case every 13 years) for *Campylobacter.*

Keywords

Veterinary Diagnostic and Production Animal Medicine

Disciplines

Agriculture | Circulatory and Respiratory Physiology | Immunology of Infectious Disease | Meat Science | Medical Immunology | Parasitology

Comments

This is a copy of an article published in the Foodborne Pathogens and Disease © 2010 Mary Ann Liebert, Inc.; Foodborne Pathogens and Disease is available online at: http://online.liebertpub.com.

FOODBORNE PATHOGENS AND DISEASE
Volume 7, Number 11, 2010

DOI: 10.1089/fpd.2010.0550

Quantitative Risk from Fluoroquinolone-Resistant *Salmonella* and *Campylobacter* Due to Treatment of Dairy Heifers with Enrofloxacin for Bovine Respiratory Disease

H. Scott Hurd,[1] Michael B. Vaughn,[2] Derald Holtkamp,[1] James Dickson,[3] and Lorin Warnick[4]

Abstract

The objective of this study was to evaluate the human health impact of using fluoroquinolones to treat bovine respiratory disease (BRD) in dairy heifers less than 20 months of age. Specifically, this study quantified the probability of persistent symptoms in humans treated with a fluoroquinolone, for a fluoroquinolone-resistant *Campylobacter*, *Salmonella*, or multidrug-resistant (MDR) *Salmonella* infection acquired following the consumption of ground beef. To comply with a Food and Drug Administration requirement for approval of enrofloxacin use in dairy heifers, a binomial event tree was constructed following Food and Drug Administration guidance 152. Release was estimated from the slaughter of dairy cattle carrying fluoroquinolone-resistant bacteria attributed to the proposed use in dairy heifers. For exposure, human foodborne exposure to *Campylobacter*, *Salmonella*, and MDR *Salmonella* after consumption of ground beef was estimated. The consequence assessment included illness, fluoroquinolone treatment, and persistent symptoms in patients treated with a fluoroquinolone. Using best available data to estimate the parameters and probabilities of each event, stochastic simulation was used to represent uncertainty and variability in many of the parameters. A scenario analysis was performed to evaluate the uncertainty of the following parameters: (1) probability of resistance development in treated animals, (2) portion of illnesses attributable to ground beef, and (3) probability of persistent symptoms in patients 18 years of age and over treated with a fluoroquinolone. The population at risk was restricted to people 18 years of age and over, as fluoroquinolones are not labeled for treatment of gastroenteritis in children. The mean annual increased risk of cases in the U.S. population (18 years of age and over) where compromised fluoroquinolone treatment resulted in persistent symptoms was estimated to be 1 in 61 billion (one case every 293 years) for *Salmonella*, 1 in 33 billion (one case every 158 years) for MDR *Salmonella*, and 1 in 2.8 billion (one case every 13 years) for *Campylobacter.*

Introduction

The vast majority of foodborne *Salmonella* and *Campylobacter* infections result in relatively mild, self-limiting illness requiring no treatment (CDC MMWR, 2004). However, some patients are hospitalized and, ignoring comorbidity, about 0.05% and 0.006% develop fatal disease from *Salmonella* and *Campylobacter* infections, respectively (Kennedy *et al.*, 2000). Antimicrobial resistance may limit treatment options for those few developing severe illness (CDC MMWR, 2004). There is concern that agricultural use of antimicrobial drugs may increase the occurrence of resistance and thereby adversely affect human health. The potential human health risks of antimicrobial use in livestock cannot be generalized and depend on the specific drug in question, administration practices, production system, and pathogens involved.

Risk assessments have become an integral part of the approval process for antimicrobial drugs used in food-producing animals, and are required by the U.S. Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) to evaluate the Human Food Safety of a proposed approval. While FDA guidelines outline a qualitative approach (FDA CVM, 2003a), we used a quantitative, event tree approach. A similar approach has previously been used to evaluate macrolide use in food animals (Hurd *et al.*, 2004).

[1]Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, Iowa.
[2]Veterinary Consulting Group, LLC, Columbia, Missouri.
[3]Animal Science, Iowa State University, Ames, Iowa.
[4]Population Medicine and Diagnostic Services, Cornell University, Ithaca, New York.

Enrofloxacin (Baytril®100; Bayer HealthCare LLC, Animal Health; Shawnee Mission, KS) was approved by the CVM in July 1998 for use in cattle for the treatment of bovine respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*. The original approval excluded the use of enrofloxacin in cattle intended for dairy production.

The objective of this study was to evaluate and quantify the human health risk of a new use for a commercially available fluoroquinolone in dairy heifers <20 months of age. The specific use would be only for treatment of respiratory disease in females <20 months old, as they are nonlactating.

Materials and Methods

A probabilistic risk assessment was conducted using a binomial event tree organized in accordance with the steps described in the U.S. FDA's Guidance Document (GD) 152, which include (1) release, (2) exposure via the foodborne route, and (3) consequence. For release, the emergence or selection of resistant bacteria attributed to the proposed use of enrofloxacin in dairy heifers was estimated. For exposure, human foodborne exposure to *Campylobacter*, *Salmonella*, and multidrug-resistant (MDR) *Salmonella* after consumption of ground beef was estimated. The consequence assessment included illness, fluoroquinolone treatment, and persistent symptoms in patients treated with a fluoroquinolone. Available data were used to estimate the parameters and distributions of each event. The population at risk was restricted to 18 years of age and over, as fluoroquinolones are not labeled for use to treat gastroenteritis in children.

Antimicrobial susceptibility testing results

Antimicrobial resistance guidelines used in this study were based on the laboratory results taken from published peer-reviewed journal articles referenced in this article. When testing details were provided, the laboratories conducting the tests followed the procedures used in the National Antimicrobial Resistance Monitoring System (NARMS) testing program and were current for the time of their studies. The interpretive criterion for susceptibility testing *Salmonella* spp. for fluoroquinolones is $\leq$1, 2, and $\geq$4 μg/mL for susceptible, intermediate, and resistant isolates, respectively. The same interpretive criterion is used for *Campylobacter* even though there are no approved CLSI/NCCLS laboratory standards (FDA CVM, 2003b, 2003c; USDA ARS, 2003).

Modeling approach

A quantitative, event tree modeling approach was used for this risk assessment. Event tree models typically identify sequences of events leading from an initiating event (animal antimicrobial use) to human health risk. In this model, the probabilities were modeled as either deterministic or stochastic parameters, depending on data reliability and availability. Deterministic parameters were represented by single, discrete point estimates, whereas stochastic parameters were represented by statistical distributions. Monte Carlo simulations were performed to create probability distributions of the model outcome (i.e., the "risk"). The model was built, and simulations performed using Microsoft Excel® 2002 (Microsoft Corp., Redmond, WA) and @Risk® 4.5 (Palisade Corp., Ithaca, NY). The outcome was defined as fluoroquinolone-resistant *Salmonella* or *Campylobacter* infections in humans resulting in persistent symptoms after physician treatment with fluoroquinolones.

Three unique features of this model were (1) potential transfers of fluoroquinolone-resistant foodborne bacteria from fluoroquinolone-treated dairy heifers to untreated cows and heifers within a farm, due to commingling; (2) potential transfers of fluoroquinolone-resistant foodborne bacteria from dairy heifers originating from farms with fluoroquinolone-treated dairy heifers to other farms that may acquire those animals, and that may as a consequence harbor fluoroquinolone-resistant foodborne bacteria; and (3) cross-contamination, during the mixing process, of ground beef containing fluoroquinolone-resistant pathogens originating from treated dairy heifers <20 months of age with ground beef free of fluoroquinolone-resistant foodborne pathogens.

The model simulated the effect of potential resistance transfer between animals and farms, regardless of the mechanism of resistance development within the treated animal. It modeled the spread between animals by allowing untreated herd mates to develop resistance and by modeling the movement of treated animals to other herds not using enrofloxacin with subsequent resistance spread to cows.

Summary of assumptions

Key assumptions made in the model are presented below. Most are conservative, that is, risk increasing.

