The Effects of Culling and Quarantine on Reducing Antibiotic Resistance in a Cohort of Beef Cattle

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Abstract

Antibiotic resistance is a global health concern that involves animals as well as humans. In zoonotic diseases, not generally fatal to humans, antibiotic resistance provides a reservoir from which pathogenic bacteria can gain resistance. Reducing antibiotic resistance in bovine infections is a key part of any plan to slow resistance in human diseases. A two-stage mathematical model is constructed in order to find the most ideal combination of isolation, treatment, and culling that reduces the number of beef cattle with antibiotic resistance at the time of maturity. New legislation, starting in 2017, will restrict the use of antibiotics in cattle feed to veterinary prescription. To compare the impact of this legislation with current practices, an additional set of parameter values is used to simulate the dynamics of antibiotic resistance among beef cattle populations. Culling rates are shown to have a negligible effect, but quarantine rates of 0.5-1 per week lead to a decreased ABR rate. We find that under the new legislation the proportion of cattle with ABR at slaughter decreases by a statistically significant amount. In addition, the number of cattle colonized with antibiotic susceptible bacteria increases. However, the proportion of sellable cattle at the time of slaughter remains roughly the same.

1 Introduction

When Alexander Fleming received the Nobel Prize in 1945, for his discovery of penicillin, he acknowledged antibiotic resistance (ABR) as a potential problem [3]. Today, we are faced with that reality. The Center for Disease Control recognizes ABR as a growing public health problem, and estimates that more than 23,000 people die each year due to antibiotic resistant infections [8].

Anytime antibiotics are used, regardless of the species to which they are given, resistant bacteria can evolve [19]. In the United States, over 24 million pounds of antibiotics are given to food animals each year [23]. The 2015 President's Council of Advisors on Science and Technology report stated that "the risks to human health posed by the agricultural use of antibiotics is [sic] appropriately a matter of very serious concern" [29]. In beef cattle, antibiotics are used in three main ways: therapeutically (to treat disease), prophylactically (to prevent sickness), and for growth promotion (to improve feed efficiency and maximize weight gain) [43]. Because cattle are kept in groups, antibiotics are often given collectively, in food and water. Antibiotics play an important role in keeping cattle healthy and in ensuring that meat is safe for human consumption. However, the development of drug resistant infections undeniably necessitates that every precaution be taken when distributing antibiotics to animals as well as people [11, 21, 39].

While the link between ABR in humans and animals is complex, it clearly exists [42, 43]. Many zoonotic diseases are not fatal to humans. However, ABR creates a reservoir of bacteria maintained within cattle and the environment from which other harmful bacteria may gain resistance through horizontal gene transfer. This is cause for great concern, especially since there are multiple antibiotics which are used to treat both human and animal conditions [42].

To combat this problem, the United States has allocated over $1.2 billion for 2016 [1]. As part of the National Action Plan for Combating Drug-Resistant Bacteria, the Veterinary Feed Directive (VFD) will no longer allow antibiotics used for growth-promotion in cattle and other food animals beginning January 1, 2017. Furthermore, any antibiotics administered through feed will require a prescription by a veterinarian [29]. This will be a major change for the cattle industry, as currently 17% of antibiotics used in food animals are for growth promotion [24].

In the past, to determine whether growth promoters are a significant cause of ABR in bacteria, researchers have employed mathematical models. Volkova *et al.* found stochastic differential equations (SDE) conceptually beneficial when modeling underlying dynamics of antimicrobial resistant *E. coli* [40]. Zaheer *et al.* concluded that subtherapeutic levels of antimicrobial drugs are not a significant cause of ABR *Mannheimia haemolytica*, although, in the development of their mathematical model, they found data that suggested the opposite [44]. This discrepancy shows further work in modeling ABR in *M. haemolytica* is needed.

Mannheimia haemolytica is the primary cause of Bovine Respiratory Disease (BRD), a condition which is responsible for 70% of morbidity and 50% of mortality in beef cattle [5, 22]. Additional bacterial causes of BRD include *Pasteurella multocida*, and *Histophilus somni*, as well as several viruses [5]. Nyamusika *et al.*, one of the few papers that addresses population dynamics of beef cattle with respect to BRD, looks at how vaccination lowers the incidence of BRD by *M. haemolytica*. The authors discover that vaccination is most effective if administered

once cattle are brought to the feedlot [28]. However, there is no consideration of the impact of prolonged exposure to antibiotics throughout the life of cattle.

The topic of ABR in population dynamics has been studied in humans repeatedly [9, 12] and numerous researchers have demonstrated the need for a connection between ABR in humans and food animals [11, 39, 43]. Smith *et al.* used a mathematical model to reveal that antibiotic use in animals has an impact on ABR in humans [34]. Therefore, it is worthwhile to pursue reducing ABR in food animals.

