

Public Health Consequences of Macrolide Use in Food Animals: A Deterministic Risk Assessment[†]

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ABSTRACT

The potential impact on human health from antibiotic-resistant bacteria selected by use of antibiotics in food animals has resulted in many reports and recommended actions. The U.S. Food and Drug Administration Center for Veterinary Medicine has issued Guidance Document 152, which advises veterinary drug sponsors of one potential process for conducting a qualitative risk assessment of drug use in food animals. Using this guideline, we developed a deterministic model to assess the risk from two macrolide antibiotics, tylosin and tilmicosin. The scope of modeling included all label claim uses of both macrolides in poultry, swine, and beef cattle. The Guidance Document was followed to define the hazard, which is illness (i) caused by foodborne bacteria with a resistance determinant, (ii) attributed to a specified animal-derived meat commodity, and (iii) treated with a human use drug of the same class. Risk was defined as the probability of this hazard combined with the consequence of treatment failure due to resistant *Campylobacter* spp. or *Enterococcus faecium*. A binomial event model was applied to estimate the annual risk for the U.S. general population. Parameters were derived from industry drug use surveys, scientific literature, medical guidelines, and government documents. This unique farm-to-patient risk assessment demonstrated that use of tylosin and tilmicosin in food animals presents a very low risk of human treatment failure, with an approximate annual probability of less than 1 in 10 million *Campylobacter*-derived and approximately 1 in 3 billion *E. faecium*-derived risk.

There is continued concern regarding antibiotic resistance in human pathogens, particularly those assumed to be of foodborne origin. Administration of antibiotics to food animals for disease prevention and growth promotion has been suggested as a significant cause of developing resistance (4, 10, 11). Some studies have reported a likely animal connection between specific farms and human illness caused by multidrug-resistant *Salmonella* (36, 70). However, the occasional occurrence of such an event cannot necessarily be generalized to an entire national or international food production and health care system. Nevertheless, if a hazardous event could conceivably happen, government authorities may implement control measures to avoid activities leading to that event. But such an approach, referred to as the “precautionary principle,” may be misdirected and counterproductive by focusing resources away from more appropriate solutions (99).

To address these topics, many government regulatory authorities, industry associations, and other organizations are proposing that risk assessment (RA) methods be applied to the issue of antibiotic resistance associated with food-

producing animals (8, 115, 124, 130). An RA combines information on the consequence of an event with the probability of occurrence of that event, within the current state of technology and common practice. The U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) has issued guidelines in their Regulatory Guidance Document 152 (115) that can be used to guide a new animal drug sponsor in preparing the overall preapproval risk estimate and corresponding risk management options to ensure that public health is not compromised. However, it can also be useful for evaluating risk from currently approved food animal drugs on a prioritized basis as indicated in appendix C of the CVM guideline.

The objective of this study was to conduct an RA for the administration to food animals of two macrolide veterinary antibiotics, tylosin and tilmicosin, consistent with the methods proposed by the CVM. Tylosin is used in poultry, swine, and cattle and is administered via medicated feed or drinking water or by injection for treatment, prevention, and control of disease or for growth performance enhancement; however, not all routes of administration or claims have been approved for each species in the United States. Tilmicosin is a semisynthetic derivative of tylosin approved for treatment and control of respiratory disease in cattle and swine. The scope of this RA included all label claim uses for both macrolides in the United States.

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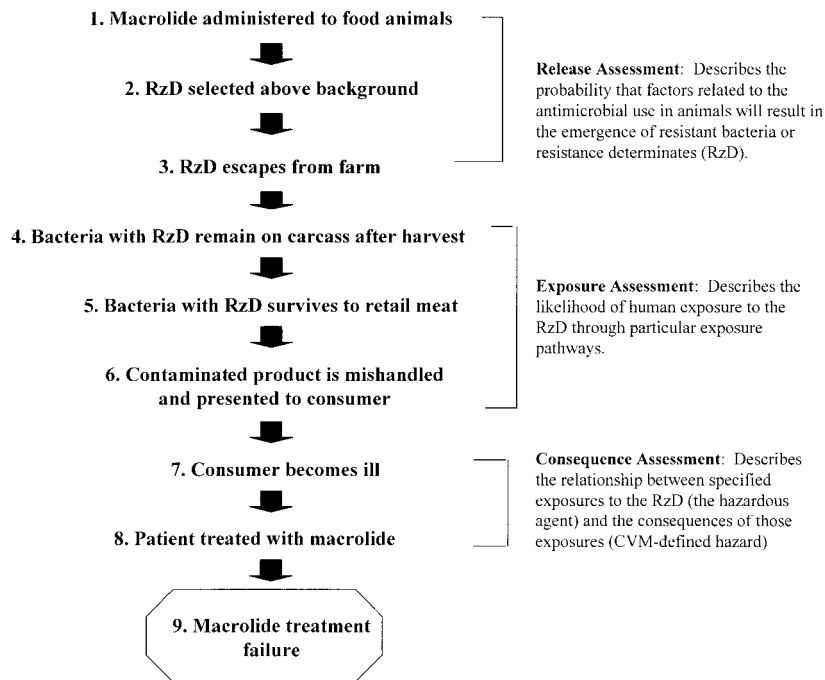


FIGURE 1. Pathway of events leading to the risk of foodborne human illness with a resistant organism due to antibiotic treatment of food animals.

MATERIALS AND METHODS

For this assessment, the hazard was defined in accordance with Guidance Document 152 as “human illness” that is (i) caused by macrolide-resistant *Campylobacter* spp. or *Enterococcus faecium*; (ii) attributable to consumption of contaminated poultry, pork, or beef; and (iii) treated with a human antibiotic of the macrolide class (115). Infection caused by *Salmonella* spp. was not addressed because this organism is neither routinely susceptible to nor widely treated by macrolides in human practice. The risk was defined and modeled as the yearly probability that an average individual in the U.S. population would be affected by the defined hazard and would experience an adverse therapeutic event (i.e., poorer efficacy than usual as manifested by longer duration of diarrhea, progression to more severe disease, or mortality).