- Ground beef is the major route of concern since pathogens in milk will be inactivated by pasteurization. Whole cuts are infrequently contaminated and usually cooked sufficiently. This assumption was consistent with FDA guidance via personal communication.
- MDR *Salmonella* are similar to other *Salmonella* except for the on-farm prevalence; the probability that a person will get ill from contaminated ground beef; the probability that the ill person will seek medical attention and be prescribed an antibiotic; and the probability that persistent symptoms will occur. With the exception of on-farm prevalence, all these parameters were increased compared to other *Salmonella*.
- MDR *Salmonella* illness was modeled as more likely to create illness and a doctor's visit and antimicrobial treatment.
- All foodborne *Campylobacter* have a 100% probability of resistance development in treated animals; this is an unrealistic but conservative assumption, due to lack of data otherwise.
- Background sensitivity/susceptibility for all three bacterial types is 100%; that is, there is no background resistance and all *Salmonella* or *Campylobacter* present in treated animals or herdmates could develop resistance due to enrofloxacin use.
- Fluoroquinolone-resistant *Salmonella* (excluding MDR) or *Campylobacter* have the same likelihood of creating illness as their susceptible counterparts.
- The number of illnesses resulting from consumption of contaminated meat is roughly proportional to the amount of contaminated meat consumed. No modeling of dose–response relationships was directly included due to lack of data on the doses presented to the consumer.

The last assumption is similar to that used by FDA (FDA CVM, 2000; Bartholomew *et al.*, 2005) for the evaluation of the impact on human health of fluoroquinolone-resistant *Campylobacter* attributed to the consumption of chicken. Although there are other published modeling approaches, this risk increasing assumption provides an upper bound on the estimates (Cox, 2005). FDA evaluated the impact of historical fluoroquinolone use in chickens and it was assumed that all currently observed resistance to fluoroquinolones on the carcasses of chickens was due to use of fluoroquinolones in chickens. However, for this analysis, fluoroquinolones had not been approved previously for use in dairy cattle intended for milk production of any age. Therefore, current fluoroquinolone resistance in *Campylobacter* spp. and *Salmonella* spp. could not be attributed to use of fluoroquinolones in dairy heifers <20 months of age (Fig. 1).

Release

Node 1 (Table 1) is the initiating event of enrofloxacin treatment of dairy heifers <20 months of age for respiratory disease. Node 2 (Tables 2 and 3) is development of resistance in *Salmonella* or *Campylobacter* residing within the treated heifer, as a function of the bacterial prevalence and the probability of resistance development in those bacteria. The potential for resistant organisms to pass through the herd, including milking cows, not just treated animals, through commingling with treated dairy heifers was evaluated. Commingling increases risk by increasing the number of animals that may eventually carry resistant organisms or plasmids when heifers and cows go to market. Additionally, it considers the possibility that herds receiving animals from treated herds may be exposed to resistant bacteria after commingling with the purchased animals. Output from Node 2 is the number of live animals (cows and heifers) in treated and untreated herds that may be carrying resistant organisms. In Node 3 (Table 4) resistant bacteria leave the farm in cows or heifers as they are culled to the slaughter market. In agreement with FDA, milk was not considered as a release route, as pasteurization will kill the bacteria of concern (Walstra *et al.*, 2006).

Exposure

In Node 4 (Table 5), viable resistant bacteria remain on the carcass after slaughter. The output of Node 4 is the number of carcasses contaminated with fluoroquinolone-resistant organisms. Node 5 (Tables 6 and 7): the most likely route of delivering resistant bacteria from beef carcasses through processing, distribution, and preparation to the consumer is through ground beef. Node 5 estimates the number of servings that will be contaminated with resistant bacteria delivered to the consumer fresh via retail or cooked via food manufacturing, food service, and quick serve restaurants. Other data that can be applied to this parameter for *Salmonella* include the NARMS retail data. However, given the low number of *Salmonella* and *Campylobacter* isolates, in this study, NARMS data were considered as supplementary evidence showing a very low probability of resistance development in treated cattle. The NARMS retail meat sampling data reported only 19 *Salmonella* isolates and 1 *Campylobacter* isolate from 1522 ground beef samples in 2002 and 2003; none were resistant to ciprofloxacin (FDA CVM, 2003b, 2003c).

Consequence

In Node 6 (Table 8) ground beef from meat that has not been properly handled or prepared is consumed and causes illness, and in Node 7 (Table 9) the ill person (18 years of age and over) is treated with a fluoroquinolone-class antibiotic. In Node 8 (Table 10) symptoms persist when human illness is treated with a fluoroquinolone. The outcome of Nodes 6

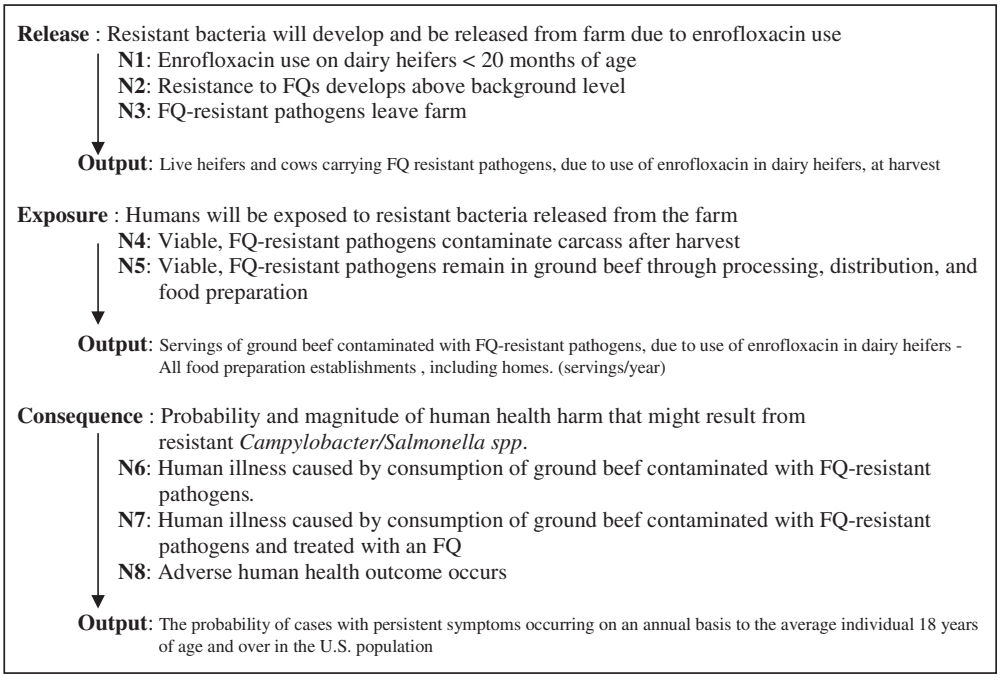

FIG. 1. Overview of model. Specific input/output details (parameters and distributions) are presented in Tables 1–10.

Table 1. Release Node 1

	Node 1: enrofloxacin used in dairy heifers < 20 months of age						
	Herds with dairy heifers only			*Herds with dairy cows and dairy heifers*			
	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
Input							
(a) Number of herds (no distribution was used)	1,629	1,629	1,629	79,811	79,811	79,811	USDA NASS (2005a), USDA NAHMS (2002, 2005), DRMS (2006)
(b) Percentage of herds in which dairy heifers may be treated with enrofloxacin (no distribution was used)	25%	25%	25%	19%	19%	19%	DMR (2005), USDA NAHMS (2005)
Model output							
Number of herds in which enrofloxacin may be used to treat dairy heifers	407	407	407	15,008	15,008	15,008	Model calculation: (a)×(b)
							Forward results to Node 2 (Table 2)

MDR, multidrug resistant.

through 8 is the number of cases of human illness where persistent symptoms occurred after treatment with a fluoroquinolone and where illness was caused by consumption of ground beef contaminated with fluoroquinolone-resistant *Campylobacter* or *Salmonella* due to use of enrofloxacin in dairy heifers <20 months of age.