While certain strains of bacteria present in beef cattle have been modeled at a molecular level, this report focuses on an entire cohort of cattle throughout their lifetime at the population level. Using a mathematical model, we compare strategies to reduce ABR in cattle with and without the use of growth promoters. We also utilize a combination of isolation, treatment, and culling to reduce ABR in cattle at the time of slaughter. This model is analyzed in the context of Bovine Respiratory Disease (BRD) and focuses on resistant and nonresistant strains of *M. haemolytica*.

This paper addresses the question of what is the best combination of culling and quarantine to reduce ABR in beef cattle? Also, how will the Veterinary Feed Directive affect ABR? The remainder of this paper is organized as follows: biological considerations are explained in Section 2 along with the model development, details of the mathematical model and other methods are included in Section 3, and details of parameter estimation are outlined in Section 4. The results of numerical simulations are in Section 5. Section 6 contains the discussion, and additional outputs are included in the Appendix.

2 Model Development

Compartments and Stages

We develop a two-stage model which tracks the development of antibiotic resistant (ABR) bacteria in a cohort of cattle from birth in a cow-calf operation through weaning at seven months (Stage 1), to a feedlot until slaughter at 22 months of age (Stage 2). It is becoming increasingly common to see a cow's life divided into these two distinct phases, as it limits transportation of cattle and therefore reduces stress, which makes cattle more susceptible to illness [14]. The model consists of six compartments, which are shown in Figure 1. We assume that all cattle are born healthy, and enter the model through compartment H. They may then become colonized with either antibiotic resistant or susceptible (ABR or ABS) *M. haemolytica*, and enter latent compartments L_r or L_w, respectively [25]. From there, they may develop symptoms and enter infectious compartments I_r or I_w. At any time, cattle from L_w and I_w may develop resistant bacteria, and move into L_r and I_r respectively [41]. Cattle in I_r are taken to the quarantine compartment Q or leave the system. Cattle exit the model through culling (the equivalent of slaughter without profit) at I_r and Q; at 22 months of age, the cattle are slaughtered. Stage 1 is run from birth to 7 months; it is then stopped, and the outputs are used as initial conditions for Stage 2, which is run from 7 to 22 months. We assume that all cattle are born into Stage 1 at a specific time, move to Stage 2 collectively, and are culled or slaughtered before natural

death can occur. Therefore, natural birth and death are not accounted for in the model.

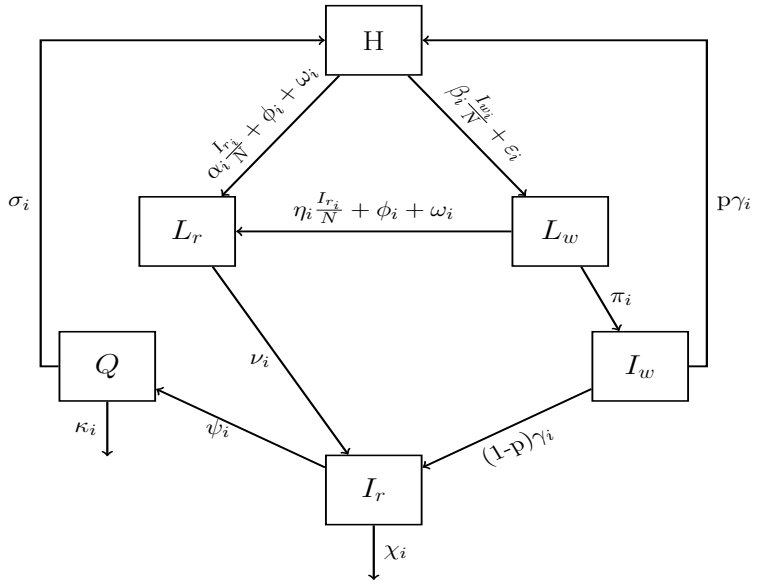

Figure 1: Movement and rates of change between cattle sub-populations with varying levels of infection. Here $i = 1, 2$ denotes the stage.

Com.	Meaning
H	Healthy cattle colonized with harmless amounts of bacteria.
L_r	Asymptomatic cattle colonized with ABR bacteria.
L_w	Asymptomatic cattle colonized with ABS bacteria.
I_r	Symptomatic, infectious cattle colonized with ABR bacteria.
I_w	Symptomatic, infectious cattle colonized with ABS bacteria.
Q	Quarantined cattle, infected with antibiotic resistant bacteria.

Table 1: Description of state variables

Bacteria Types

After birth, cattle become colonized with a variety of bacteria, generally nonpathogenic. *M. haemolytica* is commonly found in healthy cattle. There are three main serotypes (S1, S2, and S6); each of these may cause Bovine Respiratory Disease (BRD), especially when cattle are exposed to stress or viruses. Roughly 2-18% of *M. haemolytica* bacteria is antibiotic resistant [17, 22], and, of the three serotypes, S1 is the most prone to developing resistance. Cattle become

colonized with ABR bacteria through contact with other cattle, α and η, the environment ϕ, and selective pressure from antibiotics in the feed ω. Cattle become colonized with ABS bacteria through contact with other cattle β, and the environment ε.

