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Modeling the relationship between food animal health and human foodborne illness

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Abstract

To achieve further reductions in foodborne illness levels in humans, effective pre-harvest interventions are needed. The health status of food animals that are destined to enter the human food supply chain may be an important, although often overlooked, factor in predicting the risk of human foodborne infections. The health status of food animals can potentially influence foodborne pathogen levels in three ways. First, diseased animals may shed higher levels of foodborne pathogens. Second, animals that require further handling in the processing plant to remove affected parts may lead to increased microbial contamination and cross-contamination. Finally, certain animal illnesses may lead to a higher probability of mistakes in the processing plant, such as gastrointestinal ruptures, which would lead to increased microbial contamination and cross-contamination. Consequently, interventions that reduce the incidence of food animal illnesses might also help reduce bacterial contamination on meat, thereby reducing human illness. Some of these interventions, however, might also present a risk to human health. For example, the use of antibiotics in food animals can reduce rates of animal illness but can also select for antibiotic-resistant bacteria which can threaten human

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treatment options. In this study, we present a mathematical model to evaluate human health risks from foodborne pathogens associated with changes in animal illness. The model is designed so that potential human health risks and benefits from interventions such as the continued use of antibiotics in animal agriculture can be evaluated simultaneously. We applied the model to a hypothetical example of *Campylobacter* from chicken. In general, the model suggests that very minor perturbations in microbial loads on meat products could have relatively large impacts on human health, and consequently, small improvements in food animal health might result in significant reductions in human illness.

Keywords: Risk–benefit analysis; Dynamic simulation model; Food safety; *Campylobacter*; Macrolide

1. Introduction

The estimated annual incidence rates of major bacterial human foodborne infections in the U.S. decreased between 1996 and 2003 (Centers for Disease Control and Prevention, 2003). Even with these declines, the 2002 estimated annual incidence rates of U.S. *Salmonella* and *Campylobacter* human foodborne infections were 16.1 and 13.4 per 100,000, respectively. Reductions in foodborne disease have been attributed largely to pathogen reduction strategies during processing, distribution and preparation (post-harvest). Pre-harvest or on-farm interventions that seek to eliminate or decrease the levels of specific pathogens in food animals prior to their entering the slaughter plant have been explored with mixed success (Isaacson and Torrence, 2004). To achieve further reductions in foodborne illness levels, more effective pre-harvest interventions are needed.

The health status of food animals that are destined to enter the human food supply chain may be an important, although often overlooked, factor in predicting the risk of human foodborne infections. The reason why this factor has been largely ignored may be that the etiologic agents of animal disease are often different from those that cause foodborne infections. How then might food animal illness relate to human foodborne disease?

The health status of animals that are processed for meat can potentially influence foodborne pathogen levels in three ways. First, diseased animals may shed higher levels of pathogens (e.g. *Salmonella* and *Campylobacte*r) than healthy animals (Russell, 2003), thereby increasing the probability of carcass (meat) contamination and cross-contamination (Olsen et al., 2003; Rosenquist et al., 2006). Second, during the normal meat inspection process, animals with overt signs of disease will either be removed from the food chain (condemned) or will undergo further handling to remove affected parts. This increased handling may lead to increased microbial contamination and cross-contamination (Olsen et al., 2003; Rosenquist et al., 2006). Carcasses from animals with subclinical illnesses may go undetected. Third, certain animal illnesses may lead to a higher probability of mistakes in the processing plant, such as gastrointestinal ruptures. Groups of animals that have experienced illness, either clinically or subclinically, can be smaller on average and more variable in size. During processing, these factors can contribute to an increased likelihood of the gastrointestinal tract being ruptured, and this processing error can lead to increased contamination and cross-contamination. Berrang et al. (2004) found

that small but increased amounts of fecal contamination on chicken carcasses significantly increased *Campylobacter* counts on the carcass, and the prevention of such contamination on the carcass has been suggested to be the most important factor in improving the cleanliness of poultry processing (Bilgili, 2001). Therefore, reducing animal illness might play an important role in reducing the chances of carcass contamination during processing.

Airsacculitis and coccidiosis in chickens can illustrate this potential link between animal illness and human foodborne disease risk. Airsacculitis is a respiratory disease of chickens characterized in the U.S. by infection with *Escherichia coli*. Chickens with airsacculitis have adhesions in the thorax that can increase the likelihood of gastrointestinal ruptures following mechanical evisceration. Additionally, chickens with airsacculitis, as with other diseases, can have the affected portions of the meat trimmed away. As described previously, this increased handling can result in increased cross-contamination with foodborne pathogens (Olsen et al., 2003; Rosenquist et al., 2006). A recent study found that some flocks of chickens with airsacculitis lesions at the time of processing had lower average bird weights, higher levels of fecal contamination on the carcass, and increased *Campylobacter* loads on the meat than flocks without airsacculitis (Russell, 2003). The effect was observed for all meat produced in the diseased flocks, not just on meat from diseased birds, but the effect was not observed in all airsacculitis-affected flocks that were studied. Unfortunately, this single study was small, and consequently this relationship between respiratory disease status and potential microbial contamination of the meat is unclear.

Coccidiosis in chickens is a gastrointestinal parasitic disease caused by coccidia in the genus *Eimeria*. Coccidiosis rates in chickens are positively correlated with increased gastrointestinal levels of the foodborne pathogen *Clostridium perfringens* (increasing between 4 and 6 $\log_{10}$ bacteria per gram of intestinal contents by day 7 post-infection) (Kimura et al., 1976). *C. perfringens* also causes necrotic enteritis in chickens, a disease that results in increased intestinal tract fragility, which, during processing, increases the likelihood of intestinal rupture and carcass contamination with intestinal contents. Therefore, necrotic enteritis increases the risk of cross-contamination with other foodborne pathogens such as *Campylobacter* (Berrang et al., 2004). Consequently, disease in flocks of chickens might increase the human foodborne disease risks for all of the meat derived from that flock and other flocks that are processed at the same time, regardless of whether individual chickens have visible signs of disease.