Sensitivity analysis was performed to estimate the effect of uncertainty of some assumptions on the final results. Three parameters were evaluated by running 27 alternative scenarios for each bacteria using high, medium, and low estimates for each parameter. These included (1) Node 2, combinations of observed resistance to fluoroquinolones in animals treated with enrofloxacin (% of positive animals carrying resistant isolates), *Campylobacter* (100%, 75%, and 50%), *Salmonella*, and MDR *Salmonella* (100%, 20%, and 2%) with observed resistance to fluoroquinolones in animals not treated with enrofloxacin (% of positive animals carrying resistant isolates) *Campylobacter* (20%, 15%, and 10%), *Salmonella*, and MDR *Salmonella* (16.8%, 3.3%, and 0.3%); (2) Node 6, the ratio of illnesses attributed to beef per contaminated serving of ground beef after food preparation, *Campylobacter* (0.0062, 0.0005, and 0.0028), *Salmonella* (0.0324, 0.0056, and 0.0165), and MDR *Salmonella* (0.3284, 0.0566, and 0.1656); and (3) Node 8, probability that symptoms persist when human illness is treated with a fluoroquinolone for each parameter, *Campylobacter*, *Salmonella*, and MDR *Salmonella* (100%, 10%, 36%). The alternative scenarios were run using baseline values for all other parameters in the model.

Results

Table 11 summarizes the estimated risk of fluoroquinolone treatment failure (persistent symptoms) in humans treated for foodborne diseases resulting from consumption of ground beef originating from dairy heifers treated with enrofloxacin. Results are reported in two forms: expected frequency of a treatment failure case in the at risk population (18 years and older) and probability of the event happening to the average person in that population.

Baseline and worst-case scenario results are based on conditions and population assumptions at the time of the analysis.

Baseline scenarios

For *Campylobacter* the model predicts that on average one case of persistent symptoms would occur every 13 years using the baseline scenario. The mode for all simulations was one case every 18 years; 50% of all simulations predicted a risk of less than the mode. The 95% confidence interval on this distribution was one case every 38.3 years to every 6.5 years. The left skewed distribution shows that there is a remote chance of one case every 4 years for the baseline scenario.

For *Salmonella* the model predicts that one case of persistent symptoms would occur every 293 years, on average, using the baseline scenario. The mode for all simulations was one case every 501.2 years. The 95% confidence interval on this distribution was one case every 129.3 to every 1060.8 years.

Table 2. Release Node 2

Node 2a: resistance to fluoroquinolones develops above background level: Herds where enrofloxacin is used on dairy heifers <20 months of age

	Treated herds with dairy heifers only			*Treated herds with dairy cows and dairy heifers*			
	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
Input							
(a) Number of herds in which enrofloxacin may be used to treat dairy heifers	407	407	407	15,008	15,008	15,008	Output from Node 1 (Table 1)
(b) Average inventory of treated herds (animals/herd)	435	435	435	221	221	221	DRMS (2006), USDA NASS (2005a), USDA NAHMS (2002, 2003a)
(c) Prevalence of pathogens in treated herds (% of animals positive)	14.5%	4.3%	0.4%	14.0%	4.9%	0.4%	Green (2001, unpublished results), Ruegg *et al.* (2001), Harvey (2004), USDA NAHMS (1994, 2002, 2003b), Sato *et al.* (2004), Fossler (2004, 2005), Warnick *et al.* (2003a, 2003b)
(detailed data from references were used to generate a beta distribution producing a mean% with @Risk: [$s+1$, $n-s+1$])	$s=688$ $n=4745$	$s=597$ $n=13769$	$s=15$ $n=3709$	$s=4269$ $n=30592$	$s=2167$ $n=44055$	$s=15$ $n=3709$	
(d) Dairy heifers treated at some time in their life with enrofloxacin as a percentage of inventoried animals in treated herds	19.4%	19.4%	19.4%	9.7%	9.7%	9.7%	USDA NAHMS (2005), DRMS (2006)
(e) Background sensitivity to fluoroquinolones in untreated herds (% of positive animals carrying sensitive isolates) (detailed data from references were used to generate a beta distribution producing a mean% with @Risk: [$s+1$, $n-s+1$])	100.0% $s=3097$ $n=3099$	100% $s=3097$ $n=3099$	100% $s=3097$ $n=3099$	100.0% $s=3097$ $n=3099$	100.0% $s=3097$ $n=3099$	100.0% $s=3097$ $n=3099$	Sato *et al.* (2004), Halbert (2006), Ray (2004), Ray *et al.* (2004), Wells *et al.* (2001), Blau *et al.* (2005)

(*continued*)

Table 2. (Continued)

Node 2a: resistance to fluoroquinolones develops above background level: Herds where enrofloxacin is used on dairy heifers <20 months of age							
	Treated herds with dairy heifers only			*Treated herds with dairy cows and dairy heifers*			
	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
(f) Observed resistance of pathogens to fluoroquinolones in animals treated with enrofloxacin (% of positive animals carrying resistant isolates)	100.0%	2.6%	2.6%	100.0%	2.6%	2.6%	Englen *et al.* (2005), USDA ARS (2003)
(g) Observed resistance of pathogens to fluoroquinolones in animals not treated with enrofloxacin (% of positive animals carrying resistant isolates)	20.0%	0.4%	0.4%	20.0%	0.4%	0.4%	Englen *et al.* (2005), USDA ARS (2003)
(h) Probability that fluoroquinolone-sensitive pathogens develop resistance due to use of enrofloxacin in animals treated with enrofloxacin	1.000	0.026	0.026	1.00	0.026	0.026	Englen *et al.* (2005), USDA ARS (2003). Model calculation: [(f)×(1 − e)]/(e)
(i) Probability that fluoroquinolone-sensitive pathogens develop resistance due to use of enrofloxacin in animals not treated with enrofloxacin	0.200	0.004	0.004	0.200	0.004	0.004	Englen *et al.* (2005), USDA ARS (2003). Model calculation: [(g) − (1 − e)]/(e)
Model output							
Number of live animals in treated herds carrying fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers	9,136	64	6	128,619	1,018	89	Model calculation: [(a)×(b)×(d)×(c)×(h)] + [(a)×(b)×(1 − d)×(c)×(i)] Results forwarded to Node 3 (Table 4)

Table 3. Release Node 2

Node 2b: resistance to fluoroquinolones develops above background level: herds untreated with enrofloxacin							
	Untreated herds with dairy cows and dairy heifers			*Untreated herds with dairy cows only*			
	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
Input							
(a) Number of untreated herds	64,803	64,803	64,803	1,629	1,629	1,629	USDA NASS (2005a), USDA NAHMS (2002). Table 1: (79,811 – 15,008) = 64,803. Table 1: 1,629.
(b) Percentage of herds receiving dairy heifer replacements from other herds	25.4%	25.4%	25.4%	100%	100.0%	100.0%	USDA NAHMS (2004)
(c) Probability that replacement dairy heifers entering untreated herds originate from a herd where dairy heifers are treated with enrofloxacin	0.65	0.65	0.65	0.65	0.65	0.65	Bates *et al.* (2001), USDA NAHMS (2005), DMR (2005)
(d) Probability that replacement dairy heifers entering untreated herds originate from a herd where dairy heifers are treated with enrofloxacin and are carrying fluoroquinolone-resistant pathogens or resistance factor	1	1	1	1	1	1	No data available: conservatively estimated as 1
(e) Probability that replacement dairy heifers entering untreated herds carrying fluoroquinolone-resistant pathogens or resistance factor transmit them to herdmates	1	1	1	1	1	1	No data available: conservatively estimated as 1
(f) Probability that a fluoroquinolone-resistant pathogen or resistance factor is transmitted to untreated herds	0.647	0.647	0.647	0.647	0.647	0.647	Model calculation: (c)×(d)×(e)
(g) Average inventory of untreated herds (animals/herd)	221	221	221	110.63	110.63	110.63	USDA NASS (2005a), DRMS (2006), USDA NAHMS (2002, 2003a)
(h) Prevalence of pathogens in untreated herds (% of animals positive)	14.0%	4.9%	0.4%	13.7%	6.3%	0.4%	Green (2001, unpublished results), Ruegg *et al.* (2001), Harvey (2004), USDA NAHMS (1994, 2002, 2003b), Sato *et al.* (2004), Fossler *et al.* (2004, 2005), Warnick *et al.* (2003a, 2003b)

(*continued*)

Table 3. (Continued)