Antibiotic Use

Cattle receive subtherapeutic levels of antibiotics in their food continually. These antibiotics serve to inhibit the growth of bacteria, as well as to help the cattle process their feed more efficiently (growth promotion). However, constant exposure to antibiotics causes selective pressure which may lead to the development of antibiotic resistant bacteria. If cattle develop symptoms, they are treated with therapeutic levels of antibiotics, but due to the cost and time involved, cattle are not tested before treatment [37]. Thus, all symptomatic cattle, regardless of whether the infection is resistant or not, are treated with the same antibiotic. A proportion of cattle (p) from I_w respond to this treatment at rate γ and will return to H. Cattle from I_r will not recover from this treatment, and it is at this point that their resistance status will be "discovered." From this point, they will either be taken to Q for further treatment, or culled.

Horizontal Transmission

Whether the cattle are on a farm or a feedlot, they are always exposed to other cattle and environmental factors from which they may develop ABR. Therefore, at any time, cattle from H and L_w may transfer to L_r. A proportion of cattle from I_w may not respond to treatment, and instead develop an ABR infection and transfer into I_r, at rate $(1-p)\gamma$.

Bovine Respiratory Disease (BRD)

BRD is the leading cause of morbidity and mortality in cattle. It is a complex disease and highly infectious. Because stress is a major catalyst, BRD is most commonly seen after major events such as weaning and transport to a feedlot (which may involve sale at a cattle auction and cross-country travel). BRD can affect cattle at any time, but the first 30 days after transport are the most critical [15]. Signs and symptoms of BRD progress from depression, decreased appetite, increased respiratory rate, fever, and lung lesions. Cattle with BRD should be treated as early as possible; if roughly 10% of the cattle are sick, mass medication may be given to the entire herd [16]. The time to develop symptoms varies from several days to two weeks from exposure [8, 27]. In our model, a proportion of cattle in L_r and L_w pass to I_r and I_w at this rate, represented by ν and π, respectively. At this point, all symptomatic cattle (I_r and I_w) are treated with therapeutic doses of the same antibiotic used prophylactically in the general population. Cattle who remain sick, or who quickly relapse, will be assumed to carry ABR bacteria. It is assumed that cattle in L_w may develop ABR in all of the same ways as members of H.

Quarantine

Many feedlots have a hospital, or quarantine pen where sick cattle are kept for treatment. We assume that once a cow needs more than a standard round of antibiotics, it is either culled, or moved to this pen (Q), where further treatment can be administered without the risk that the disease will be spread to other cattle. From Q, a proportion of cattle recover and rejoin H, or, if treatment fails, they may be culled.

Culling

Antibiotic treatment is expensive, especially if the entire herd requires treatment. For this reason and to reduce the spread of antibiotic resistant bacteria, cattle may be culled from either I_r or Q. Conservative estimates list the mortality rate of BRD at 5-10% of those infected [22]. In addition, the rancher may decide to cull an especially sick cow, or a cow who has already suffered multiple infections, as these cattle are not worth as much at slaughter [33]. The rate of cows culled for either of these reasons will be reflected in the culling terms χ and κ.

3 Methods

Stage Structure

We track a single cohort of beef cattle through the two stages of the model, which is summarized by the flow chart in Figure 2, and given by differential equations (1 - 6). The state variables are summarized in Table 1, and parameter definitions summarized in Table 2.