There are several different methods for developing a usable quantitative model of risk. The one most consistently recommended and most transparent is the event hazard or fault scenario (98, 122, 123). This type of model identifies the chain of key events necessary to proceed from an initiating input to the hazard of interest and allows for some estimation of probability at each “link” or step, given the availability of necessary data. It can be represented (i) graphically, as a simple flowchart; (ii) mathematically, as a nested binomial model; (iii) as an equation of conditional probabilities; or (iv) by a variety of computer simulation techniques (92).

Due to data and resource constraints associated with a full-scale stochastic quantitative RA, the CVM has recommended what has been termed a *qualitative* RA. This method uses high, medium, and low estimates for each of the three analyzed components: release, exposure, and consequence assessment. However, we have elected to use a determinist quantitative model (74), recognizing that some data might be limited and may need to be approximated. This approach provides greater transparency regarding calculations and assumptions at each point in the chain of events. Additionally, this approach allows for revision of the analysis as improved data estimates become available.

Overall assumptions. This RA was limited to two agents (tylosin and tilmicosin) in the same antimicrobial class (macrolides). Erythromycin, an important human macrolide, is infrequently used in food animal production, is not indicated for non-therapeutic use, and was not considered here (83). Even though other antimicrobial agents in the macrolide–lincosaminide–streptogramin B (MLS_B) class, including lincomycin and virginiamycin, exhibit some cross-resistance with macrolides (127) and are also used in food animals, this RA was restricted to tylosin and tilmicosin, consistent with CVM guidelines. Guidance Document 152 also suggests that only a single drug be considered by the sponsoring company, but this assessment modeled tylosin and tilmicosin together due to their close structural relationship. The commodities included in this assessment were limited to swine, poultry, and nondairy beef cattle. Currently, there are no CVM-approved indications for tylosin and tilmicosin in dairy cattle.

Consistent with CVM guidance, foodborne transmission of an antimicrobial resistance determinant (RzD; a genetic element that confers antimicrobial resistance) was considered the most likely hazard and was the only route modeled. We did not independently analyze specific “at-risk” populations (very young, elderly, or immunocompromised) in this model, since such demographic subdivisions have not been explicitly directed by the Guidance Document. Additionally, the final risk estimate was so low that further apportioning was not meaningful, and the data required for such an exercise are sparse.

The organisms evaluated were *Campylobacter* spp. and *E. faecium*. Although differences in host range are known for *Campylobacter jejuni* and *Campylobacter coli*, the species were not separated. *Salmonella* was not considered because treatment of human salmonellosis with macrolides is neither indicated nor practiced in the United States due to well-known inherent resistance of that bacterium to macrolides (39, 116). Enterococci were modeled, not because they cause foodborne illness, but because they are frequently regarded as a reservoir of macrolide resistance genes. These genes may reside in commensal bacteria that colonize food animals and could possibly serve as a reservoir of resistance for microbes that are pathogenic for humans (27, 57, 76,

89). It has been suggested that *E. faecium* from food animals may transfer RzD to human *E. faecium* during transient passage through the human intestinal tract (51, 97, 129).

Model description. Figure 1 summarizes the modeled chain of events (steps) necessary to lead to the defined hazard. For human illness to occur as a result of tylosin and tilmicosin administration, a number of events must occur. In brief, tylosin and tilmicosin must be administered to food animals. An increased prevalence of RzD must occur in the intestinal bacterial flora of the animals due to tylosin and tilmicosin administration. The resistant bacteria (*Campylobacter* spp. or *E. faecium* containing macrolide resistance genes) must leave the place of administration (e.g., farm or feedlot). The RzD must move from the intestinal or fecal material in the treated animal and contaminate the carcass, rinse fluids, and/or neighboring carcasses during slaughter and processing operations. The RzD must remain on contaminated carcasses after processing, storage, and placement into the retail sales environment. The meat product must then be mishandled, undercooked, or otherwise improperly prepared such that human infection or colonization can occur. For *Campylobacter* spp., the inoculating dose must be sufficient to cause the person to become ill, to seek medical treatment, and to be treated with a macrolide that would consequently be ineffective due to the RzD. As shown in Figure 1, this event model is consistent with the CVM-defined hazard as an illness (i) caused by foodborne bacteria with a RzD (release component), (ii) attributed to a specified animal-derived commodity (exposure component), and (iii) treated with a human use drug of the same class (consequence component). Additionally, our consequence included some estimate of the probability that treatment would be ineffective.

Modeling methods. Each event or node was represented in a separate worksheet of an Excel spreadsheet software program (Microsoft, Richmond, Wash.). Quantities or probabilities associated with each node were entered into the worksheet, combined with output from the previous sheet, and carried forward to the next sheet. The final result is an estimate of expected illness per capita-year in the United States for which human macrolide treatment is presumed to fail or to be compromised from the presence of resistant bacteria due to administration of tylosin and tilmicosin to food animals. The following paragraphs provide a detailed description of each node, associated assumptions, and parameter estimates used in the model.

For each event, the likely probabilities or frequencies were modeled based on available data. When numbers were uncertain, a more conservative, or higher-risk, estimate was used to avoid underestimating potential hazards. Uncertainty distributions of inputs and resulting outputs were not modeled, since this study was meant to be an initial evaluation following Guidance Document 152 for a qualitative RA, as opposed to a fully quantitative analysis. Specific caveats for the assumptions and approach within each node are described to present opportunities to improve the next iteration of this model.

Node 1: tylosin or tilmicosin administered to food animals. The model begins with the administration of tylosin and tilmicosin to swine, cattle, or poultry (broilers and turkeys combined). All uses of tylosin and tilmicosin were considered (e.g., therapeutic, disease prevention, disease control, and growth promotion) relevant to CVM-approved label claims for each food animal species. Although some animals might have received both medicated feed and an injection of a macrolide, they could not be easily distinguished in the database and thus were counted as two exposures. Furthermore, even a single dose was considered an

exposure, even though 60 days of feed medication most likely does not have the same effect on resistance selection as a single injection. Adjustments for these parameters could be made in a subsequent version of the model.