Antibiotics are often used in food animals for therapeutic purposes and for growth promotion. Antibiotics administered in feed at low doses over several weeks raise concern about their potential to increase rates of antibiotic resistance, posing a risk to human health. However, these applications also improve animal health and promote size uniformity among animals in the herd or flock (Casewell et al., 2003), and as previously described, could lead to decreased levels of pathogen contamination on meat and decreased foodborne pathogen disease risks. Antibiotic uses in animals can therefore have potential human health risks and benefits.

The objective of this study was to develop a mathematical model to evaluate the relationship between on-farm animal health status, animal health interventions and human foodborne disease risks. The model provides a new means for assessing pre-harvest animal health intervention strategies, such as the use of antibiotics in animals, and the potential

human health risks and benefits from these interventions. Cox previously used a Rapid Risk Rating Technique to evaluate the potential risks and benefits of virginiamycin use in food producing animals (Cox, 2005). The approach described in this study develops a more general dynamic model that makes it possible to evaluate foodborne pathogen risks associated with changes in animal illness rates.

2. Materials and methods

2.1. Dynamic model development

The model was developed as a set of differential equations to provide a dynamic systems approach. The model allows the simultaneous assessment of the potential human health risks and benefits associated with alterations in the incidence of illness in food animal populations.

The complete model consists of the following ordinary differential equations:

$$\frac{\mathrm{dIH}}{\mathrm{d}t} = [c + d \times \mathrm{IA} + e(1 - \mathrm{IA})] \times (1 - \mathrm{IH}) - h \times \mathrm{IH} \quad (1)$$

$$\frac{\mathrm{dRH}}{\mathrm{d}t} = (A + B) \times (1 - \mathrm{RH}) - q \times \mathrm{RH} \quad (2)$$

Let IH denote the fraction of humans who are ill with a specific foodborne disease. Its rate of change, modeled by Eq. (1), is determined by the pool of ''susceptibles'' (those without illness), of size $1 - \mathrm{IH}$, that flows into the ill pool at a rate that depends on: a background rate of illness c (not affected by consumption of the modeled animal product), a rate d that is proportional to the illness rate per serving from ill animal populations and a rate e that is proportional to the illness rate per serving from healthy animal populations. IA is the ''ill animal'' (or ill flock) fraction and $(1 - \mathrm{IA})$ is the healthy animal fraction. Humans with illness recover at a rate h. If the mean duration of illness is approximately 6 days and the time to recovery is modeled as exponentially distributed, then $h = 1/6$ per day. In steady-state equilibrium, $\mathrm{dIH}/\mathrm{d}t = 0$ and hence $[c + d \times \mathrm{IA} + e \times (1 - \mathrm{IA})] \times (1 - \mathrm{IH}) = h \times \mathrm{IH}$. For IH and IA close to 0, this simplifies to $\mathrm{IH} \approx (c + e)/h$.

Similarly, let RH denote the fraction of human illness cases caused by resistant bacteria. For simplicity, each illness is treated here as either resistant or non-resistant, although in reality resistance may emerge and/or be selected for during the course of treatment. Then the rate of change of RH is modeled by Eq. (2) above. In other words, the population of foodborne bacteria causing human illnesses is assumed to flow from the antibiotic-susceptible type (comprising a fraction $(1 - \mathrm{RH})$ of the bacterial population) to the antibiotic-resistant type at a rate proportional to the sum of the selection pressures from antibiotic use in animals (A) and other sources (B). The reverse transition rate per resistant bacterium cell per unit time in the absence of selection pressure is q; thus, the total reverse flow is $q \times \mathrm{RH}$ when the fraction of resistant bacteria is RH. In steady-state equilibrium, $\mathrm{dRH}/\mathrm{d}t = 0$, and so $(A + B) \times (1 - \mathrm{RH}) = q \times \mathrm{RH}$. If RH is close to 0, then this simplifies to $\mathrm{RH} \approx (A + B)/q$.

2.2. Hypothetical example related to campylobacteriosis and macrolide use in poultry

2.2.1. Model justification

A major challenge of this modeling approach at the current time is finding sufficient data to develop parameter estimates. Because campylobacteriosis in humans, particularly associated with the consumption of chicken, has been modeled previously, this system was used as an initial hypothetical example. Thus, the initial application of our mathematical model examined the effect that increases in illness rates in chickens have on *Campylobacter* infections in humans. Baseline model estimates of human health impacts were based on our current understanding of the food chain leading to foodborne campylobacteriosis and antibiotic treatment. The net human health effects from changes in animal illness rates were then estimated.

A second application of the model was to evaluate the human health risks and benefits of antibiotic use in chicken production. The use of macrolide antibiotics in broiler chicken production was chosen for evaluation because macrolides are also used in human medicine for treating cases of campylobacteriosis. Macrolides select for chromosomal point mutations conferring resistance in *Campylobacter*. Members of this antibiotic class are sometimes used to treat human campylobacteriosis and can be administered as a feed additive in chicken production for performance gains. Approximately 600 million chickens were administered macrolides in 2001 in the U.S. (Hurd et al., 2004). This use may reduce the incidence of necrotic enteritis by modulating *C. perfringens* colonization (Kimura et al., 1976) as well as the mucolytic activity of the intestinal bacterial population (Collier et al., 2003), and consequently can contribute to intestinal integrity and size uniformity of birds in the flock as well as to the maintenance of the health status of the chicken flock. Macrolides therefore have the potential to decrease *C. perfringens* levels resulting in decreases in necrotic enteritis as well as the subsequent reduction in carcass contamination with *Campylobacter* spp.

It must be emphasized that both of these applications of the model are challenging due to the paucity of data on which to estimate the model parameters. Our hope is that the model can be used to identify parameters that are particularly important in predicting the outcome and thus warrant further research to generate more precise parameter estimates. In theory, the model enables the simultaneous assessment of the potential human health risks due to increased macrolide-resistant *Campylobacter* infections and potential human health benefits due to decreased *Campylobacter* loads on chicken meat following macrolide use in chickens. In actuality, the results of the model are only as good as the parameter estimates, which in this hypothetical example, have considerable uncertainty associated with them. The development of this hypothetical example also helps illustrate the types of data that are required to estimate the burden of illness in humans associated with illness in food animals.