Node 2b: resistance to fluoroquinolones develops above background level: herds untreated with enrofloxacin							
	Untreated herds with dairy cows and dairy heifers			*Untreated herds with dairy cows only*			
	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
(detailed data from references were used to generate a beta distribution producing a mean% using @Risk: [$s+1$, $n-s+1$])	$s=4269$ $n=30592$	$s=2167$ $n=44055$	$s=15$ $n=3709$	$s=3093$ $n=22550$	$s=495$ $n=7869$	$s=15$ $n=3709$	
(i) Background sensitivity of pathogens to fluoroquinolones in untreated herds (% of positive animals carrying sensitive isolates)	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	Sato *et al.* (2004), Halbert (2006), Ray (2004), Ray *et al.* (2004), Blau *et al.* (2005), Wells *et al.* (2001)
(detailed data from references were used to generate a beta distribution producing a mean% using @Risk: [$s+1$, $n-s+1$])	$s=3097$ $n=3099$	$s=3097$ $n=3099$	$s=3097$ $n=3099$	$s=3097$ $n=3099$	$s=3097$ $n=3099$	$s=3097$ $n=3099$	
(i) Observed resistance of pathogens to fluoroquinolones in animals not treated with enrofloxacin-untreated herds (% of positive animals carrying resistant isolates)	20.0%	0.4%	0.4%	20.0%	0.4%	0.4%	Englen *et al.* (2005), USDA ARS (2003)
(k) Probability that fluoroquinolone-sensitive pathogens develop resistance due to use of enrofloxacin in animals not treated	0.200	0.004	0.004	0.200	0.004	0.004	Englen *et al.* (2005), USDA ARS (2003) Model calculation: [(j) − (1 − i)]/(i)
Model output							
Number of live animals in untreated herds carrying fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers (head) entering the untreated herd	258,686	1872	164	3196	30	2	Model calculation: (a)×(f)×(g)×(h)×(k) (note: model rounds) Results forwarded to Node 3 (Table 4)

Table 4. Release Node 3

	Node 3: fluoroquinolone-resistant pathogens leave farm												
	Treated herds with dairy heifers only			*Treated herds with dairy cows and dairy heifers*			*Untreated herds with dairy cows and dairy heifers*			*Untreated herds with dairy cows only*			
	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
Input													
(a) Live animals carrying fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers (hd)	9,136	64	6	128,619	1,018	89	258,686	1,872	164	3,196	30	2	Output from Nodes 2a and 2b (Tables 2 and 3)
(b) Percent of animals harvested annually	2.4%	2.4%	2.4%	15.2%	15.2%	15.2%	15.2%	15.2%	15.2%	28.0%	28.0%	28.0%	Warnick (1994), USDA NAHMS (2002, 2003a), DRMS (2006), USDA ERS (2006), USDA NASS (2004)
(c) Probability that fluoroquinolone-resistant pathogens persists in live animals and is present at harvest	1	1	1	1	1	1	1	1	1	1	1	1	Given lack of data, conservatively estimated at 100%
(d) Live animals carrying fluoroquinolone-resistant pathogens at harvest (head/year)	219	2	0	19,550	155	14	39,320	285	25	895	8	1	Model calculation: (a)×(b)×(c)
Model output													
Live dairy heifers and cows carrying fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers at harvest (head/year)	59,985	449	39	59,985	449	39	59,985	449	39	59,985	449	39	Model calculation: add appropriate pathogen columns from row (d).
													Forward results to Node 4 (Table 5)

Table 5. Exposure Node 4

Node 4: viable, fluoroquinolone-resistant pathogens contaminate carcass after harvest				
	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
Input				
(a) Live dairy heifers and cows carrying fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers at harvest (head/year)	59,985	449	39	Output from Node 3 (Table 4)
(b) Probability a carcass from a live animal, whether carrying pathogens or not, becomes contaminated with pathogen	0.012	0.012	0.012	USDA FSIS (1994, 2006)
Model output				
Carcasses contaminated with fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers (carcasses/year)	711.1	5.3	0.5	Model calculation: (a)×(b) (note: numbers not exact as model rounds throughout calculation) Forward results to Node 5a (Table 6)

Table 6. Exposure Node 5

Node 5a: viable, fluoroquinolone-resistant pathogens remain in ground beef through processing, distribution, and food preparation				
	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
(a) Carcasses contaminated with fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers (carcasses/year)	711.1	5.3	0.5	Output from Node 4 (Table 5)
(b) Probability that ground beef from a carcass contaminated with pathogens is contaminated	1	1	1	NAS (2002)
(c) Multiplier due to mixing of meat from carcasses contaminated by pathogens with that of noncontaminated carcasses	2.00	2.00	2.00	J. Dickson (pers. comm.)
(d) Average dressed carcass weight (kg/carcass)	285	285	285	Rogers (2004)
(e) Percentage of carcass that is processed into ground beef	80%	80%	80%	Roberts (1999)
(f) Quantity of ground beef from carcasses (kg)	324,241	2,414	211	Model calculation: (a)×(b)×(c)×(d)×(e)
(g) Percentage of ground beef from carcasses that is distributed to quick service restaurants	58%	58%	58%	
(h) Percentage of ground beef from carcasses that is distributed to manufacturing	5%	5%	5%	NCBA (2004)
(I) Percentage of ground beef from carcasses that is distributed to food service	34%	34%	34%	
(j) Percentage of ground beef from carcasses that is distributed to retail/home consumption	3%	3%	3%	
Quantity of ground beef from carcasses distributed to quick serve restaurants (kg/year)	188,060	1,400	122	Model calculation: (f)×(g)
Quantity of ground beef from carcasses distributed to manufacturing (kg/year)	16,212	121	11	Model calculation: (f)×(h)
Quantity of ground beef from carcasses distributed to food service (kg/year)	110,242	821	72	Model calculation: (f)×(i)
Quantity of ground beef from carcasses distributed to retail/home consumption (kg/year)	9,727	72	6	Model calculation: (f)×(j)

Table 7. Exposure Node 5

Node 5b: viable, fluoroquinolone-resistant pathogens remain in ground beef through processing, distribution, and food preparation

	Quick service restaurants			*Manufacturing*			*Food service*			*Retail/home consumption*			
	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
Input													
(a) Quantity of ground beef from carcasses distributed (kg/year)	188,060	1,400	122	16,212	121	11	110,242	821	72	9,727	72	6	Output from Node 5 (Table 6)
(b) Average serving size of ground beef (kg/serving)	0.1135	0.1135	0.1135	0.085	0.085	0.085	0.1135	0.1135	0.1135	0.085	0.085	0.085	Roberts (1999), MDE (2005)
(c) Probability that a serving of ground beef remains contaminated with pathogens (*Campylobacter*, *Salmonella*, or MDR *Salmonella*) when prepared in Quick Service Restaurants, Manufacturing, Food Service, or Retail/ Home Consumption (servings/year)	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.001	0.001	0.001	0.005	0.005	0.005	NCBA (2004)
(d) Servings of ground beef contaminated with fluoroquinolone-resistant pathogens (*Campylobacter*, *Salmonella*, or MDR *Salmonella*) due to use of enrofloxacin in dairy heifers when prepared in Quick Service Restaurants, Manufacturing, Food Service, or Retail/Home Consumption (servings/year)	166	1	0.1	19	0.1	0.1	971	7	1	572	4	0.4	Model calculation: [(a)/(b)]×(c)
Model output													
Servings of ground beef contaminated with fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers—all food preparation establishments, including homes (servings/year)	1,728	13	1	1,728	13	1	1,728	13	1	1,728	13	1	Model calculation: add appropriate pathogen columns from row (d) Forward results to Node 6 (Table 8)

Table 8. Consequence Node 6

Node 6: human illness caused by consumption of ground beef contaminated with fluoroquinolone-resistant pathogens	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
Input				
(a) Servings of ground beef contaminated with fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers—all food preparation establishments (servings/year)	1,728	13	1	Output from Node 5 (Table 7)
(b) Ratio of illnesses attributed to beef per contaminated serving of ground beef after food preparation. Ratio was simulated in a separate spreadsheet used to perform a separate Monte Carlo simulation to estimate a distribution for this ratio. The distribution was then sampled to run the main model. Values shown are means of the distribution.	0.0028	0.0165	0.1656	USDA NASS (2004, 2005b), USDA FSIS (1994, 2006), J. Dickson (pers. comm..), Rogers (2004), USDA ERS (2006), Roberts (1999), Census Bureau (2002), Flint *et al.* (2005), Mead *et al.* (1999), Altekruse *et al.* (1999), CDC (1990–2004, 2003), Wheeler *et al.* (1999), Samuel *et al.* (2004), Friedman *et al.* (2004), de Wit *et al.* (2000), Flint *et al.* (2005), Voetsch *et al.* (2004), Rocourt *et al.* (2003), Danish Zoonoses Centre (2003), Champion *et al.* (2005), FDA CVM (2003b), Nielsen *et al.* (2006), Hald *et al.* (2004)
Model output				
Number of human illness cases caused by consumption of ground beef contaminated with fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers (U.S. cases/year)	4.84	0.21	0.19	Model calculation: (a)×(b)
				Forward results to Node 7 (Table 9)

FDA, Food and Drug Administration.