Annual estimates of the number of fed cattle (92.6% of total cattle), swine, chickens, and turkeys that were harvested in 2001 were 32.9 million, 98 million, 8,426 million, and 268 million, respectively (107). Estimates of tylosin and tilmicosin use were based on the number of animals treated for any purpose as reported from quarterly national mail surveys of producers, which were 49% of cattle, 50% of swine, and 7.5% of chickens (33, 86). Based on these independent commercial surveys of tylosin and tilmicosin use, we estimated the number of cattle, swine, and broilers exposed or treated in that year to be 16.1 million, 49 million, and 632 million, respectively. These data appear to be relatively consistent with estimates obtained from other sources (106, 108, 109). Approximately 2.2 million doses of tylosin were administered to turkeys in 2002 for treatment of *Mycoplasma* (87), but no tylosin and tilmicosin feed additive uses are approved in turkeys. For subsequent calculations in this model, data for broilers and turkeys were combined (634.2 million) under the heading of poultry.

Node 2: resistance selected above background. After an animal is treated with tylosin or tilmicosin, there is some chance that macrolide resistance may be selected above background levels in resident *E. faecium* and/or *Campylobacter* spp. This probability is a function of three factors: (i) presence of *E. faecium* and/or *Campylobacter* spp. in treated animals, (ii) intrinsic or background susceptibility of these bacteria, and (iii) mutation or RzD acquisition with survival of newly resistant strains. These probabilities were separately estimated for *Campylobacter* spp. and *E. faecium* by multiplying together the (a) reported prevalence of *Campylobacter* spp. and *E. faecium* in animals, (b) estimated background levels of macrolide susceptibilities of *Campylobacter* spp. and *E. faecium* in animals, and (c) probability that resistant bacteria will develop and thrive to levels at which human isolates are resistant. Our final estimates for these parameters are shown in Table 1.

The prevalence of *E. faecium* in livestock (factor a) was conservatively assumed to be 100% for all commodities, since there were no data available. For *Campylobacter* spp., some livestock survey data were available. A survey conducted by Nielsen et al. (77) reported that 47% of cattle, 46% of swine, and 36% of broiler carcasses contained one or more *Campylobacter* spp. Another survey by Garcia et al. (38) indicated that 55% of steers, 40% of bulls, 40% of heifers, and 22% of cows carry *C. jejuni*. Swine also carry *C. jejuni*, but they are the primary reservoir of *C. coli* (78). *Campylobacter* spp. has been isolated from 78.6% of swine intestinal contents (79). A survey of swine raised in the Texas prison system reported 70 to 100% of pigs were infected, mostly (60%) with *C. coli* (45). For poultry, there have been limited data regarding on-farm prevalence. *Campylobacter* spp. was recovered from 94% of cloacal swabs from birds at the slaughtering plant, which may not accurately represent on-farm prevalence (22). A study of broiler flocks showed most flocks (87%) will have *Campylobacter* spp., and prevalence varies greatly within farms, up to 100%, with a median of approximately 50% (100). Among infected turkey flocks, prevalence appears to be 70 to 80% (29). For this RA, we estimated the *Campylobacter* spp. prevalence was 50, 80, and 50% in poultry, swine, and cattle, respectively (Table 1).

The existing background level of macrolide resistance (factor b) could be due to intrinsic features of the organism, previous antibiotic use, or use of other agents exhibiting cross-resistance (i.e., virginiamycin and lincomycin). Use of virginiamycin or lin-

TABLE 1. Assessment of the adverse human health impact attributable to the use of macrolides in food animals: key parameters and results

Components/binomial events	Poultry		Swine		Beef cattle	
	<i>Campylobacter</i> spp.	<i>Enterococcus faecium</i>	<i>Campylobacter</i> spp.	<i>Enterococcus faecium</i>	<i>Campylobacter</i> spp.	<i>Enterococcus faecium</i>
Release						
1. Animals exposed to tylosin and tilmicosin (millions) ^a	634.2	634.2	49.0	49.0	16.1	16.1
2. Probability that RzD develops in exposed animals as a function of ^b :	1%	70%	2%	86%	1%	89%
a) Bacteria present in animals	50%	100%	80%	100%	50%	100%
b) Susceptible bacteria in population	90%	70%	95%	86%	99%	89%
c) Resistance in human isolates	3%	100%	3%	100%	3%	100%
3. Probability that RzD escapes from farm ^c	100%	100%	100%	100%	100%	100%
Exposure						
4. Probability that bacteria with RzD remain on carcass after slaughter ^d	88%	100%	32%	31%	4%	8%
Exposure and consequence						
5.-7. Ratio (β) that contaminated serving leads to human illness ^e	8.6×10^{-6}	8.6×10^{-6}	8.6×10^{-6}	8.6×10^{-6}	8.6×10^{-6}	8.6×10^{-6}
Consequence						
8. Probability of cases of diarrhea treated with a macrolide ^f	3%	0.0001%	3%	0.0001%	3%	0.0001%
9. Probability that treatment fails if infection by bacteria with RzD is treated with a macrolide ^g	50%	100%	50%	100%	50%	100%
Risk						
Annual probability of adverse health events in the United States due to treatment of RzD-caused foodborne infection with a macrolide ^h	<1 in 14 million	<1 in 3 billion	<1 in 53 million	<1 in 21 billion	<1 in 236 million	<1 in 29 billion

^a Based on industry use surveys for all uses of tylosin and tilmicosin (treatment, control, prevention, performance).
^b Function of the prevalence of the bacterium in animals, the percentage of susceptible population, and the likelihood of RzD-containing bacteria to develop above background levels and thrive.
^c Assumes all animals will carry RzD to slaughter.
^d *Campylobacter* spp. based on FSIS data, assuming all have some fecal (*E. faecium*) contamination.
^e Based on comparisons of FSIS data for all *Campylobacter* spp. relative to CDC FoodNet data for human illness. Overestimated for *E. faecium*.
^f Based on FDA fluoroquinolone risk assessment interpretation of disease reporting, treatment, etc. (114).
^g Publications of clinical responses show less than 50% failures.
^h Risk is very low by FDA guidelines (114).

comycin may select for cross-resistance to tylosin and tilmicosin, but the fraction of macrolide resistance attributed to these agents is difficult to extract. Data on the human health risk from virginiamycin use in poultry are available (30). Estimates vary considerably for *Campylobacter* spp. For example, swine (mostly *C. coli*) isolates in Belgium, Germany, and Canada were 30 to 83% susceptible (3, 20, 120). In Denmark, approximately 60% of *Campylobacter* spp. are macrolide susceptible (31). Poultry and cattle isolates of *C. jejuni* were 85 to 100% susceptible (3, 17, 31, 49, 68, 120). For cattle, 2.2 and 7.7% of *C. jejuni* and *C. coli*, respectively, were resistant to erythromycin (35). Since most human illness is caused by *C. jejuni* (67), these lower *Campylobacter* spp. resistance levels were used in the model. For *E. faecium*, we very conservatively estimated a 10 to 20% lower degree of background susceptibility than *Campylobacter* spp. (1, 48).