2.2.2. Background rate of human illness

The baseline U.S. public health burden due to sporadic, domestically acquired *Campylobacter* cases was expressed in the model as Illness Days per Year. This quantity can be estimated as $IH_0 \times N \times 365$ days, where IH_0 is the baseline per capita daily fraction of people ill with *Campylobacter* (Table 1) and N is the population size of the U.S. IH_0 can be estimated from the number of reported *Campylobacter* cases in the U.S. per person per

Table 1
Input parameters for the model

Parameter	Symbol	baseline value	Range evaluated	Reference
Prevalence of illness in chickens at baseline	IA_0	0.01		
Prevalence of illness in chickens after intervention	IA_{new}	0.02	0.015–0.06	
Fraction of *Campylobacter* in chickens resistant to macrolides at baseline	RA_0	0.05		U.S. Department of Agriculture (2005)
Fraction of *Campylobacter* in chickens resistant to macrolides after intervention	RA_{new}	0		
Potency ratio on chicken servings derived from ill vs. healthy chickens	D	5	1–20	Russell (2003)
Proportion of campylobacteriosis cases in humans attributable to chicken at baseline	FA_0	0.57	0.1–0.9	U.S. Food and Drug Administration (2005)
Fraction of selection pressure affecting macrolide resistance in *Campylobacter* due to macrolide use in chickens	F_0	0.999	0.5–0.999	
Daily per capita fraction of humans with campylobacteriosis at baseline	IH_0	8.38E−5		Mead et al. (1999), Centers for Disease Control and Prevention (2003)
Fraction of human *Campylobacter* resistant to macrolides at baseline	RH_0	0.01		Centers for Disease Control and Prevention (CDC) (2005)
Fraction of humans with campylobacteriosis that are prescribed a macrolide	f	0.5	0.25–1.0	U.S. Food and Drug Administration (2005)
Duration of human illness from *Campylobacter* that is not treated with a macrolide (days)	h_s	6		Nelson et al. (2004)
Duration of human illness from resistant *Campylobacter* treated with a macrolide (days)	h_r	8		Nelson et al. (2004)

year, the amount of underreporting for cases of *Campylobacter*, and the duration of illness with *Campylobacter*. Assuming 13.4×10^{-5} illnesses per person per year (Centers for Disease Control and Prevention, 2003), 6.01 days per illness and an underreporting bias of 38 (Mead et al., 1999), $IH_0 = 8.38 \times 10^{-5}$. Thus, this calculation gives an estimate of 8.93×10^6 total *Campylobacter* Illness Days per Year.

To calculate the average duration of illness used above, we first assumed that the number of illness days per episode of infection is different for macrolide-susceptible and macrolide-resistant *Campylobacter* infections. We assumed that a macrolide-resistant *Campylobacter* infection that is treated with a macrolide will result in an extended illness. In general, data are lacking on the duration of illness in antibiotic-resistant versus

antibiotic-susceptible infections, and this includes data on macrolide-resistant *Campylobacter* infections. Because one report suggested that the duration of illness is 2 days longer for fluoroquinolone-resistant *Campylobacter* infections that are treated with a fluoroquinolone, we assumed in this model that macrolide-resistant *Campylobacter* will respond in the same fashion. Consequently, a macrolide-resistant infection that is treated with a macrolide would result in 8 days of illness instead of 6 days for all other *Campylobacter* infections (Nelson et al., 2004). The 2 days of clinical benefit postulated here applies to the subset of cases (estimated to be 0.6%) that are severe enough to warrant antibiotic therapy (Buzby et al., 1996).

The average duration of illness was then calculated as the weighted average of macrolide-resistant *Campylobacter* infections receiving a macrolide (8 days of illness) and all other *Campylobacter* infections (6 days of illness). The average duration of illness, ID_0, can then be expressed as: $ID_0 = RH_0 \times f \times h_r + (1 - (RH_0 \times f)) \times h_s$, where RH_0 is the fraction of human *Campylobacter* isolates that are resistant to macrolides, f is the fraction of patients receiving macrolide treatment for campylobacteriosis and h_r and h_s are the durations of illness for macrolide-resistant and macrolide-susceptible *Campylobacter* infections, respectively. At baseline, we assumed (Table 1) $RH_0 = 1\%$ (Centers for Disease Control and Prevention (CDC), 2005), $f = 50\%$, and h_r and h_s are 8 and 6 days, respectively. According to CDC-FoodNet surveillance data, approximately 55% of campylobacteriosis patients who are prescribed an antibiotic receive fluoroquinolones (U.S. Food and Drug Administration, 2005). Assuming that fewer than 10% of those fluoroquinolone-treated cases eventually switch to erythromycin or another macrolide, the total fraction of severe campylobacteriosis cases treated with macrolides is at most 0.5, and thus our baseline value $f = 50\%$. Therefore, at baseline, $ID_0 = (0.01 \times 0.5 \times 9 \text{ days}) + ((1 - (0.01 \times 0.5)) \times 7 \text{ days}) = 6.01$ days.

2.2.3. Changes in human illness due to changes in animal illness

The model differentiates between chicken and non-chicken causes of campylobacteriosis in humans. The risk of campylobacteriosis from chicken was partitioned into the risk from consumption of meat derived from ill animals versus healthy animals. The daily per-capita rate of campylobacteriosis in humans under steady-state conditions can be derived from Eq. (1) as $[c + d \times IA + e \times (1 - IA)] \times (1 - IH) = h \times IH$, where c is the rate of campylobacteriosis from non-chicken sources, d the rate of campylobacteriosis from chicken servings derived from ill animals, e the rate of campylobacteriosis from chicken servings derived from healthy animals, IA the prevalence of illness in chickens, IH the fraction of the human population affected with campylobacteriosis and h is the daily rate of recovery from campylobacteriosis.