For MDR *Salmonella* the model predicts that one case of persistent symptoms would occur every 158 years, on average, using the baseline scenario. The mode for all simulations was less than one case every 292 years. The 95% confidence interval on this distribution was one case every 67.8–647.2 years.

Worst-case scenarios

Worst-case scenarios are reported where all treated animals develop resistance, where underreporting, attribution, and carcass contamination are at their maximum, and where the probability of persistent symptoms in treated patients is 100%.

The worst-case scenario for *Campylobacter* estimates a mean risk of only one case every 2.2 years. The upper-bound (95th percentile) estimate from the worst-case scenario shows that one case of persistent symptoms might occur every 1.1 years, a risk of 1 in 210 million and qualitatively describable as "very low."

The worst-case scenario for *Salmonella* estimates a mean risk of one case every 1.4 years. The upper-bound (95th percentile) estimate from the worst-case scenario shows one case of persistent illness every 0.7 years

The worst-case scenario for MDR *Salmonella* estimates a mean risk of one case every 0.8 years. The upper-bound (95th percentile) estimate from the worst-case scenario shows one case of persistent illness every 0.4 years.

Discussion

Multiple conservative, parameter estimations were used throughout the model. Some of the parameters, such as attribution (Node 6), resistance development in untreated herd mates (Node 2), and probability of persistent symptoms (Node 8), should be at or near zero. Unrealistically, this model did not place much of the probability density near zero. Therefore, the mean frequency baseline results shown in Table 11 should be viewed as upper bounds on the risk or worst case.

Additionally, the multiple scenarios simulated showed that even with all the worst case and unlikely assumptions we made, the risks were very low. For example, the worst case assumes that MDR *Salmonella* would always (100%) develop resistance in treated heifers, are 10 times more likely to cause human illness, and would always (100%) produce persistent symptoms in treated patients. Clearly, these are unrealistic assumptions, especially given the low to zero levels of ciprofloxacin resistance being reported by NARMS after Baytril100 use in beef cattle since 1999 (FDA CVM, 2003c).

The sensitivity analysis showed that results were most sensitive to changes in Node 6 (Ratio of Illnesses Attributed to

Table 9. Consequence Node 7

Node 7: human illness caused by consumption of ground beef contaminated with fluoroquinolone-resistant pathogens is treated with a fluoroquinolone	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
Input				
(a) Cases of human illness caused by consumption of ground beef contaminated with fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers (U.S. cases/year)	4.84	0.21	0.19	Output from Node 6 (Table 8)
(b) Probability the patient seeks medical help	0.17	0.17	0.28	FDA CVM (2000), Herikstad *et al.* (2002), de Wit (2000), Wheeler *et al.* (1999), McNulty (1987), Hurd (2004), Voetsch *et al.* (2004), Molbak *et al.* (1999), Dechet *et al.* (2006)
(references used to create a triangular distribution in @Risk: [min, most likely, max])	(5%,15%,30%)	(5%,15%,30%)	(5%,30%,50%)	
(c) Probability an antimicrobial is prescribed and the antimicorbial is a fluoroquinolone	0.27	0.27	0.33	FDA CVM (2000), de Wit *et al.* (2000), Wistrom (1995), Tabibian *et al.* (1987), Chan *et al.* (2003), CDC MMWR (2004), Allos (2001), Molbak *et al.* (1999), Dechet *et al.* (2006)
(references used to create a triangular distribution in @Risk: [min, most likely, max])	(10%,20%,50%)	(10%,20%,50%)	(10%,30%,60%)	
Model output				
(d) Cases of human illness treated with a fluoroquinolone, caused by consumption of ground beef contaminated with fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers (U.S. cases/year)	0.215	0.009	0.018	Model calculation: (a)×(b)×(c) (note: model rounds) Forward results to Node 8 (Table 10)
(e) U.S. 2000 Census population of persons old enough to be treated for foodborne illness with an antimicrobial (persons 18 years of age and over)	209,128,094			Census Bureau (2002)
The rate of illness occurring on an annual basis to the average individual 18 years of age and over in the U.S. population (illnesses/1,000,000,000)	1.028	0.045	0.084	Model calculation: (d)/[(e)/1,000,000.000]
The probability of illness occurring on an annual basis to the average individual 18 years of age and over in the U.S. population	0.0000000010	0.000000000045	0.0000000001	Model calculation: (d)/(e)

Table 10. Consequence Node 8

Node 8: adverse human health outcome occurs				
	Campylobacter	Salmonella	*MDR* Salmonella	*Reference*
Input				
(a) Cases of human illness treated with a fluoroquinolone, caused by consumption of ground beef contaminated with fluoroquinolone-resistant pathogens due to use of enrofloxacin in dairy heifers (U.S. cases/year)	0.2151	0.0094	0.0176	Output from Node 7 (Table 9, row [d])
(b) Probability that symptoms persist when human illness is treated with a fluoroquinolone	0.36	0.36	0.36	Kuschner *et al.* (1995), Sirinavin and Garner (2000), Wistrom (1992, 1995), Dryden *et al.* (1996), Nelson *et al.* (2004), Sanders *et al.* (2002)
Output				
(c) Cases of human illness where symptoms persist after treatment with a fluoroquinolone and where illness was caused by consumption of ground beef contaminated with fluoroquinolone-resistant pathogen due to use of enrofloxacin in dairy heifers (U.S. cases/year)	0.077 (1 case every 13 years)	0.003 (1 case every 294.4 years)	0.006 (1 case every 158.1 years)	Model calculation: (a)×(b)
(d) U.S. 2000 Census population of persons old enough to be treated for foodborne illness with an antimicrobial (persons 18 years of age and over)	209,128,094			Census Bureau (2002)
The rate of persistent symptoms occurring on an annual basis to the average individual 18 years of age and over in the U.S. population (illnesses/1,000,000,000)	0.370	0.016	0.030	Model calculation: (c)/[(d)/1,000,000,000]
The probability of cases with persistent symptoms occurring on an annual basis to the average individual 18 years of age and over in the U.S. population	1 in 2702 million	1 in 61566 million	1 in 33053 million	Model calculation: (1/[(c)/(d)])/1,000,000

Beef per Contaminated Serving of Ground Beef Following Food Preparation). Assumptions made about the portion of all foodborne illness attributable to a specific commodity should be made carefully. This finding is not surprising given that this one parameter reflects many illness impacting processes such as handling, cooking, and bacterial dose. Additionally, the importance of this parameter demonstrates the important role of standard food hygiene practices in reducing antibiotic resistance risk. Risk would increase if there were to be a highly virulent and prevalent pathogen whose source was predominately meat.