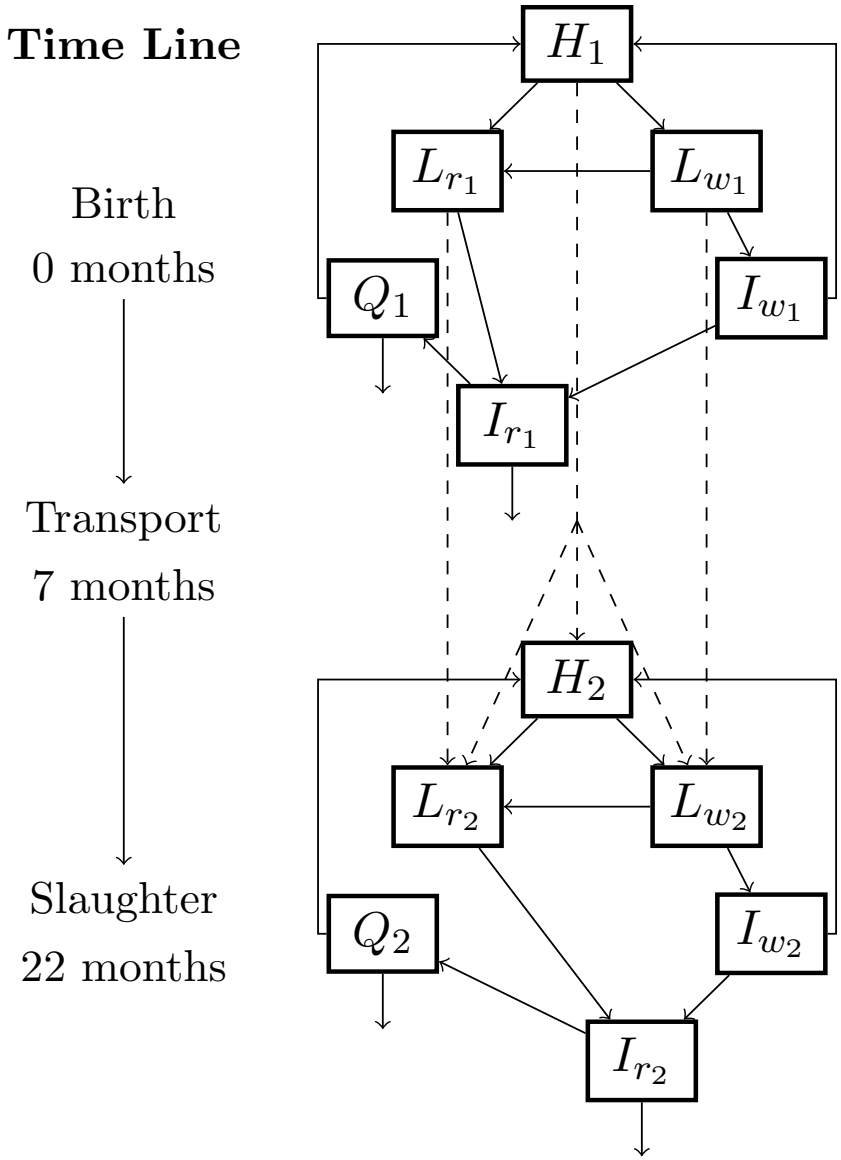

Figure 2: Flow chart illustrating stage structure

The following system of ordinary differential equations (ODEs) is used to examine the change in ABR *M. haemolystica* infected cattle:

$$\begin{aligned}
\dot{H}_i &= -\alpha_i H_i \frac{I_{r_i}}{N_i} - H_i(\phi_i + \omega_i) - \beta_i H_i \frac{I_{w_i}}{N_i} - \varepsilon_i H_i + p_i \gamma_i I_w + \sigma_i Q_i && (1)\\
\dot{L}_{r_i} &= \alpha_i H_i \frac{I_{r_i}}{N_i} + H_i(\phi_i + \omega_i) + \eta_i L_{w_i} \frac{I_{r_i}}{N_i} + L_{w_i}(\phi_i + \omega_i) - \nu_i I_{r_i} && (2)\\
\dot{L}_{w_i} &= \beta_i H_i \frac{I_{w_i}}{N_i} + \varepsilon_i H_i - \eta_i L_{w_i} \frac{I_{r_i}}{N_i} - L_{w_i}(\phi_i + \omega_i) - \pi_i I_{w_i} && (3)\\
\dot{I}_{r_i} &= \nu_i I_{r_i} + (1 - p_i)\gamma_i I_{w_i} - I_{r_i}(\psi_i + \chi_i) && (4)\\
\dot{I}_{w_i} &= \pi_i L_{w_i} - \gamma_i I_{w_i} && (5)\\
\dot{Q}_i &= \psi_i I_{r_i} - Q_i(\sigma_i + \kappa_i) && (6)
\end{aligned}$$

where $i = 1, 2$ for Stage 1 and Stage 2 respectively, and $N = H + L_r + L_w + I_r + I_w + Q$. At the beginning of the system ($t = 0$) the population enters the system healthy, therefore $N(0) = H$. Both stages use the same set of six equations but with differing parameter values to account for the change in conditions from the breeder farm to the feedlot. At the end of Stage 1 ($t = 28$weeks), the visibly healthy cows from H, L_r, and L_w will be transported to the feedlot, while the cattle in I_r, I_w, and Q will not [35]. The transition from cow-calf operation to feedlot is stressful on the cattle, and as a result, a proportion of healthy cattle contract BRD. The initial conditions for Stage 2 are given by:

$$\begin{aligned}
H_2(t_1) &= (1 - \delta)H_1(t_1)\\
L_{r_2}(t_1) &= L_{r_1}(t_1) + z\delta H_1(t_1)\\
L_{w_2}(t_1) &= L_{w_1}(t_1) + (1 - z)\delta H_1(t_1)
\end{aligned}$$

where δ is the proportion of H that develop BRD due to the stress of transport, and z is the proportion of infections with ABR *M. haemolytica*. The duration of Stage 2 is 68 weeks, at the end of which the cattle are slaughtered at 22 months (t_2) of age [35].

Because the system runs for a fixed time, not indefinitely, usual techniques of finding equilibrium points, stability analysis, and other analytical techniques are unnecessary. Instead, numerical techniques such as uncertainty quantification, graphical displays, and perturbation of parameters are used to determine the characteristics of the system.