Because we lacked specific estimates for c, d and e, we define identifiable ratios $C = c/e$ and $D = d/e$. D expresses the amount of risk associated with a chicken serving from ill versus healthy animals; it is interpreted as a risk potency ratio. The parameter D was modeled under the assumption of a linear no-threshold dose–response that might actually underestimate the human foodborne disease risks. Under a potentially more realistic non-linear (e.g. log-exponential) dose–response assumption, changes in Illness Days per Year could be more than an order of magnitude greater than in the linear dose–response assumption (Cox and Popken, 2006). To deal with the fact that many dose–response

relations are not linear (typically, upward-curving, or "convex", over the exposure levels of interest), we interpret the linear dose–response model as giving bounds on the true changes in risk caused by changes in the corresponding exposures. For example, if the true (but perhaps unknown) dose–response relation is convex (upward-curving) over the exposure range of interest, and if the current level of exposure via poultry causes an incremental risk that could be prevented by setting it to 0, then the slope of the line from (0, 0) to the current (exposure, risk) level provides a plausible upper bound on the reduction in risk that would be achieved by eliminating exposure (by assuming that 100% of the risk would be removed) and a plausible lower bound on the increase in risk that would be caused by an increase in exposure. To draw confident conclusions comparing the changes in risk caused by different interventions, we can exploit such bounds derived from the linear-model approximation to the true (perhaps multivariate non-linear) but uncertain exposure-response relation (Cox, 2006).

A ratio of $D = 1$ implies no difference in the risk of *Campylobacter*-contaminated chicken servings from ill versus healthy animals. The potency ratio (D) does not separate the percentage of carcasses contaminated from the microbial load on individual carcasses, but under a more realistic dose–response relationship, microbial load would be the more important predictor of the risk of human illness (Rosenquist et al., 2003, 2006). At baseline, we set the parameter D equal to 5 (Table 1). This estimate was based on a study that observed at least a 1 log increased load of *Campylobacter* on poultry processed from airsacculitis-positive flocks versus airsacculitis-negative flocks (Russell, 2003), which would give a D equal to 10. Because this effect was not observed in all replicates of the study, we used a 1/2 log increase in *Campylobacter* load on poultry which would give a value for D approximately equal to 5. However, the impact of D on the model was estimated by varying this parameter from 1 to 20 (Table 1).

To calculate the level of illness in humans due to changes in animal illness (IA_{new}), we have $IH_{new} = 1/\{1 + [(1 - IH_0)/IH_0] \times [C + D \times IA_0 + (1 - IA_0)]/[C + D \times IA_{new} + (1 - IA_{new})]\}$, where IA_0 is the prevalence of illness in chickens at baseline, IA_{new} the prevalence of illness in chickens after intervention, IH_0 the baseline per capita daily fraction of humans ill with *Campylobacter* and IH_{new} is the per capita daily fraction of humans ill with *Campylobacter* after intervention (Table 1, with derivation in Appendix A). In this calculation, the ratio C, which reflects the relationship between non-chicken and healthy chicken sources of campylobacteriosis in humans, is expressed as $[D \times IA_0 + (1 - IA_0)] \times [(1 - FA_0)/FA_0]$, where FA_0 is the proportion of campylobacteriosis in humans that can be attributed to chicken. We have used a baseline value of 57% for FA_0 (U.S. Food and Drug Administration, 2005).

2.2.4. Changes in human illness due to changes in antibiotic resistance

The impact that changes in antibiotic use in animal agriculture have on human health was also modeled. In our specific hypothetical example, the effect of macrolide use in chickens on macrolide resistance in *Campylobacter* infecting humans was modeled under steady-state conditions derived from Eq. (2) as $(A + B) \times (1 - RH) = q \times RH$, where A reflects the relative contribution to macrolide resistance in human *Campylobacter* from macrolide use in chickens, B indicates the relative contribution from all other sources, q the rate at which macrolide-resistant *Campylobacter* return to macrolide-susceptibility and RH

is the fraction of *Campylobacter* infections in humans that are macrolide-resistant. Through mathematical rearrangements (derivation in Appendix B) we have $RH_{new} = 1/[1 + ((1 - RH_0)/RH_0) \times [(1 - F_0) + (RA_{new}/RA_0) \times F_0]]$, where RH_0 is the fraction of human *Campylobacter* infections resistant to macrolides at baseline, RH_{new} the fraction of human *Campylobacter* infections resistant to macrolides after the removal of tylosin use in chickens, RA_0 the fraction of *Campylobacter* in chickens resistant to macrolides at baseline, RA_{new} the fraction of *Campylobacter* in chickens resistant to macrolides after the theoretical removal of macrolides and F_0 is the fraction of selection pressure affecting macrolide resistance in *Campylobacter* that is due to tylosin use in chickens. The fraction of selection pressure affecting macrolide resistance in *Campylobacter* that is due to macrolide feed additive use in chickens, F_0, is defined as $A_0/(A_0 + B_0)$. We assume that $B_{new} = B_0$, as changes in the use of macrolides in chickens are not expected to affect contributions to macrolide resistance in human *Campylobacter* from non-chicken sources. We also assume that $A_{new} = (RA_{new}/RA_0) \times A_0$. After the mathematical rearrangement of the formula for RH_{new}, the variable q, the reverse transition rate per resistant bacterium cell per unit time in the absence of selection pressure, is not needed. Under the steady-state conditions we assume that $RA_{new} = 0$, or that macrolide resistance levels in *Campylobacter* of chicken drop to 0 after the theoretical removal of macrolide uses.

2.3. Outcome measures

We evaluated the risks associated with increases in animal illness rates with the outcome measure Percentage Change in Human Illness Days per Year which we calculated as (New Illness Days per Year − Old Illness Days per Year)/Old Illness Days per Year. We added another outcome measure to relate the human health risks and benefits of macrolide use: a risk:benefit ratio termed Illness Days Caused per One Illness Day Prevented. This outcome measure is calculated as Excess Illness Days per Year/$[(ID_0 - ID_{new}) \times$ (Old Illness Days per Year/$ID_0)]$, where ID_0 and ID_{new} are the Old Mean Duration of campylobacteriosis and the New Mean Duration of campylobacteriosis, respectively. ID_{new} is calculated as $ID_{new} = RH_{new} \times f \times h_r + (1 - RH_{new}) \times f \times h_s$. Illness Days Caused per One Illness Day Prevented was only used in those model scenarios that incorporated an intervention strategy, such as macrolide use.