The probability that a resistant organism will develop and thrive within a treated animal (factor c) was difficult to estimate (62). Ideally, data on resistance before and after drug exposure are needed, but feeding studies were only available for *E. faecium*. Tylosin fed to pigs and chickens at therapeutic levels demonstrated development of resistance (26, 47, 56). Aarestrup and Carstensen (2) reported resistance selection in enterococci at growth promotion levels (30 µg/g) in pigs. In contrast, Davies and Roberts (32) found that carcasses from swine fed tylosin at growth promotion concentrations did not differ from nonmedicated swine with respect to the prevalence of macrolide-resistant *E. faecium*. Since dose response of resistance development was not evaluated, the probability of RzD development was conservatively set at the maximum of 100% for *E. faecium*.

For *Campylobacter* spp. this probability was estimated from resistance levels found in human source isolates. Nachamkin et al. (72) noted that resistance to erythromycin in *Campylobacter* spp. isolates from humans was 2% from 1982 to 1992 and remained at less than 5% through 2001. The SENTRY Antimicrobial Surveillance Program in 2001 reported an erythromycin-resistance rate in *C. jejuni* of 3% (13). Macrolide resistance among *C. jejuni* isolates has been reported since the 1970s (55, 117–119, 125), and rates remain generally unchanged or are decreasing. Lacey (59) noted that approximately 1% of human isolates were resistant to tylosin. The erythromycin-resistant *Campylobacter* spp. rates ranged from 0 to 11% of isolates tested since 1989 (34). Other studies have reported relatively low ranges of erythromycin resistance over many years of surveillance (21, 41, 60, 69, 75, 84, 85, 103). Thailand had widely variable results from 0% macrolide resistance in U.S. Armed Forces personnel and sampled animals to 11 to 53% resistance in institutionalized children (90, 102). This resistance rate assumption (factor c) seems reasonable, since it represents the current situation after many years of tylosin and tilmicosin use and also reflects data from U.S. government programs such as National Antimicrobial Resistance Monitoring System (NARMS) and FoodNet (23, 24). Furthermore, it may reflect the ability of RzD-containing *Campylobacter* spp. populations to occur and thrive among non-RzD populations in each commodity.

Node 3: RzD escapes from the farm. RzD can theoretically leave the farm or place of drug administration via a variety of routes. However, since the hazard was defined as foodborne illness, the model focused on RzD leaving the farm in market animals. In most cases, the probability of RzD leaving the production site will be near 100%, since it is assumed that all animals were being grown for food production. If treatment with tylosin and tilmicosin was discontinued at some time before marketing, it is possible that the prevalence of macrolide resistance could be diminished. Future quantitative analysis should address this possi-

bility. However, we conservatively assumed that any treatment resulting in the development of RzD would have a 100% probability of leaving the farm in the market animals (cattle, swine, and poultry).

Node 4: bacteria with RzD remain on carcass after harvest. U.S. meat producers have made significant progress in implementation of hazard analysis critical control point and thereby reduced carcass contamination levels of *Salmonella*, a result that implies similar reductions for other bacterial contaminants (113). However, some carcasses are still contaminated with *Campylobacter* spp., a small proportion of which may contain RzD. The Food Safety and Inspection Service (FSIS) data derived from surveys from 1992 through 1997 (*Campylobacter* spp.) appeared to provide the most relevant data on the percentage of contaminated swine, poultry, and beef carcasses in slaughter facilities. These data indicate that approximately 32% of swine carcasses, 88% of poultry carcasses, and 4% of beef carcasses were contaminated with *Campylobacter* spp. (Table 1). Unfortunately, the FSIS data do not distinguish between *C. jejuni* and *C. coli*. Nationwide figures were obtained from the U.S. Department of Agriculture (USDA) microbiological baseline data collection program from 1994 and 1995 for broiler chickens (111), beef cattle (110), and hogs (112).

We were unable to identify data for enterococcal contamination of carcasses. Therefore, we used *Escherichia coli* as an indicator of contamination from intestinal contents and/or fecal matter. The FSIS data similar to those reported for *Campylobacter* spp. indicated that approximately 31% of swine carcasses, 100% of poultry carcasses, and 8% of beef carcasses were contaminated with *E. coli* (110–112).

For this analysis, we assumed that all ground meat coming from contaminated swine (21%) or beef (43%) dressed carcasses would be contaminated (50). For poultry, we assumed the entire 4- to 5-lb contaminated carcass would produce contaminated meat product. Table 2 shows the resulting number of carcasses and kilograms of meat contaminated with RzD-bearing *E. faecium* and *Campylobacter* spp. that is the output from this node. We did not consider domestically consumed imported meat products, and we assumed all meat produced in the United States was consumed in the country of origin.

Node 5: bacteria carrying RzD survives to retail meat case. There is considerable evidence that *Campylobacter* spp. does not survive well under refrigeration (12, 66). Therefore, we would expect that the amount of meat contaminated at retail sources would be less than that measured on carcasses immediately after slaughter (133). Consequently, the risk should be reduced accordingly. However, there are few national estimates of retail prevalence that are as reliable and nationally applicable as FSIS carcass statistics. There are inconsistencies in sampling techniques, number of packages tested, storage times, and laboratory methods in these studies. Due to the inconsistencies in retail studies and the consequence of retail prevalence being only partly a function of wholesale carcass prevalence (48), retail data were not entered directly into the model, but the effect of this node was considered as described below.