Addition of Natural Variation

In a biological system such as a cattle feedlot, there is a lot of natural variation. This occurs in the form of farming practices, immune systems of individual cows, weather and seasonal changes, among other things. ODE systems provide information on how average behavior changes over time. However, slight changes in parameters will result in different deterministic outputs. Therefore, an ODE system may show differences that are not significant once demographic variation is taken into account [20]. In order to expand upon the results from our

deterministic model and ensure that observed differences are meaningful, a system of stochastic differential equations (SDE) is used. The stochastic equations are created from a combination of the ordinary differential equations and additional terms comprised of a random proportion of the standard deviation of each transition rate in the system [2]. Each drift term, calculated using Wiener processes, encompasses all expected variations in a given transition. The stochastic differential equations are as follows:

$$\begin{aligned}\dot{H}_i = & -\alpha_i H_i \frac{I_{r_i}}{N_i} - H_i(\phi_i + \omega_i) - \varepsilon_i H_i - \beta_i H_i \frac{I_{w_i}}{N_i} + p_i \gamma_i I_w + \sigma_i Q_i - \sqrt{\alpha_i H_i \frac{I_{r_i}}{N_i}}\, W_1 \\ & - \sqrt{H_i(\phi_i + \omega_i)}\, W_2 - \sqrt{\varepsilon_i H_i}\, W_3 - \sqrt{\beta_i H_i \frac{I_{w_i}}{N_i}}\, W_4 + \sqrt{p_i \gamma_i I_w}\, W_4 + \sqrt{\sigma_i Q_i}\, W_6 \end{aligned} \tag{7}$$

$$\begin{aligned}\dot{L}_{r_i} = & \alpha_i H_i \frac{I_{r_i}}{N_i} + H_i(\phi_i + \omega_i) + \eta_i L_{w_i} \frac{L_{r_i}}{N_i} + L_{w_i}(\phi_i + \omega_i) - \nu_i I_{r_i} + \sqrt{\alpha_i H_i \frac{I_{r_i}}{N_i}}\, W_1 \\ & + \sqrt{H_i(\phi_i + \omega_i)}\, W_2 + \sqrt{\eta_i L_{w_i} \frac{I_{r_i}}{N_i}}\, W_7 + \sqrt{L_{w_i}(\phi_i + \omega_i)}\, W_8 - \sqrt{\nu_i I_{r_i}}\, W_9 \end{aligned} \tag{8}$$

$$\begin{aligned}\dot{L}_{w_i} = & \beta_i H_i \frac{I_{w_i}}{N_i} + \varepsilon_i H_i - \eta_i L_{w_i} \frac{I_{r_i}}{N_i} - L_{w_i}(\phi_i + \omega_i) - \pi_i I_{w_i} + \sqrt{\beta_i H_i \frac{I_{w_i}}{N_i}}\, W_4 \\ & + \sqrt{\varepsilon_i H_i}\, W_3 - \sqrt{\eta_i L_{w_i} \frac{I_{r_i}}{N_i}}\, W_7 - \sqrt{L_{w_i}(\phi_i + \omega_i)}\, W_8 - \sqrt{\pi_i I_{w_i}}\, W_{10} \end{aligned} \tag{9}$$

$$\begin{aligned}\dot{I}_{r_i} = & \nu_i I_{r_i} + (1 - p_i)\gamma_i I_{w_i} - I_{r_i}(\psi_i + \chi_i) + \sqrt{\nu_i I_{r_i}}\, W_9 + \sqrt{(1 - p_i)\gamma_i I_{w_i}}\, W_{11} \\ & - \sqrt{I_{r_i}(\psi_i}\, W_{12} - \sqrt{\chi_i I_{r_i}}\, W_{13} \end{aligned} \tag{10}$$

$$\dot{I}_{w_i} = \pi_i L_{w_i} - \gamma_i I_{w_i} + \sqrt{\pi_i L_{w_i}}\, W_{10} - \sqrt{\gamma_i I_{w_i}}\, W_6 \tag{11}$$

$$\dot{Q}_i = \psi_i I_{r_i} - Q_i(\sigma_i + \kappa_i) + \sqrt{\psi_i I_{r_i}}\, W_{13} - \sqrt{\sigma_i Q_i}\, W_6 - \sqrt{\kappa_i Q_i}\, W_{14} \tag{12}$$

where $i = 1, 2$ for Stage 1 and Stage 2, and $j = 1, 2, ..., 14$ for the Wiener trajectories where each transition rate has a corresponding W. See Table 4 in the appendix for a layout of the transitions for each random event. Each W_j corresponds to a random number from a *iid* $W_j \sim N(0, 1)$. For a more complete theoretical discussion of the stochastic process used in this paper, refer to Allen *et al.* [2].