The approach used in Node 6 (Table 8) relies upon what is observed and known about the level of foodborne illness attributed to ground beef relative to the estimated number of servings of ground beef that were contaminated with each of the foodborne pathogens modeled. It assumes that the number of illnesses resulting from consumption of contaminated meat is roughly proportional to the amount of contaminated meat consumed if the level of contamination is held fixed (Bartholomew *et al.*, 2005). Key processes between the farm and the consumer were modeled to project the relative increase in the number of servings of ground beef contami-

Table 11. Predicted Case Frequency and Probability of Persistent Symptoms of Foodborne Disease in an Average Individual 18 Years of Age and Over in the United States, Treated with Fluoroquinolones, After Consumption of Ground Beef Containing Foodborne Pathogen(s) Originating from Dairy Heifers (<20 Months of Age) Treated with Enrofloxacin

		Campylobacter	Salmonella	*MDR* Salmonella
Mean	Case frequency	1 every 13.2 years	1 every 293.4 years	1 every 157.9 years
	Probability	1 in 2.8 billion	1 in 61.4 billion	1 in 33.1 billion
Mode	Case frequency	1 every 18.2 years	1 every 501.2 years	1 every 292 years
	Probability	1 in 3.8 billion	1 in 104.9 billion	1 in 61.1 billion
95% prediction interval	Case frequency	(6.5–38.3) years	(129.3–1,060.8) years	(67.8–647.2) years
	Probability	(1.4–8) billion	(27.1–221.9) billion	(14.2–135.4) billion

nated by fluoroquinolone-resistant *Campylobacter*, *Salmonella*, or MDR *Salmonella*. The ratio of illnesses attributed to beef per contaminated serving of ground beef after food preparation is modeled in a separate spreadsheet used to perform a separate Monte Carlo simulation to estimate a distribution for this ratio. The distribution was then sampled to run the main model.

We do not distinguish among different levels of contamination (e.g., 1 CFU per ton, which might cause no harm, vs. 1 billion CFUs per oz, which presumably would be much more hazardous). In reality, it is plausible that average levels of contamination cause little or no harm, and that our estimates are upper bounds, driven by occasional pockets of high concentrations, rather than by average levels of contamination.

The purpose of Node 1 was to estimate the number of dairy operations where Baytril100 would be used if approved for respiratory disease treatment in dairy heifers <20 months of age. It is important to understand the structure of the U.S. dairy industry and the management of replacement heifers to understand the potential risk of Baytril100 use in dairy replacement heifers; heifers are raised to enter the milking herd, not the food chain. Very few dairy heifers are sold for slaughter because of their value for milk production and breeding. Most illness and treatment occurs during the first few months of life, long before they begin milking. Heifers are commingled with others of similar age and are sometimes sold to other farms. Heifers are often kept in separate facilities from milking cows until the time of their first calving when milking begins.

MDR serovars of *Salmonella* such as Newport and Typhimurium DT104 are of concern to human health for two reasons. They are thought more likely to acquire resistance to antibiotics like enrofloxacin and to cause human illness that is difficult to treat. To address these concerns, it was assumed that any MDR *Salmonella* would have a higher probability of resistance acquisition on-farm. Additionally, two other parameters were increased compared to nonresistant *Salmonella*: the probability that an ill patient will seek medical attention and the probability that an antibiotic will be prescribed (Node 7).

Uniquely, this model considers not only the development of resistance in treated herds, but also the transfer of resistant bacteria or genetic determinants through the movement of cattle to operations that are not using enrofloxacin. Other models focus on resistance development in treated animals only.

Our model focused on foodborne transmission of fluoroquinolone-resistant *Salmonella* and *Campylobacter* via ground beef. Routes of transmission other than foodborne were not considered in the model because the majority of dairy cattle meat goes into ground beef and pasteurization eliminates pathogens in milk (NCBA, 2004; Walstra *et al.*, 2006).

Quantitative risk assessment is a widely used method to evaluate the probability of specific hazards and guide policy decisions. For this model we used an event tree approach that allowed inclusion of stochastic elements to account for biological variability and uncertainty for key parameters. Models, quantitative or qualitative, always have weaknesses. The key question is whether these weaknesses consistently over- or underestimate (bias) the risk. We used several approaches to insure that the model results would represent conservative (higher) risk estimates, to evaluate the effect of parameters for which little scientific data were available and to account for indirect transmission pathways.

This study was conducted to fulfill CVM's requirement to complete a risk assessment for all new antimicrobial products and uses. The model presented in this article takes into account any potential resistant organisms introduced into the dairy herd from treated heifers, including spread through commingling with the potential of entering the food supply from slaughtered dairy cows.

While FDA GD 152 recommends a qualitative risk assessment approach, the "FDA does not intend to exclude quantitative risk assessment in favor of a qualitative process" (FDA CVM, 2003a). The qualitative risk of using injectable antimicrobials in treating individual food-producing animals is inherently low. When reliable information is available, the use of a quantitative model allows a detailed study of multiple risk factors. Since fluoroquinolones are considered critically important to human health, the merging of quantitative estimates with qualitative classifications allows reviewers to gain additional insight into the magnitude of qualitative risk classifications.

Conclusions

Mean annual risk estimates of 1 in 2.8 billion, 61.4 billion, and 33.1 billion for *Campylobacter*, *Salmonella*, and MDR *Salmonella*, respectively, can be considered qualitatively very low. These estimates are arguably conservative and upper-bounded due to the multiple conservative parameter estimates incorporated into the model such as the inclusion of resistance spread to commingled and untreated herd mates, the potential movement of resistance bacteria with sold dairy heifers, and the mixing of ground beef. This modeled risk is hypothetical and the actual risk could well be even lower.

Acknowledgments

Special thanks go to Pam Triplett and Ruth Lamley, Bayer Animal Health, for input on organization of the article and references and Sasidhar Malladi, Iowa State University, for mathematical modeling assistance.

Disclosure Statement

At the time the Risk Assessment was conducted, Drs. Hurd, Holtkamp, Dickson, and Warnick were paid by Bayer Animal Health as Consultants and Dr. Vaughn was employed by Bayer Animal Health. Dr. Vaughn was paid by Bayer Animal Health to oversee the writing and submission of this paper, after retiring from Bayer Animal Health.

References

Allos BM. Campylobacter jejuni infections: update on emerging issues and trends. Clin Infect Dis 2001;32:1201–1206.

Altekruse SF, Stern NJ, Fields PI, *et al. Campylobacter jejuni*—an emerging foodborne pathogen. Emerg Infect Dis 1999;5:28–35.

Bartholomew MJ, Vose DJ, Tollefson LR, *et al.* A linear model for managing the risk of antimicrobial resistance originating in food animals. Risk Anal 2005;25:99–108.

Bates TW, Thurmond MC, and Carpenter TE. Direct and indirect contact rates among beef, dairy, goat, sheep, and swine herds in three California counties, with reference to control of potential foot-and-mouth disease transmission. Am J Vet Res 2001;62:1121–1129.

Blau DM, McCluskey BJ, Ladely SR, *et al. Salmonella* in dairy operations in the United States: prevalence and antimicrobial drug susceptibility. J Food Prot 2005;68:696–702.

[CDC] Centers for Disease Control and Prevention. Foodborne Outbreak Response and Surveillance Unit. United States Foodborne Disease Outbreaks. Annual Listing of Foodborne Disease Outbreaks, United States. 1990–2004. Available at www.cdc.gov/foodborneoutbreaks/outbreak_data.htm, accessed May 19, 2006.

[CDC] Centers for Disease Control and Prevention. FoodNet Annual Reports. 2003. Available at www.cdc.gov/foodnet/reports.htm, accessed August 2, 2006.

[CDC MMWR]. Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. MMWR Morb Mortal Wkly Rep: Recommendations and Reports 2004;53:1–33. Available at www.cdc.gov/mmwr/PDF/rr/rr5304.pdf, accessed May 19, 2006.

Census Bureau, United States Department of Commerce, Economics and Statistics Administration, United States Census Bureau. U.S. Summary 2000: Census 2000 Profile. 2002. Available at www.census.gov/prod/2002pubs/c2kprof00-us.pdf, accessed May 19, 2006.

Champion OL, Gaunt MW, Gundogdu O, *et al.* Comparative phylogenomics of the food-borne pathogen *Campylobacter jejuni* reveals genetic markers predictive of infection source. Proc Natl Acad Sci USA 2005;102:16043–16048.

Chan SS, Ng KC, Lyon DJ, *et al.*. Acute bacterial gastroenteritis: a study of adult patients with positive stool cultures treated in the emergency department. Emerg Med J 2003;20:335–338.