Node 6: mishandling and presentation of infective dose for consumption. Before a contaminated product can cause human illness or passage of RzD, it must be mishandled in some way such that a sufficient dose of bacteria will survive for human consumption. There is evidence that the consumer has little regard for appropriate sanitation measures during and after food preparation (6, 58, 93). Some information on the types of mishandling

TABLE 2. Probability that organisms remain on carcass after slaughter to give contaminated meat

Organism	Probability of contaminated carcasses (%)	No. of contaminated carcasses	Carcass weight (kg)	Contaminated meat from carcass (%)	Contaminated meat (kg)
Swine					
<i>Campylobacter</i> spp.	32	357,803	63.36	21	4,683,968
<i>Enterococcus faecium</i>	31	13,074,331	63.36	21	171,154,873
Cattle					
<i>Campylobacter</i> spp.	4	9,576	258.09	43	1,058,594
<i>E. faecium</i>	8	1,147,842	258.09	43	126,888,761
Poultry					
<i>Campylobacter</i> spp.	88	7,533,828	2.27	100	17,122,336
<i>E. faecium</i>	100	443,912,403	2.27	100	1,008,891,824

that led to outbreaks has been published (15, 19, 42). However, national rates on the frequency of mishandling these commodities were not available. Therefore, the effects of these situations were combined with the results from other nodes (see below).

Sophisticated models of bacterial growth are accessible to predict the expected dose after mishandling or improper preparation, but they were not useful without information on the frequency or duration of consumer misuse or pathogen prevalence at retail. Therefore, microbial growth models were not applied in this assessment.

Node 7: consumer becomes ill due to consumption of organism containing RzD. Limited data are available on the dose response of humans to oral consumption of *Campylobacter* spp. and *E. faecium*. Data on the human dose required to cause illness is often based on older studies (14). The World Health Organization suggested that a dose of 500 to 800 CFU might be sufficiently infectious for *Campylobacter* spp. (14, 88, 131). Conversely, one study of *E. faecium* showed that doses as high as 10^7 CFU did not cause illness or even long-term colonization in human volunteers (97). Human illness from orally ingested (meatborne) *E. faecium* is extremely rare, and it is not considered a foodborne disease. Bacteremia due to *E. faecium* is most often acquired in the hospital environment in patients with defined risk factors (126). Usually the sources of invasive *E. faecium* infections in humans have been concurrent infections of the urinary tract, abdomen, or cutaneous wounds. It is possible that these bacteria could have obtained RzD from foodborne animal sources, which is an area for further investigation.

The output from this node is the number of illnesses associated with RzD attributed to meatborne *Campylobacter* spp. and *E. faecium*. However, since we did not model the exposure dose to humans from node 6, we could not directly calculate the number of illnesses due to that exposure dose. Therefore, calculations for this node were combined with other nodes, using the ratio method as described below, to create the final output from node 7.

Ratio method (applied to nodes 5 to 7). Due to the previously cited weaknesses and gaps in available data for organism prevalence at retail sale, probability of consumer mishandling, dose presented to consumer, and probability of illness (nodes 5, 6, and 7), a ratio method was used that collapses the output from these three nodes into a single calculation. The FSIS data (node 4) provided a reliable national estimate of wholesale carcass contamination. The Centers for Disease Control and Prevention FoodNet data provides a reasonable national estimate of human *Campylobacter* spp. illness (24). The latter data are equivalent to

the output from node 7 ignoring the RzD issue (i.e., modeling all *Campylobacter* spp. cases from meat). In other words, even though information is extremely limited for accurately estimating the individual probabilities for nodes 5, 6, and 7, the combined probability of these three nodes can be estimated. Therefore, the probability of human campylobacteriosis from a meal that originated from a contaminated carcass can be approximated. Briefly, the number of all human *Campylobacter* spp. cases is simply divided by the number of *Campylobacter* spp.–contaminated servings. The resulting ratio (β) was then used with the results from node 4 to produce the number of human illnesses due to RzD-bearing *Campylobacter* spp. The data used and the resulting proportionality constants are described in more detail in equation 1 and the following paragraphs.

$$C/[\sum (NC_i \times CW_i \times CR_i)/SS] = \beta \quad (1)$$

where C equals annual number of human cases attributable to foods of animal origin (FoodNet), regardless of RzD; NC_i equals number of animal carcasses produced annually for each commodity (pork, beef, poultry); CW_i equals average weight of dressed carcass; CR_i equals carcass contamination rate per serving for each commodity based on FSIS data; SS equals average serving size (approximately 0.11 kg); and β equals ratio equivalent to the probability that a contaminated carcass will produce illness after wholesale and retail processing, consumer preparation, and consumption.

For *Campylobacter* spp., the 2002 FoodNet rate of 13.37 laboratory-diagnosed cases per 100,000 (24) was multiplied by an estimate of 38-fold underreporting and the U.S. population of 280 million to produce a national estimate of 1.42 million cases (67). However, not all those cases should be attributed to meat consumption. *Campylobacter* spp. infections can occur due to contact with infected pets, raw milk, contaminated water, and other sources (9, 37, 114). Therefore, for this analysis, a conservative estimate of 90% ($n = 1.28$ million) of total cases was attributed to consumption of the specified meat products. The resulting ratio was estimated as 8.6×10^{-6} . A similar method was used by the FDA for *Campylobacter* spp. from chicken, with a resulting value for β of 7×10^{-5} (114). The difference in these ratios may be due to the FDA assumption that all fluoroquinolone-resistant *Campylobacter* spp. was derived from chicken. In contrast, our constant included the relative impact of pork, beef, and turkey in addition to chicken and was adjusted for human cases attributed to sources other than meat. The ratio outcomes for both the FDA RA and the present model have not included an in-depth analysis of causality and dose-response relationships. Competing risk fac-

TABLE 3. Weighted average from FDA fluoroquinolone risk assessment for diagnosis of *Campylobacter infection*^a

	Weighted average (%)	Nonbloody stool rate (%) ^b	Bloody stool rate (%) ^c
Seeks care	23.5	20.5	33.2
Specimen	17.7	15.1	26.1
Tested for <i>Campylobacter</i> spp.	94.5	94.5	94.5
Accurately diagnosed	75.0	75.0	75.0

^a From U.S. FDA CVM (114).

^b Nonbloody stool cases = 1,219,294 per year.

^c Bloody stool cases = 378,582 per year.

tors and at-risk subpopulations (e.g., very young, elderly, and immunocompromised) were recognized as very important, but they were not independently analyzed.