3. Results

3.1. Changes in human illness due to changes in animal illness

As the potency ratio on chicken servings derived from ill versus healthy chickens (D) increases, there is a substantial increase in the level of human campylobacteriosis. In addition, small increases in IA_{new} also produced large increases in campylobacteriosis Illness Days per Year. For example, in the baseline model ($IA_0 = 0.01$, $IA_{new} = 0.02$) the Percentage Change in Human Illness Days per Year increased between 0.56 and 9.1% for potency ratio values (D) ranging from 2 to 20. The logic is simple: if animal illness rates were to increase by 1%, and if each serving from an ill animal carries five times the risk of a

serving from a healthy one (i.e., if $D = 5$), then the relative increase in the human illness rate from chicken servings will be approximately (99%) × 1 + (1%) × 5 = 1.04, i.e., a 1% increase in ill animals would create a 4% increase in human illness attributed to chicken.

3.2. Changes in human illness due to changes in macrolide resistance

Although removing macrolide use from chickens results in a predicted decrease in the proportion of macrolide-resistant *Campylobacter* infections, the increased rate of ill animals that might theoretically result from this change leads to a large increase in the level of *Campylobacter*-contaminated chicken under the assumptions modeled in our hypothetical example. The increased rate of subsequent foodborne human disease creates an increase in human illness days, and thus the reduced human illness associated with decreasing levels of macrolide-resistant *Campylobacter* infections is counterbalanced. At the baseline value of $D = 5$, the modeled values of IA_{new} increase the number of Illness Days Caused per One Illness Day Prevented by 5.6–64.8 (Fig. 1A). For a potency ratio of 20 and an animal illness level (IA_{new}) of 6%, the Percentage Change in Human Illness Days per Year increases by 45.3% (Fig. 2A). Under the model assumptions, the rates of change in the model outcomes demonstrate that small increases in the level of animal illness (IA_{new}) substantially increase the risk of human campylobacteriosis (Figs. 1A and 2A).

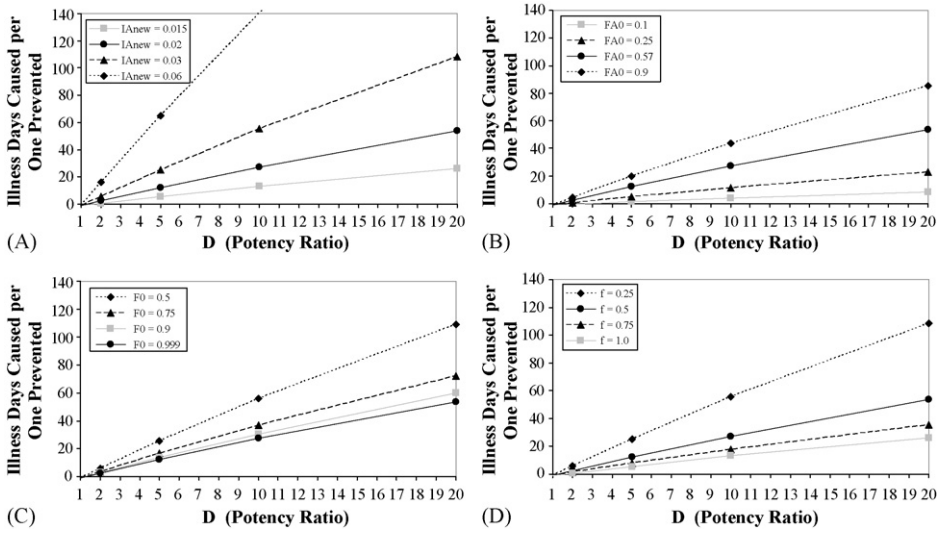

Fig. 1. Changes in human illness due to *Campylobacter* expressed as Illness Days Caused per One Illness Day Prevented. The ratio is shown as a function of D, the potency ratio between chicken servings from ill vs. healthy chickens. All other parameters are held constant at their baseline values. (A) Model evaluated for different values of IA_{new}, the prevalence of ill chickens after intervention. (B) Model evaluated for different values of FA_0, the proportion of campylobacteriosis cases in humans attributable to chicken at baseline. (C) Model evaluated for different values of F_0, the fraction of selection pressure affecting macrolide resistance in *Campylobacter* due to macrolide use in chickens. (D) Model evaluated for different values of f, the fraction of humans with campylobacteriosis that are prescribed a macrolide. Baseline parameter values are solid lines.