Cox LA Jr. Some limitations of a proposed linear model for antimicrobial risk management. Risk Anal 2005;25:1327–1332.

Danish Zoonoses Centre. Danish Institute for Food and Veterinary Research. Ministry of Food, Agriculture and Fisheries. Annual Report on Zoonoses in Denmark. 2003. Available at www.dfvf.dk/files/filer/zoonosecentret/publikationer/annual%20report/annual_report_2003-endelig.pdf, accessed May 19, 2006.

de Wit MA, Hoogenboom-Verdegaal AM, Goosen ES, *et al.* A population-based longitudinal study on the incidence and disease burden of gastroenteritis and *Campylobacter* and *Salmonella* infection in four regions of the Netherlands. Eur J Epidemiol 2000;16:713–718.

Dechet AM, Scallan E, Gensheimer K, *et al.* Outbreak of multidrug-resistant *Salmonella enterica* serotype Typhimurium definitive type 104 infection linked to commercial ground beef, northeastern United States, 2003–2004. Clin Infect Dis 2006;42:747–752.

[DMR] Doane Marketing Research. *Doane Marketing Research Animal Health Market Study (2003–2005)*. St. Louis, MO: Doane Marketing Research, 2005.

[DRMS] Dairy Records Management System. Dairy Metrics (2004). 2006. Available at www.drms.org, accessed January 24, 2006.

Dryden MS, Gabb RJ, and Wright SK. Empirical treatment of severe acute community-acquired gastroenteritis with ciprofloxacin. Clin Infect Dis 1996;22:1019–1025.

Englen MD, Fedorka-Cray PJ, Ladely SR, *et al.* Antimicrobial resistance patterns of *Campylobacter* from feedlot cattle. J Appl Microbiol 2005;99:285–291.

[FDA CVM] United States Food and Drug Administration, Center for Veterinary Medicine. The human health impact of fluoroquinolone resistant *Campylobacter* attributed to the consumption of chicken. 2000. Available at www.fda.gov/ohrms/dockets/98fr/bkg0002.pdf, accessed May 19, 2006.

[FDA CVM] United States Food and Drug Administration, Center for Veterinary Medicine. Guidance for industry 152: evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. 2003a. Available at www.fda.gov/cvm/Guidance/fguide152.pdf, accessed May 19, 2006.

[FDA CVM] United States Food and Drug Administration, Center for Veterinary Medicine. NARMS Retail Meat Annual Report, 2002. 2003b. Available at www.fda.gov/cvm/coversheet.htm, accessed June 29, 2006.

[FDA CVM] United States Food and Drug Administration, Center for Veterinary Medicine. NARMS Retail Meat Annual Report, 2003. 2003c. Available at www.fda.gov/cvm/Documents/NARMSRetailMeatRpt2003.pdf, accessed June 29, 2006.

Flint JA, Van Duynhoven YT, Angulo FJ, *et al.* Estimating the burden of acute gastroenteritis, foodborne disease, and pathogens commonly transmitted by food: an international review. Clin Infect Dis 2005;41:698–704.

Fossler CP, Wells SJ, Kaneene JB, *et al.* Prevalence of *Salmonella* spp on conventional and organic dairy farms. J Am Vet Med Assoc 2004;225:567–573.

Fossler CP, Wells SJ, Kaneene JB, *et al.* Cattle and environmental sample-level factors associated with the presence of *Salmonella* in a multi-state study of conventional and organic dairy farms. Prev Vet Med 2005;67:39–53.

Friedman CR, Hoekstra RM, Samuel M, *et al.* Risk factors for sporadic *Campylobacter* infection in the United States: a case-control study in FoodNet sites. Clin Infect Dis 2004;38(Suppl 3):S285–S296.

Green AM, Kaneene JB, Ruegg PL, *et al.* Patterns of occurrence of *Campylobacter* in organic and conventional dairy farms in midwestern and northeastern United States. 2001. In: *Proceedings of the 82nd Annual Meeting of the Conference of Research*

Workers in Animal Diseases (CRWAD), St. Louis, MO, 11–13 November 2001.

Halbert LW, Kaneene JB, Ruegg PL, *et al.* Evaluation of antimicrobial susceptibility patterns in *Campylobacter* spp. isolated from dairy cattle and farms managed organically and conventionally in the midwestern and northeastern United States. J Am Vet Med Assoc 2006;228:1074–1081.

Hald T, Vose D, Wegener HC, *et al.* A Bayesian approach to quantify the contribution of animal-food sources to human salmonellosis. Risk Anal 2004;24:255–269.

Harvey RB, Droleskey RE, Sheffield CL, *et al. Campylobacter* prevalence in lactating dairy cows in the United States. J Food Prot 2004;67:1476–1479.

Herikstad H, Yang S, Van Gilder TJ, *et al.* A population-based estimate of the burden of diarrhoeal illness in the United States: FoodNet, 1996–1997. Epidemiol Infect 2002;129:9–17.

Hurd HS, Doores S, Hayes D, *et al.* Public health consequences of macrolide use in food animals: a deterministic risk assessment. J Food Prot 2004;67:980–992.

Kennedy M, Vugia D, Fiorentino T, *et al.* FoodNet 1996 to 1998: data on deaths and invasive illnesses demonstrate the severity of *Salmonella* and *Listeria*. Presented at the 2nd International Conference on Emerging Infectious Diseases, Atlanta, GA, July 16–19, 2000. Available at www.cdc.gov/foodnet/pub/publications/2000/kennedy_2000.pdf, accessed May 19, 2006.

Kuschner RA, Trofa AF, Thomas RJ, *et al.* Use of azithromycin for the treatment of *Campylobacter enteritis* in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. Clin Infect Dis 1995;21:536–541.

McNulty CA. The treatment of *Campylobacter* infections in man. J Antimicrob Chemother 1987;19:281–284.

Mead PS, Slutsker L, Dietz V, *et al.* Food-related illness and death in the United States. Emerg Infect Dis 1999;5:607–625.

[MDE] Michigan Department of Education, Lansing, MI. *Invitation to Bid*. 2005.

Molbak K, Baggesen DL, Aarestrup FM, *et al.* An outbreak of multidrug-resistant, quinolone-resistant *Salmonella enterica* serotype Typhimurium DT104. N Eng J Med 1999;341:1420–1425.

[NAS] Committee on the Review of the USDA. *E.coli* O157:H7, Farm-to-Table Process Risk Assessment. *Escherichia coli* O157:H7 in ground beef: review of a draft risk assessment. 2002. Available at darwin.nap.edu/books/0309086272/html/R1.html, accessed May 19, 2006.

[NCBA] National Cattlemen's Beef Association. Usage and volumetric assessment of beef in foodservice. 2004. Conducted by Technomic, Inc., Chicago, IL.

Nelson JM, Smith KE, Vugia DJ, *et al.* Prolonged diarrhea due to ciprofloxacin- resistant *Campylobacter* infection. J Infect Dis 2004;190:1150–1157.

Nielsen EM, Fussing V, Engberg J, *et al.* Most *Campylobacter* subtypes from sporadic infections can be found in retail poultry products and food animals. Epidemiol Infect 2006; 134:758–67.

Ray KA. Antimicrobial susceptibility of *Salmonella* isolates from organic and conventional dairy farms. Presented at the 2004 Annual Conference on Antimicrobial Resistance sponsored by NFID (National Foundation for Infectious Diseases), Bethesda, MD, 2004.

Ray K, Warnick LD, Mitchell R, Kaneene JB, Ruegg PL, Wells SJ, Fossler CP, Halbert LW. Salmonella antimicrobial resistance patterns on midwest and northeast dairy farms. Proceedings of the 2004 Annual Meeting of the American Association of Bovine Practitioners, Fort Worth, TX, 2004.

Roberts T, Malcolm SA, and Narrod CA. Probabilistic risk assessment and slaughterhouse practices: modeling contamination process control in beef destined for hamburger. In *Probabilistic Safety Assessment PSA '99: Risk-Informed Performance-Based Regulation in the New Millennium*. Modarres M (ed.). La Grange Park, IL: American Nuclear Society, 1999, pp. 809–815. Available at www.ers.usda.gov/briefing/IndustryFoodSafety/pdfs/psa9.pdf, accessed May 19, 2006.