For *E. faecium*, it could be argued that none of the infections are acquired from meat, since it is a normal commensal microorganism in the human gastrointestinal tract. On the other hand, RzD from meat could possibly be transferred to a distinct minority of the resident enterococcal population in humans. To our knowledge, there are no data available documenting this possibility. Because there was no information available other than the rates of enterococcal infection in human practice, the proportionality constant for *E. faecium* was assumed to be the same as *Campylobacter* spp. However, this assumption clearly overstates the true ratio if resistance data from other drugs cross-resistant with macrolides are used as a guide.

Node 8: ill patient is treated with macrolide class antibiotic. The output from node 8 could be considered as the probability of the CVM-defined hazard. For this risk to result, the illness must be treated with a macrolide class agent. The probability of this event for *Campylobacter* spp. results from the probabilities of (i) the patient seeking medical care, (ii) submission of a culture, (iii) positive test result for *Campylobacter* spp., (iv) accurate diagnosis, and (v) use of a macrolide. Although this statistical approach may overestimate the probability, estimates for the probability of these occurrences, based on weighted averages of bloody versus nonbloody stools, are shown in Table 3 (114). The probability of changing therapy from the empiric regimen to a macrolide after *Campylobacter* spp. diagnosis was assumed to be 100% (standard of practice). However, in routine practice, the initial therapy would rarely be changed in the absence of frank clinical failure.

It is likely that routine practice would not result in macrolide use for diarrhea. Examination of published practice guidelines (43) shows that infectious diarrhea is a complex series of disorders that require a thorough clinical and epidemiological evaluation that includes, among many other considerations, the possibility of consumption of mishandled food products. Demands for cost containment in health care have limited the application of diagnostic tests (cultures, toxin tests, parasite studies) and also the prescription of antimicrobial therapy. Infectious Disease Society of America guidelines for community-acquired or traveler's diarrhea (especially accompanied by significant fever or blood in stool) dictate that samples should be cultured or tested for key pathogens, including *Campylobacter* spp. (43), and therapy should consider a fluoroquinolone or a macrolide (if "resistant" *Campylobacter* spp. is suspected). However, surveys show infrequent and decreasing use of the stool culture (25), driven by the self-limited course of illness and routine delays in the available results, thus providing little guidance to immediate therapeutic choices. This situation leads physicians to consider antimicrobial and/or supportive treat-

ments, and the most common antibiotics selected are fluoroquinolones and trimethoprim/sulfamethoxazole rather than macrolides (5, 39, 43, 64). Therapy for *Campylobacter* spp., if known from diagnosis or positive culture, would be erythromycin (500 mg twice daily for 5 days), but this course usually will not be prescribed unless a fluoroquinolone-treated case worsens, possibly because of resistance or severe underlying disease. However, some experts (39) still recommend a fluoroquinolone (ciprofloxacin) or possibly azithromycin for first-line therapy of *Campylobacter* spp. gastroenteritis.

Node 9: infection with a resistant organism results in clinical treatment failure. The overall risk was defined as the probability of the defined hazard (node 8) times the consequence, defined as treatment failure. Treatment failure can have numerous definitions, including (i) death attributable to the episode, (ii) persistence of presenting symptoms and laboratory test abnormalities, or (iii) lack of bacteriological evidence of pathogen eradication at designated evaluation intervals. To address the probability of therapeutic failure, established rates of resistance, frequency of serious infections requiring culture, and published outcomes need to be examined.

Administration of a macrolide to a patient from whom a macrolide-resistant *Campylobacter* spp. was documented by a diagnostic culture has been very uncommon; when *Campylobacter* spp. was identified, the symptoms had usually resolved and susceptibility test results rarely accompanied the laboratory organism identification. Susceptibility testing results available from surveillance networks showed the erythromycin-resistance rate in *C. jejuni* was only 1.3%, a decrease from 8% in 1997 (23). These lower resistance rates correspond to concurrently lower rates of occurrence of *Campylobacter* spp. (-27%) in the FoodNet database from 1996 through 2001 (24). These reductions were likely influenced by successful implementation of the USDA FSIS's Pathogen Reduction/Hazard Analysis and Critical Control Point regulations (82).

Therefore, the risk of *Campylobacter* spp. treatment failure was conservatively estimated at 50% (Table 1), realizing that fatalities are very rare and that numerous alternative agents are available in human medical practice, including older oral agents such as amoxicillin/clavulanic acid and the more recently released fluoroquinolones (101). Cultures of patient stool samples are not commonly performed unless bloody gastrointestinal illness occurs. Even in bacteremias, therapeutic success rates approach 90% (only 2.5 to 5% attributable mortality) for therapy of either susceptible or resistant isolates (25, 81, 96). Although we might assume that all macrolide-resistant strains (approximately 1 to 2% in the United States) would fail treatment with erythromycin when presenting as serious life-threatening infections, this conclusion is simply not valid. Clinical case reports for *Campylobacter* spp. (80, 81, 90) indicate that significant numbers of patients (67 to 97%)

have favorable clinical outcomes when treatment was initiated with a drug to which the organism was resistant. This outcome was further supported by a report in which cefotaxime achieved a bacteriological cure rate of 55 to 64% of cases regardless of their susceptibility testing category, whereas clinical failures were encountered in nearly 10% of patients having susceptible isolates (104).

The SENTRY Antimicrobial Surveillance Program has monitored bloodstream infections since 1997 worldwide, and *Campylobacter* spp. bacteremias accounted for only 0.011% of cases among 35,479 episodes in North America (1997 to 2002) compared with the worldwide *Campylobacter* spp. bacteremia rate of 0.016% in 2002 (52, 53). Few large case studies of invasive campylobacteriosis are available for review to assess the human health care consequences (81, 96). In both reviews, patients infected with *Campylobacter* spp. had severe underlying illnesses associated with immune compromise and one third of cases in the Spanish series were hospital acquired (81). Erythromycin resistance was low (6%), and the attributable mortality ranged from only 2.5 to 5% (81, 96). These rates differ significantly from those of other causes of bloodstream infections, where mortality rates have ranged from 11.9% for *Staphylococcus aureus* to 18.7% for the *Enterobacteriaceae* (126). Furthermore, the low morbidity and mortality of *Campylobacter* spp. infections was minimized by low or decreasing rates of disease and macrolide resistance (approximately 1 to 3% in the United States (24). The combined risks of *Campylobacter* spp. bacteremia and macrolide resistance at 1.3% from the NARMS program indicates the probability of 1.4 erythromycin-resistant *Campylobacter* spp. bacteremia per million positive blood cultures (e.g., one to two cases per year in the United States) (23, 91).