4 Parameter Estimation

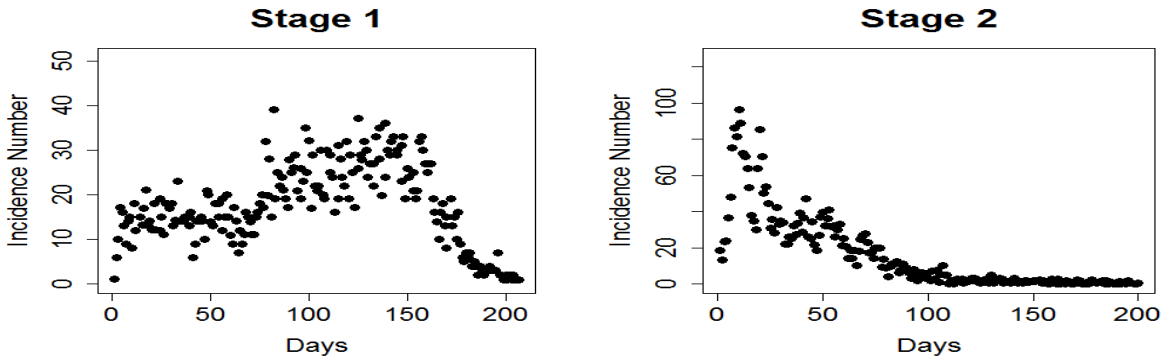

Figure 3: Daily incidence of BRD for 31,243 calves and 18,112 feedlot cattle (data from [36, 37])

Parameter values were found primarily in literature. Those that were not found were estimated using the data provided in Snowder *et al.* (2005) and (2006) for Stage 1 and 2 respectively [36, 37]. All values were assumed to be the same for Stage 1 and Stage 2 unless otherwise stated.

Terms α, β and η represent effective contact rates between infectious and healthy or latent cattle respectively. *M. haemolytica* is not directly contagious between cattle [38]. Instead, Bovine Respiratory Disease (BRD) is spread through a population via the contagiousness of viruses. Viruses associated with BRD have a 30% chance of causing enough damage for *M. haemolytica* to develop into BRD [30]. We assume that 1 contact per week per cow is sufficient to transmit the virus. Therefore, assuming that each cow comes into contact with at least 1 other cow once per week and that proportions of sick cattle are similar in each pen, α, β and η will be represented by: $(\frac{3 \text{ BRD cases}}{10 \text{ contacts}})(1 \frac{\text{contacts}}{\text{week}}) = 0.3\frac{\text{BRD cases}}{\text{week}}$.

The rate at which cattle develop antibiotic resistance (ABR) due to selective pressure by medicated feed (ω) was calculated by observing the change in antibiotic susceptibilities over several years. Based on these changes, rate of developing ABR ranges from $\frac{0.0002}{\text{week}}$ to $\frac{0.001}{\text{week}}$ [17]. An arbitrary value of $\frac{0.0005}{\text{week}}$ was selected.

The proportion of successful treatments, p, was found to range from 0.71 to 0.86 with a best estimate of 0.86 [17, 41]. Average duration of treatment ranges from 3 days to 2 weeks [4, 8, 26]. A recommended treatment duration of 2 weeks was selected, resulting in a value of $\frac{1}{2\text{weeks}}$ for γ [27]. This value was also used for ψ as it is assumed that after 1 round of treatment fails, cattle will be brought to quarantine.

Average amount of time spent in quarantine was found to be 30 days [31] while the probability of successful treatment was found to be 0.389 [41]. A value of σ was calculated to be: $(0.389)(\frac{7}{30\text{weeks}})=\frac{0.091}{\text{weeks}}$ while the κ was calculated to be $(1-0.389)(\frac{7}{30\text{weeks}})=\frac{0.142}{\text{weeks}}$.

The culling rate from I_r, χ, varies greatly as it is up to a farmer's discretion whether or not a cow should be quarantined or killed. A minimal value of $\frac{0.001}{\text{weeks}}$ was arbitrarily selected.

Data fitting using least square analysis was used to estimate values for ϕ, ε, and π. Rates

of developing symptoms from the latent classes π and ν, were assumed to be equal. Parameter estimation for Stage 1 revealed the following: $\pi = \nu = \frac{0.1156}{\text{week}}$, $\phi = \frac{0.0000175}{\text{week}}$ and $\varepsilon = \frac{0.0089}{\text{week}}$. For Stage 2, the values were estimated to be: $\pi = \nu = \frac{0.00429}{\text{week}}$, $\phi = \frac{0.000492}{\text{week}}$ and $\varepsilon = \frac{0.00967}{\text{week}}$. Values were fitted to data shown in Figure 3.

Alternative values of ω and ε were also estimated to predict changes in incidences of ABR and illness that will occur after 2017 legislation is put into action. $\hat{\omega}$ was set to $\frac{0}{\text{weeks}}$ as it would be ideal that selective pressures would be completely removed once antibiotics are no longer included in feed. Additionally, ε is increased by a factor of 1.3 as that is the estimated rate increase for developing bacterial infections in the absence of daily antibiotics. Therefore, $\hat{\varepsilon}_i = 1.3\ \varepsilon_i$ [18].