Rocourt J, Moy G, Vierk K, *et al. The Present State of Foodborne Disease in OECD Countries*. Geneva, World Health Organization, 2003. Available at www.who.int/foodsafety/publications/foodborne_disease/oecd/en/, accessed May 19, 2006.

Rogers CA, Fitzgerald AC, Carr MA, *et al.* On-farm management decisions to improve beef quality of market dairy cows. J Dairy Sci 2004;87:1558–1564.

Ruegg PL, Kaneene JB, Warnick LD, *et al.* Weekly shedding of *Campylobacter jejuni* on 12 midwest and northeast dairy farms. J Dairy Sci 2001;84(Suppl 1):114.

Samuel MC, Vugia DJ, Shallow S, *et al*. Epidemiology of sporadic *Campylobacter* infection in the United States and declining trend in incidence, FoodNet 1996–1999. Clin Infect Dis 2004; 38(Suppl 3):S165–S174.

Sanders JW, Isenbarger DW, Walz SE, *et al.* An observational clinic-based study of diarrheal illness in deployed United States military personnel in Thailand: presentation and outcome of *Campylobacter* infection. Am J Trop Med Hyg 2002; 67:533–538.

Sato K, Bartlett PC, Kaneene JB, *et al.* Comparison of prevalence and antimicrobial susceptibilities of *Campylobacter* spp. isolates from organic and conventional dairy herds in Wisconsin. Appl Environ Microbiol 2004;70:1442–1447.

Sirinavin S and Garner P. Antibiotics for treating *Salmonella* gut infections (review). Cochrane Database Syst Rev 2000;2: CD001167.

Tabibian N, Clarridge JE, Smith JL, *et al.* Clinical impact of stool cultures for *Campylobacter* in adults with acute or chronic diarrhea. South Med J 1987;80:709–711.

[USDA ARS] United States Department of Agriculture, Agricultural Research Service. Annual veterinary isolates data. 2003. Available at www.ars.usda.gov/Business/docs.htm?docid=6750, accessed May 19, 2006.

[USDA ERS] United States Department of Agriculture, Economic Research Service. Red Meat Yearbook (94006). 2006. Available at www.usda.mannlibcornell.edu/data-sets/livestock/94006/(URL no longer available), accessed January 11, 2006.

[USDA FSIS] United States Department of Agriculture, Food Safety and Inspection Service. Nationwide Beef Microbiological Baseline Data Collection Program: Steers & Heifers, October 1992–September 1993, Part 2. 1994. Available at www.fsis.usda.gov/OPHS/baseline/steer2.pdf, accessed May 19, 2006.

[USDA FSIS] United States Department of Agriculture, Food Safety and Inspection Service. Progress Report on *Salmonella* Testing of Raw Meat and Poultry Products, 1998–2005. 2006. Available at www.fsis.usda.gov/science/Progress_Report_Salmonella_Testing/, accessed May 19, 2006.

[USDA NAHMS] United States Department of Agriculture, National Animal Health Monitoring System. Salmonella *in Dairy Calves*. 1994. Available at www.aphis.usda.gov/vs/ceah/ncahs/nahms/dairy/ndhep/drsalm1.pdf, accessed May 19, 2006.

[USDA NAHMS] United States Department of Agriculture, National Animal Health Monitoring System. Dairy 2002; Part I: Reference of Dairy Health and Management in the United

States, 2002. p. 39. Available at http://nahms.aphis.usda.gov/dairy/dairy02/Dairy02Pt1.pdf, accessed May 19, 2006.

[USDA NAHMS] United States Department of Agriculture, National Animal Health Monitoring System. Dairy 2002; Part II: Changes in the United States Dairy Industry, 1991–2002. 2003a. Available at www.aphis.usda.gov/vs/ceah/ncahs/nahms/dairy/dairy02/Dairy02Pt2.pdf, accessed May 19, 2006.

[USDA NAHMS] United States Department of Agriculture, National Animal Health Monitoring System. *Salmonella* and *Campylobacter* on U.S. Dairy Operations. 2003b. Available at www.aphis.usda.gov/vs/ceah/ncahs/nahms/dairy/dairy02/Dairy02SalCampy.pdf, accessed May 19, 2006.

[USDA NAHMS] United States Department of Agriculture, National Animal Health Monitoring System. Dairy 2002; Animal Disease Exclusion Practices on U.S. Dairy Operations, 2002. 2004. Available at www.aphis.usda.gov/vs/ceah/ncahs/nahms/dairy/dairy02/Dairy02_biosecurity.pdf, accessed May 19, 2006.

[USDA NAHMS] United States Department of Agriculture, National Animal Health Monitoring System. Dairy 2002; Part IV: Antimicrobial Use on U.S. Dairy Operations, Dairy 2002. 2005. Available at http://nahms.aphis.usda.gov/dairy/dairy02/Dairy02Pt4_AntibioticUse.pdf, accessed May 19, 2006.

[USDA NASS] United States Department of Agriculture, National Agricultural Statistics Service. Livestock Slaughter 2003 Summary, March 2004. 2004. Available at http://usda.mannlib.cornell.edu/reports/nassr/livestock/pls-bban/lsan0304.pdf, accessed December 12, 2005.

[USDA NASS] United States Department of Agriculture, National Agricultural Statistics Service. Fact Finders for Agriculture. Milk Production. 2005a. Available at http://usda.mannlib.cornell.edu/reports/nassr/dairy/pmp-bb/2005/mkpr0205.pdf, accessed May 19, 2006.

[USDA NASS] United States Department of Agriculture, National Agricultural Statistics Service. Livestock Slaughter 2004 Summary, March 2005. 2005b. Available at http://usda.mannlib.cornell.edu/reports/nassr/livestock/pls-bban/lsan0305.pdf, accessed May 19, 2006.

Voetsch AC, Van Gilder TJ, Angulo FJ, *et al.* FoodNet estimate of the burden of illness caused by nontyphoidal *Salmonella* infections in the United States. Clin Infect Dis 2004;38(Suppl 3): S127–S134.

Walstra P, Wouters J, and Geurts T. Milk for liquid consumption. In: *Dairy Science and Technology*, 2nd edition. Boca Raton, FL: CRC Press, Taylor and Francis Group, LLC, 2006, pp. 421–445.

Warnick LD. The association of calfhood morbidity with first-lactation performance and milking herd survival in New York Holstein herds [Dissertation]. Cornell University, Ithaca, NY, 1994.

Warnick LD, Kaneene JB, Ruegg PL, *et al.* Evaluation of herd sampling for *Salmonella* isolation on midwest and northeast US dairy farms. Prev Vet Med 2003a;60:195–206.

Warnick LD, Kanistanon K, McDonough PL, *et al.* Effect of previous antimicrobial treatment on fecal shedding of *Salmonella enterica* subsp. *enterica* serogroup B in New York dairy herds with recent clinical salmonellosis. Prev Vet Med 2003b; 56:285–297.

Wells SJ, Fedorka-Cray PJ, Dargatz DA, *et al.* Fecal shedding of *Salmonella* spp. by dairy cows on farm and at cull cow markets. J Food Prot 2001;64:3–11.

Wheeler JG, Sethi D, Cowden JM, *et al.* Study of infectious intestinal disease in England: rates in the community, presenting to general practice, and reported to national surveillance. The Infectious Intestinal Disease Study Executive. Br Med J 1999;318:1046–1050.

Wistrom J, Jertborn M, Ekwall E, *et al.* Empiric treatment of acute diarrheal disease with norfloxacin: a randomized, placebo-controlled study. Swedish Study Group. Ann Intern Med 1992;117:202–208.

Wistrom J and Norrby SR. Fluoroquinolones and bacterial enteritis, when and for whom? J Antimicrob Chemother 1995; 36:23–29.

Address correspondence to:
H. Scott Hurd, D.V.M., Ph.D.
Veterinary Diagnostic and Production Animal Medicine
College of Veterinary Medicine
Iowa State University
1801 University Blvd.
VMRI Building 4
Ames, IA 50011

E-mail: shurd@iastate.edu