For *E. faecium*, resistance to macrolides predominates at levels of more than 95% in human isolates (63, 71). Therefore, any change in RzD would minimally affect very few clinical isolates, a situation that would not be strictly a foodborne illness but would only be a potential reservoir that does not necessarily imply risk. Studies of the antibiotic-resistant *E. faecium* reservoirs that might occur in the human gastrointestinal tract offer little evidence of RzD persistence or transfer. For example, vancomycin-resistant *E. faecium* from animals, when consumed by human volunteers, failed to colonize or persist (97). Virulence factors in *E. faecium* have been significantly lower in occurrence among animal strains (2%) when compared with human *E. faecium* isolates (35 to 42%), questioning transfer of more dangerous determinants to human hosts (44). Furthermore, transfer of a RzD from poultry *E. faecium* to human *E. faecium* was unsuccessful in favorable in vitro mating experiments such that coselection of vancomycin-resistant enterococci (VRE) and macrolide resistance by MLS_B agents has been questioned (16). *E. faecium* from poultry possessing RzD have been suggested as a human health hazard for transfer into human *E. faecium* strains, thus compromising human therapy with quinupristin/dalfopristin (94, 95). However, this concept was not borne out by recent analysis of contemporary human *E. faecium* bacteremia isolates for 2002 that failed to detect any such RzD-containing strains among 169 episodes from 32 different medical centers in the United States (54). All of these study results occurred at the time of intense scrutiny and were associated with a documented decline in antibiotic use in food animals (7). Despite these considerations, a failure probability of 100% was conservatively assigned to the therapy of a macrolide-resistant strain with erythromycin, driven by the inherent high level of macrolide resistance in *E. faecium* and the very remote possibility of erythromycin use in human practice.

For serious invasive enterococcal infections, the occurrence

TABLE 4. Sensitivity analysis of various parameters regarding treatment failure and probability of resistance development to macrolides from animals exposed to tylosin or tilmicosin on the risk of human campylobacteriosis

Probability of treatment failure if treated with macrolide (node 9) (%)	Probability of significant resistance development in treated animal (node 2) (%)	Resulting risk 1 in X million ^a
25	3 ^b	21.9
50 ^b	3 ^b	10.9
100	3 ^b	5.5
25	15	4.4
50 ^b	15	2.2
100	15	1.1
25	30	2.2
50 ^b	30	1.1
100	30	0.55
50 ^b	100	0.33

^a Pork, beef, and poultry combined. Compare to FDA FQ of 1 in 0.03 million (114).

^b Parameter used for best estimate shown in Table 1.

of bacteremias continues to be high (10.2%) in the United States and numerous therapeutic regimens remain active. However, erythromycin is *not active* against 95% or more of all enterococcal bacteremia strains (63, 71). Therefore, the probability of using a macrolide for therapy of a serious enterococcal infection in human medicine would be remote and could have serious medical-legal consequences. The probability of macrolide use for enterococcal sepsis was judged to be extremely rare (i.e., 1 in 1 million), and this low number drives much of the remaining RA for these infections. Regardless, the probability of treatment failure in case of macrolide treatment of *E. faecium* infection was set at 100% (Table 1).

RESULTS AND DISCUSSION

This RA model estimated that the probability of human illness in the United States due to macrolide-resistant campylobacteriosis was slightly less than 1 in 10 million for all meat commodities combined (Table 1). For poultry, beef, and pork, the probabilities were slightly less than 1 in 14 million, 1 in 53 million, and 1 in 236 million, respectively. The FDA RA for fluoroquinolone-resistant *Campylobacter* spp. in chickens reported a risk of approximately 1 in 30,000, which was described qualitatively as low (114). In relation to this precedent, the risk for *Campylobacter* spp. from tylosin and tilmicosin use could be described as very low or remote. The risk of any macrolide-resistant *Campylobacter* spp. illness treated with a macrolide (node 8) before consideration of treatment failure was less than 1 in 5.5 million for all commodities combined.

This model also indicated far less than one potential case per year of macrolide treatment failure from food-derived enterococcal infections in the United States (1 in 3 billion). This result is due to the combined low level of macrolide susceptibility in *E. faecium* (node 2) and the extremely low probability that enterococcal infections would be treated with a human use macrolide (node 9).

Some parameters had a large degree of associated uncertainty, so we evaluated their effect with a simple sensitivity analysis. The results for various settings in node 9 (probability of treatment failure) and node 2 (probability of RzD development) for *Campylobacter* spp. are shown in Table 4. This table shows that for the overall risk to reach as high as 1 in 1 million, one must assume a 30% probability of resistance development in the treated animals (node 2, factor 3), which is 10 times higher than estimates. This result is not the probability that one mutation will occur but that the mutant population will compete with the wild-type population of the same species to a degree that will present a sufficiently infectious dose when consumed as a mishandled food product. Table 4 also shows that changes in other parameter estimates will cause linear changes in resulting risk.

Many of the assumptions and parameter estimates made in this model are very conservative, thus increasing the risk estimate. The estimated risk from poultry was highest due to the large number of potentially contaminated servings generated by the assumption that 100% of the 2.3-kg poultry carcasses, if contaminated, would produce contaminated infective servings (10^2 to 10^6 CFU; Table 2). This assumption may correct for such issues as cross-contamination of kitchen surfaces and utensils, but the result is still probably overestimated. We included all therapeutic tylosin and tilmicosin uses and assumed 100% escape of RzD from the farm and 50% failure rate for treatment of a macrolide-resistant *Campylobacter* spp. infection with a macrolide. We also assumed that a single treatment was equivalent to long-term feeding for growth promotion, thereby inflating the estimated effects on some animals exposed to tylosin and tilmicosin. However, despite all of these very conservative assumptions, the results demonstrate a very low risk from any macrolide administration to food animals (Table 1).