Parm.	Definition	Estimate	Reference
$\alpha_1,\ \alpha_2$	Effective rate of contact from L_r to H	0.3/week	[30, 38]
$\beta_1,\ \beta_2$	Effective rate of contact from L_r to L_w	0.3/week	[30, 38]
$\eta_1,\ \eta_2$	Effective rate of contact from I_w to H	0.3/week	[30, 38]
ϕ_1	Rate of contracting ABR infection from environment	.0000175/week	
ϕ_2		.000492/week	
$\omega_1,\ \omega_2$	Rate of spontaneous development of resistance due to interaction with antibiotics	0.0005/week	[17]
ε_1	Rate of developing ABS infection due to environment,	.0089/week	
ε_2	stress, etc (amplification of bacteria)	.00967/week	
$\gamma_1,\ \gamma_2$	Rate of treatment in I_w	0.5/week	[4, 8, 26, 27]
$p_1,\ p_2,$	Proportion of successful treatment in I_w	0.86	[17, 41]
$\sigma_1,\ \sigma_2$	Rate of successful treatment in Q	0.091/week	[31, 41]
ν_1	Rate of developing symptoms from L_r	.1156/week	
ν_2		.00429/week	
π_1	Rate of developing symptoms from L_w	.1156/week	
π_2		.00429/week	
$\psi_1,\ \psi_2$	Rate of going to Q from L_r	0.5/week	[4, 8, 26, 27]
$\chi_1,\ \chi_2$	Culling rate from I_r	0.001/week	
$\kappa_1,\ \kappa_2$	Culling rate from Q	0.142/week	[31, 41]
	Transition to Stage 2		
δ	Proportion of cattle infected due to travel	0.105	[10, 32]
z	Proportion of travel-induced ABR infections	0.02	[17, 22]
	2017 Legislation		
$\hat{\omega}$	Rate of spontaneous development of resistance due to interaction with antibiotics	0/week	
$\hat{\varepsilon}_1$	Rate of developing ABS infection due to environment,	1.3 ε_1/week	[18]
$\hat{\varepsilon}_2$	stress, etc (amplification of bacteria)	1.3 ε_2/week	

Table 2: Parameter Descriptions and Values

5 Numerical Simulations

ODE Results

Figure 4 shows the number of cattle in each compartment over time using parameter values representative of current practices (Table 2). This pattern is compared to Figure 5, which displays the predicted number of cattle in each compartment after the new legislation is put into place. Comparisons between the two figures predict an increase in the number of cattle colonized with latent antibiotic susceptible (ABS) bacteria along with a drop in the number of healthy cattle and cattle colonized with latent antibiotic resistant (ABR) bacteria. An increase in the latent class size indicates an increased risk of cattle developing ABS infection after 2017. These results are consistent with previous predictions that after new legislation is implemented, the number of cattle with some level of bacterial colonization will increase [24].

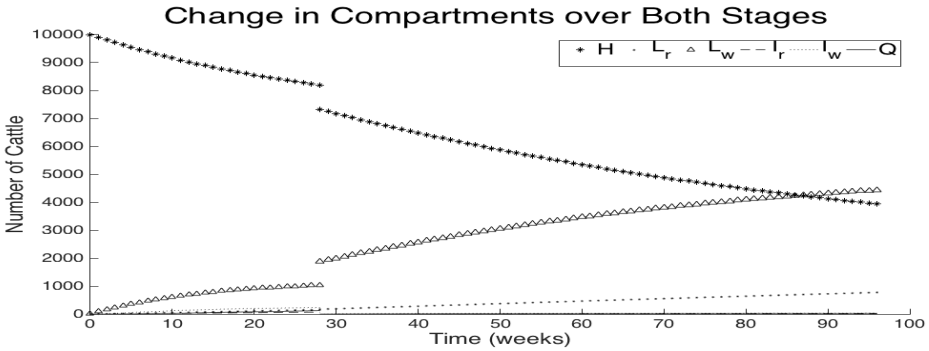

Figure 4: Change in classes during current practices

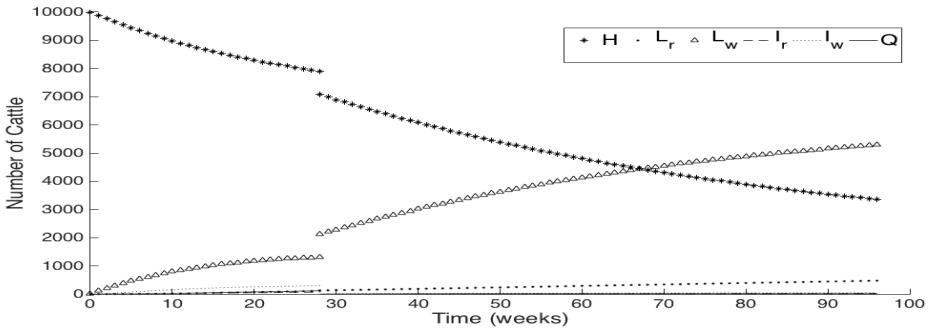

Figure 5: Change in classes under new legislation

Additional numerical analysis of the model focused on the proportion of observably healthy cattle colonized by ABR *M. haemolytica*, Ω, the ratio of cattle with ABR to the observably healthy cattle, Λ; and the proportion of the total herd that appear healthy, Θ.