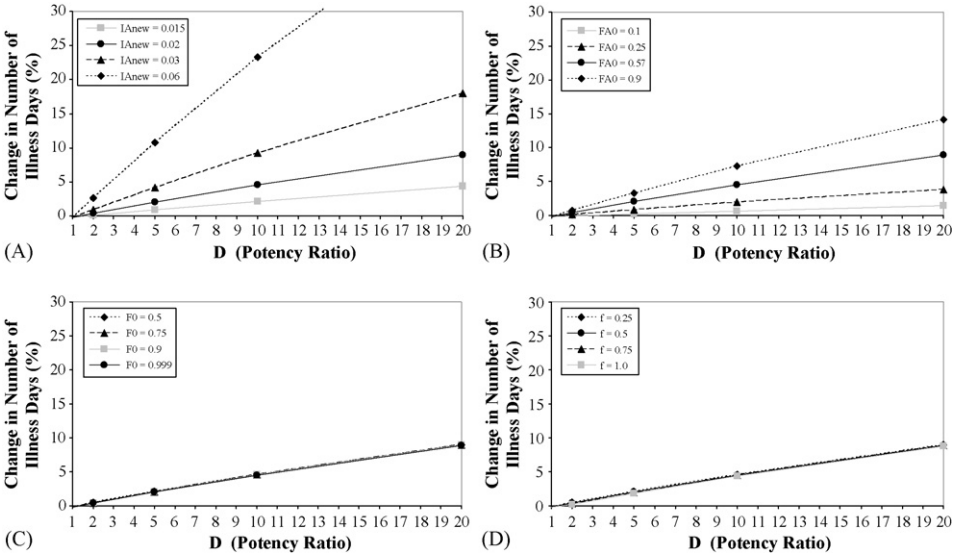

Fig. 2. Changes in the total number of human Illness Days per Year due to *Campylobacter* expressed as a percentage change from baseline. The percentage change in illness days is shown as a function of *D*, the potency ratio between chicken servings from ill vs. healthy chickens. All other parameters are held constant at their baseline values. (A) Model evaluated for different values of IA_{new}, the prevalence of ill chickens after intervention. (B) Model evaluated for different values of FA_0, the proportion of campylobacteriosis cases in humans attributable to chicken at baseline. (C) Model evaluated for different values of F_0, the fraction of selection pressure affecting macrolide resistance in *Campylobacter* due to macrolide use in chickens. (D) Model evaluated for different values of *f*, the fraction of humans with campylobacteriosis that are prescribed a macrolide. Baseline parameter values are solid lines.

The percentage of human *Campylobacter* cases attributable to chicken consumption (FA_0) was also associated with human illness. The model shows that as FA_0 increases from the baseline value of 57% (U.S. Food and Drug Administration, 2005) to 90%, the Percentage Change in Human Illness Days per Year increases from 2.0 to 3.3% (Fig. 2B). The fraction of the selection pressure on *Campylobacter* that is due to the use of macrolides in chickens (F_0) and the proportion of humans with campylobacteriosis prescribed a macrolide (f) are negatively associated with Illness Days Caused per One Illness Day Prevented (Fig. 1C and D). However, these variables do not substantially affect the Percentage Change in Human Illness Days per Year (Fig. 2C and D), implying that while decreased macrolide use (f) and macrolide selection pressures (F_0) reduce the number of human illness days associated with macrolide-resistant *Campylobacter* infections, this reduction is small compared to the increased number of human illness days associated with increased *Campylobacter* infections resulting from increased animal illness.

3.3. Sensitivity analysis for potency ratio

We performed a sensitivity analysis to determine the minimum values for *D*, the potency ratio between chicken servings from ill versus healthy animals, that would result in an

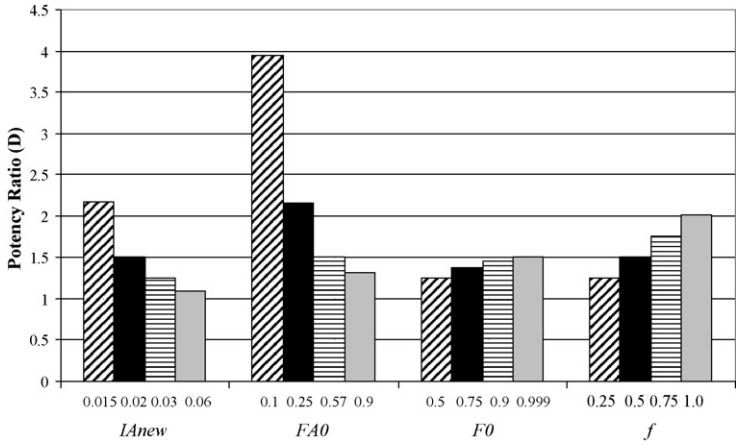

Fig. 3. Critical threshold values for D, the potency ratio between chicken servings from ill vs. healthy chickens. The value of D above which there is an excess number of illness days is shown for the input parameter estimates of the variables IA_{new}, the prevalence of ill chickens after intervention, FA_0, the proportion of campylobacteriosis cases in humans attributable to chicken at baseline, F_0, the fraction of selection pressure affecting macrolide resistance in *Campylobacter* due to macrolide use in chickens and f, the fraction of humans with campylobacteriosis that are prescribed a macrolide. Above each variable name are the input parameter values for that variable. A D value of 1 indicates no difference in *Campylobacter* contamination between ill and healthy animals. All other parameters in the model are held constant at their baseline values.

excess number of human Illness Days per Year. This parameter clearly had a large impact on model outcomes but remains a parameter that is highly uncertain. The only study that was used to inform the parameter in this model was a small study that had variable results (Russell, 2003).

Using the same parameter estimates for the scenarios previously modeled, we solved the equations for a value of the potency ratio (D) that would give one Illness Day Caused per One Illness Day Prevented. In most of the scenarios modeled with varied parameter estimates, this value for D was very close to 1 (Fig. 3). A value of $D = 10$ can imply a 10-fold increase (1 log) in the microbial load of the chicken serving. A value for D of less than 2 represents a possibly undetectable increase in microbial load using current laboratory methods. Consequently, our model suggests that minor perturbations in microbial loads on meat products may have relatively large negative impacts on human health. Microbial quantification methods with enhanced precision would be needed to detect such small yet biologically important changes.

4. Discussion

This study has proposed a dynamic simulation model linking changes in animal illness to possible resulting changes in human foodborne illness. The model may have broad utility for predicting changes in human illness as a consequence of changes to animal production systems. The parameter estimates that were used in our hypothetical

example of the model were developed from a variety of sources. This study is one of the first attempts to relate animal illness to human foodborne illness, and consequently, some of the parameters were estimated with data that were not necessarily specific to macrolide resistance in *Campylobacter*. We chose this example because in general there were more data available about chicken consumption, campylobacteriosis, and macrolide use and resistance. For the most part, the data were specific to the U.S. and therefore the relationships might not be globally generalizable. However, the most important aspect of the presented model is the identification of specific parameters that are in need of further study and to generate a prediction that can now be tested in empirical studies.