Additionally, the estimate that 90% of campylobacteriosis is foodborne is probably inflated. In a recent study in Canada (73), approximately 20% of human *Campylobacter* spp. isolates were genetically related to genotypes found in poultry, whereas Wu et al. (132) estimated 10% for Taiwan. Despite the difficulties of interpreting such genetic similarity data, it seems likely that both poultry and humans are exposed to common reservoirs (e.g., water), accounting for some or all of the overlap between the genotypes found in them (and in other animals, such as lamb). But the extent of the overlaps suggests that poultry is probably not a predominant source for human *Campylobacter* spp., consistent with recent epidemiological findings (73). Related to this question, Willems et al. (128) analyzed 255 VRE strains from hospitalized and nonhospitalized persons and various animal sources in nine different countries to clarify sources of VRE. The analysis identified four major genogroups and suggested that an attribution of 10 (11.5%) of 87 hospitalized patients to chicken sources would be an upper bound.

The procedure that we used to derive the ratio (β) incorporates simplifying and possibly incorrect assumptions of causality. For example, it assumes that all cases that are deemed attributable to foods of animal origin are caused

specifically and uniquely by foodborne contamination, even though attributed risk estimates typically reflect statistical associations rather than causation. It assumes there is no background contribution (or nonzero intercept term) in the creation of human cases attributed to foods of animal origin, even though other sources, such as water, probably account for some larger proportion of such cases (40). Finally, β is calculated from aggregate population data, uncorrected for potential confounders, modifiers, covariates, and aggregation effects. Such aggregate statistical relations may misrepresent individual-level risk relationships. Despite these limitations, the ratio assumption is simple and widely used. If all of its implicit assumptions are satisfied, it can provide a useful description of a causal relation. We assumed that it is appropriate in the current context, while recognizing that this key assumption should be tested further.

One goal of an RA is transparency, implying that the approach taken and results obtained are clear to all who study it. We consider this quantitative approach to be more transparent and interpretable than a qualitative analysis. The difficulty we encountered with the qualitative approach was (i) the conversion of frequency or prevalence estimates into categories and (ii) the combination of these categories across a continuous farm-to-patient scenario. Since the assignment of frequency or prevalence into H, M, and L risk categories is entirely subjective without well-accepted definitions, the meaning of the results is likely to be ambiguous or disputed. Because the entire farm-to-patient system was modeled, and each node is dependent on the previous step, it is problematic to qualitatively categorize each of the individual components of the model (exposure, release, and consequence) as H, M, or L. Furthermore, if each of the nine stages of the model were categorized as H, M, or L, the interpretive tables of the guidance document make summing these nine individual H, M, and L rankings even more problematical and difficult for assigning overall risks.

One of the values of RA is identification of additional information that can be used to direct future research. This intent was a prime consideration that led to full descriptions of nodes 5, 6, and 7, even though the results were not directly used in the final calculations. This RA had its greatest uncertainty in nodes 2 and 9. Data on the probability of treatment failure due to macrolide-resistant *Campylobacter* spp. and *E. faecium* may become available from existing or newly developing data. However, data for node 2 (probability of resistant determinant development) clearly requires further experimental study.

Generally, an RA is not intended to evaluate benefits derived from the particular behavior or practice deemed of risk. However, assessment of any policy will enter into the greater public debate, which overtly or inherently must consider the cost (risk) and benefit relationship. The macrolide products (tylosin and tilmicosin) have been beneficial to animal health, which most likely translates into beneficial effects on both food quality and food safety. Tylosin reduces liver abscesses in feedlot cattle by its action against *Fusobacterium necrophorum* (61) and has been effective against the most troublesome form of liver abscess. In stud-

ies by Brown et al. (18) and Heinemann et al. (46), reduction of severe abscesses in tylosin-treated animals ranged from 85 to 94.5%. Although tylosin does not have a label claim for necrotic enteritis, its in vitro spectrum includes gram-positive organisms such as *Clostridium perfringens*, which is associated with necrotic enteritis in chickens (121). Infections in turkeys have been reduced with use of antibiotics in feed (28). In swine, tylosin is used to control proliferative enteritis (ileitis) caused by *Lawsonia intracellularis* (65, 105). Improvements in feed conversion efficiencies of swine under field conditions are typically in the range of 3 to 5%, and the improvements in average daily weight gain range from 3 to 4% for finishers, 5 to 10% for grower finishers, and 10 to 15% for starter pigs. These gains in efficiency reflect the improved general animal health status resulting from infection control, and healthier conditions of food animals can lead to safer meat supplies and food products for the public consumer.

Denmark banned the use of antimicrobial growth promoters (AGP) for finishing pigs in 1998 and for all uses in swine in 2000. The resulting increased health problems in newly weaned pigs caused Danish veterinarians to prescribe more therapeutic antimicrobial agents. The Danish Veterinary Institute (31) indicated that total antibiotic use (feed grade and therapeutic) increased from 74 tons in 1999 to 80 tons in 2000 to 94 tons of active ingredient in 2001. These Danish results suggest that a U.S. ban on AGP could potentially have negative impacts on both animal and human health if the ban increased total drug use in U.S. swine herds. Furthermore, the types of therapeutic antibiotics used would be more front-line products (i.e., similar to those currently used to treat human infectious illnesses). Such events could further aggravate the antibiotic resistance issues. An increase in therapeutic antibiotics in livestock could outweigh any benefit caused by a reduction in AGP, a possibility that must be determined by structured RA (9, 124).

In summary, this CVM Guidance Document 152-based RA has produced a unique farm-to-patient, deterministic analysis using extensive available scientific and governmental numerical data. It demonstrates that tylosin and tilmicosin use in livestock presents a low qualitative risk with an approximate probability of less than 1 in 10 million and less than 1 in 3 billion for foodborne illness from *Campylobacter* spp. and *E. faecium*, respectively. These results indicate that current uses of macrolides in cattle, poultry, and swine appear to create a risk much lower than the potential benefit to food safety, animal welfare, and public health. This result and other potential models of risk (9, 124) must be systematically applied in the balanced appraisal of hazards and risks for antibiotic use in food animals.

Expanded discussion and the spreadsheet model are available at: www.ifss.iastate.edu.

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