In our current model, the observation of large increases in Illness Days per Year following small increases in animal illness levels suggests that agricultural management strategies may have significant impacts on human health. This finding was based on the assumption behind the relationship between IA and *D*, namely that servings of meat from ill animals represent an increased foodborne disease risk when compared to servings of meat from healthy animals. Additional field studies are needed to validate this assumption. The potency ratio, *D*, relating microbial loads of foodborne pathogens on meat derived from ill animals versus healthy animals, has critical importance in assessments of foodborne disease risks. Most studies that have investigated foodborne pathogen contamination on meat have focused on the prevalence of samples that are positive for the organism. These prevalence measures are largely irrelevant for predicting risks that depend on the quantity of pathogens ingested, as most foodborne illnesses are expected to come from the right tail (i.e., exceptionally high region) of the frequency distribution of microbial loads on meats. Although the study by Russell (2003) was small and needs replication, a strength of this study is that it differentiates between prevalence and load and demonstrates that servings of meat derived from ill flocks of chickens may have higher microbial loads. In the linear no-threshold dose–response used in our model, only average load affects risk of foodborne illness in humans. Under more realistic dose–response relationships, microbial load measurements are the only useful predictors of human health risk, a point that has been emphasized by WHO in its risk assessments for *Salmonella* (World Health Organization and Food and Agriculture Organization of the United Nations, 2002).

Although the removal of feed additive uses of macrolides in chickens might benefit human health by decreasing the proportion of macrolide-resistant *Campylobacter* infections, we predict from the results of the hypothetical example that the increased rate of clinically and subclinically ill animals could harm human health by increasing the level of *Campylobacter*-contaminated chicken. Over time, additional management changes might be attempted to reduce animal illness, but immediately following the removal of the antibiotic, animal illness levels might be expected to increase, at least slightly (Casewell et al., 2003). Because the potential human health benefits from continued animal antibiotic use (for example, due to reduced *Campylobacter* loads) may outweigh the potential increase in human health risks (for example, due to increased resistant *Campylobacter* loads), further clarification of the net human health impact from interventions should be carefully assessed prior to implementation of changes in antibiotic use policy. It should be emphasized, however, that this comparison of potential

risks and benefits is related only to changes in the number of campylobacteriosis cases and the number of days of diarrheal illness. We have not included risk management decisions related to other repercussions of macrolide resistance; only excess days of diarrhea from treating a resistant infection were modeled. In the future, additional impacts of macrolide resistance, such as the potential for patient mortality, could be modeled in a similar risk–benefit approach.

This approach of modeling benefits and risks of different management strategies in animal production systems should have broad relevance. For example, it should be feasible to evaluate the human health benefits and risks of organic meat production when compared to conventional meat production. This example could be particularly relevant, as there is often a public perception that organically reared (antibiotic-free) animals produce a healthier and more wholesome meat product (Kouba, 2003). Because of the possibility that organic chicken can have higher rates of disease and higher rates of *Campylobacter* contamination at the time of slaughter than conventionally reared chicken (Heuer et al., 2001; Cui et al., 2005; Van Overbeke et al., 2006), the model that we have developed predicts that the benefits gained by decreases in resistance on organic chicken could be outweighed by the increased human health risks of higher foodborne disease risks. As previously described, this effect could be missed entirely if the focus were on prevalence of contamination rather than microbial load.

The example that we have used focused on the relationship between animal illness and animal antibiotic uses. The model has other areas of utility, and one area in which this model would be useful is in relation to vaccination programs. For example, respiratory diseases significantly impact food animal production and result in the use of antibiotics in prophylactic, metaphylactic and therapeutic manners. A vaccine that reduces the incidence of respiratory disease in animal populations would affect the model in several key areas. First, the parameter IA would be reduced due to a lowering of the animal illness prevalence. By reducing IA there would be a reduction in d, the rate of illness associated with meat from ill animals, but an increase in e, the rate of illness associated with meat from healthy animals. If d is greater than e, as we have assumed in this model, then there would be an overall reduction in bacterial contamination of the meat. Because there would be fewer ill animals, the amount of antibiotic needed would also be reduced, and therefore, the parameter A would be reduced. Fewer resistant foodborne infections would be attributable to the animal use of antibiotics. Finally, if there were also a vaccine targeted against a foodborne pathogen at the preharvest level, we might also have an overall reduction in pathogen load on the farm which could translate to a reduction in both d and e, the rate of illness associated with meat from both ill and healthy animals. If this reduction were proportionally greater in the ill versus the healthy animals, we would also see a reduction in the potency ratio, D. Reductions in animal disease levels on the farm could be a key way in which to reduce the incidence of foodborne illness in human populations.

The approach we have used of assessing potential risks and benefits simultaneously may have utility for a broad range of microbial hazards and antibiotic uses. Unfortunately, many assessments of risk that subsequently influence risk management actions fail to address the unintended consequences of these actions. Our risk–benefit approach attempts to evaluate whether these unintended consequences will create more

harm than was posed by the initial risk prior to action. Overall, reducing human exposure to foodborne pathogens such as *Campylobacter* is the most effective way to reduce human illness associated with *Campylobacter*, regardless of whether the *Campylobacter* is antibiotic resistant or susceptible. Reducing levels of animal illness could be one effective pre-harvest means for reducing levels of foodborne pathogens on meat products, and this possibility needs to be studied in repeat investigations with increased rigor.

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Appendix A. Mathematical rearrangement for IH_{new}

$$\frac{\mathrm{dIH}}{\mathrm{d}t} = [c + d \times \mathrm{IA} + e \times (1 - \mathrm{IA})] \times (1 - \mathrm{IH}) - h \times \mathrm{IH}.$$

At equilibrium we have:

$$[c + d \times \mathrm{IA} + e \times (1 - \mathrm{IA})] \times (1 - \mathrm{IH}) = h \times \mathrm{IH}, \text{ and}$$
$$\mathrm{IH} = \frac{C + D \times \mathrm{IA} + (1 - \mathrm{IA})}{C + D \times \mathrm{IA} + (1 - \mathrm{IA}) + (h/e)},$$

where $C = c/e$ is the background ratio, $D = d/e$ the relative potency ratio, h the average recovery rate for humans and $1 - \{C/[C + D \times \mathrm{IA} + (1 - \mathrm{IA})]\} = \mathrm{FA}$ is the chicken-borne illness fraction.

For the internal parameters IH_0, IA_0, D, FA, IA_{new} we have:

$$1 - \mathrm{FA}_0 = \frac{C}{C + D \times \mathrm{IA} + (1 - \mathrm{IA})}, \quad C = [D \times \mathrm{IA}_0 + (1 - \mathrm{IA}_0)] \times \left[\frac{1 - \mathrm{FA}_0}{\mathrm{FA}_0}\right],$$

$$[C + D \times \mathrm{IA}_0 + (1 - \mathrm{IA}_0)] \times e \times (1 - \mathrm{IH}_0) = h \times \mathrm{IH}_0, \text{ and}$$
$$e = \frac{h \times \mathrm{IH}_0}{[C + D \times \mathrm{IA}_0 + (1 - \mathrm{IA}_0)] \times (1 - \mathrm{IH}_0)}.$$

Thus, $(h/e) = [(1 - \mathrm{IH}_0)/\mathrm{IH}_0] \times [C + D \times \mathrm{IA}_0 + (1 - \mathrm{IA}_0)]$.

For the output, we have:

$$\begin{aligned}\mathrm{IH}_{\mathrm{new}} &= \frac{C + D \times \mathrm{IA}_{\mathrm{new}} + (1 - \mathrm{IA}_{\mathrm{new}})}{C + D \times \mathrm{IA}_{\mathrm{new}} + (1 - \mathrm{IA}_{\mathrm{new}}) + (h/e)} \\ &= \frac{1}{1 + (h/e)/[C + D \times \mathrm{IA}_{\mathrm{new}} + (1 - \mathrm{IA}_{\mathrm{new}})]} \\ &= \frac{1}{1 + [(1 - \mathrm{IH}_0)/\mathrm{IH}_0] \times [C + D \times \mathrm{IA}_0 + (1 - \mathrm{IA}_0)]/[C + D \times \mathrm{IA}_{\mathrm{new}} + (1 - \mathrm{IA}_{\mathrm{new}})]},\end{aligned}$$

where $C = [D \times \mathrm{IA}_0 + (1 - \mathrm{IA}_0)] \times [(1 - \mathrm{FA}_0)/\mathrm{FA}_0]$.

Appendix B. Mathematical rearrangement for $\mathrm{RH}_{\mathrm{new}}$

$$\frac{\mathrm{dRH}}{\mathrm{d}t} = (A + B) \times (1 - \mathrm{RH}) - q \times \mathrm{RH}.$$

At equilibrium we have:

$$(A + B) \times (1 - \mathrm{RH}) = q \times \mathrm{RH}, \quad \text{and} \quad \mathrm{RH} = \frac{A + B}{A + B + q}.$$

Assume that $B_{\mathrm{new}} = B_0$, or in words, a change in macrolide use in chickens does not change the contribution to resistance from all non-chicken sources. In reality, human prescriptions may increase if IH increases.

Assume $A_{\mathrm{new}} = (\mathrm{RA}_{\mathrm{new}}/\mathrm{RA}_0) \times A_0$.

Assume that $A_0/(A_0 + B_0) = F_0$, where F_0 is the fraction of the total contribution to macrolide resistance that is attributable to macrolide use in chickens.

For the internal parameters A, B and q we have:

$$A_0 = F_0 \times (A_0 + B_0) = \frac{F_0 \times q \times \mathrm{RH}_0}{1 - \mathrm{RH}_0},$$

$$B_0 = A_0 \times \left[\left(\frac{1}{F_0}\right) - 1\right] = F_0 \times q \times \left[\frac{\mathrm{RH}_0}{(1 - \mathrm{RH}_0)}\right] \times \left[\left(\frac{1}{F_0}\right) - 1\right],$$

$$A_{\mathrm{new}} = \left(\frac{\mathrm{RA}_{\mathrm{new}}}{\mathrm{RA}_0}\right) \times A_0 = \left(\frac{\mathrm{RA}_{\mathrm{new}}}{\mathrm{RA}_0}\right) \times F_0 \times q \times \left[\frac{\mathrm{RH}_0}{1 - \mathrm{RH}_0}\right],$$

$$B_{\mathrm{new}} = B_0,$$

and

$$q = \frac{0.693}{5} \quad (\text{if half-life} = 5\,\text{years}).$$

For the output, we have:

$$\mathrm{RH}_{\mathrm{new}} = \left(\frac{A_{\mathrm{new}} + B_{\mathrm{new}}}{A_{\mathrm{new}} + B_{\mathrm{new}} + q}\right) = \frac{1}{1 + q/(A_{\mathrm{new}} + B_{\mathrm{new}})}.$$

Note that:

$$\begin{aligned}
&\frac{q}{B_{\mathrm{new}} + A_{\mathrm{new}}} \\
&= \frac{q}{F_0 \times q \times [\mathrm{RH}_0/(1-\mathrm{RH}_0)] \times [(1/F_0) - 1] + (\mathrm{RA}_{\mathrm{new}}/\mathrm{RA}_0) \times F_0 \times q \times \mathrm{RH}_0/(1-\mathrm{RH}_0)} \\
&= \frac{1}{[\mathrm{RH}_0/(1-\mathrm{RH}_0)] \times [(1-F_0) + (\mathrm{RA}_{\mathrm{new}}/\mathrm{RA}_0) \times F_0]} \\
&= \frac{1-\mathrm{RH}_0}{\mathrm{RH}_0 \times [(1-F_0) + (\mathrm{RA}_{\mathrm{new}}/\mathrm{RA}_0) \times F_0]}.
\end{aligned}$$

Thus, $\mathrm{RH}_{\mathrm{new}}$ does not depend on q.

Suppressing all internal parameters, we can express the output directly in terms of the inputs, as:

$$\mathrm{RH}_{\mathrm{new}} = \frac{1}{1 + (1-\mathrm{RH}_0)/(\mathrm{RH}_0 \times [(1-F_0) + (\mathrm{RA}_{\mathrm{new}}/\mathrm{RA}_0) \times F_0])}.$$

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