$$\begin{aligned}
\Omega &= \frac{L_r}{H + L_r + L_w} \\
\Lambda &= \frac{L_r + I_r + Q}{H + L_r + L_w} \\
\Theta &= \frac{H + L_r + L_w}{H + L_r + L_w + I_r + I_w + Q}
\end{aligned}$$

Minimizing Ω at t_1 (28 weeks) results in the fewest number of cattle colonized with ABR bacteria that are moved to the feedlot. At t_2 (96 weeks), minimizing Ω results in the smallest proportion of ABR bacteria to possibly get into food. Minimizing Λ reduces the contribution of cattle to the reservoir of ABR. Because fewer than 1% of cattle are in both the I_r and Q classes at any point in time, the difference between Λ and Ω is negligible; therefore, results focus only on Ω. In Stage 1, Θ is the proportion of cattle that move to the feedlot at time t_1, and in Stage 2 Θ is the proportion of cattle that get slaughtered at time t_2. Maximizing Θ at t_1 and t_2 results in the highest proportion of profitable cattle, but not necessarily the highest number as minimizing death is not taken into account. Furthermore, each proportion is relative to the stage and number of other cattle in the system at each point in time and not to the initial number of cattle entered into the system. Therefore, all graphical representations of Θ are analyzed in the context of Ω.

Under current antibiotic use, the objective functions reveal that over 22 months, the proportion of cattle with ABR increases while the proportion of observably healthy cattle decreases slightly (Fig. 6). Additionally, comparing outputs of objective functions under current legislation to predictions for 2017 reveals a drop in the proportion of cattle with ABR bacteria at slaughter (Ω) after legislation is put into place. However, the proportion of observably healthy cattle (Θ) only shows a slight difference in Stage 1, with no discernible differences in Stage 2 when comparing 2016 to 2017.

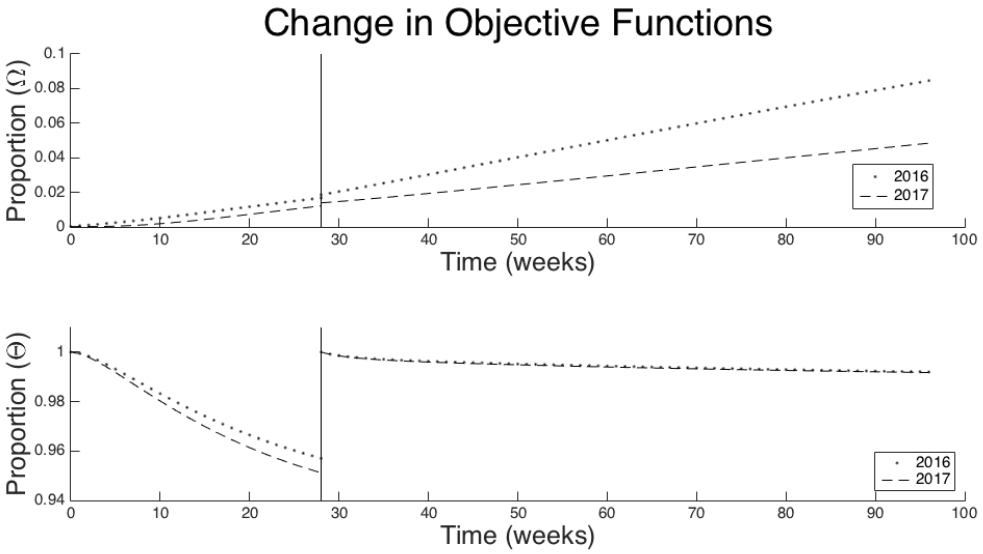

Figure 6: Outputs of ODE Solved Numerically

Uncertainty Quantification & Sensitivity Analysis

Uncertainty Quantification (UQ) is a global sensitivity analysis that assesses the impact of variation in each parameter on the output of interest. This report uses Latin Hypercube Sampling (LHS) along with Partial Rank Correlation Coefficient (PRCC) to analyze how sensitive Ω and Θ are to a change in each parameter [6, 7]. Intervals of $\pm 10\%$ of nominal values found in Table 2 were used for the LHS and assumed to be uniformly distributed.

UQ reveals that under current legislation, the proportion of slaughtered cattle colonized by antibiotic resistant (ABR) bacteria (Ω) is most sensitive to the probability of successful treatment (p), the rate at which infectious cattle are brought into quarantine (ψ), and the rate of developing ABR *M. haemolytica* through feed and the environment (ω and ϕ) (Fig. 7). Therefore, the most meaningful changes would result from decreasing parameters ϕ, and ω and increasing p and ψ (Fig. 7).

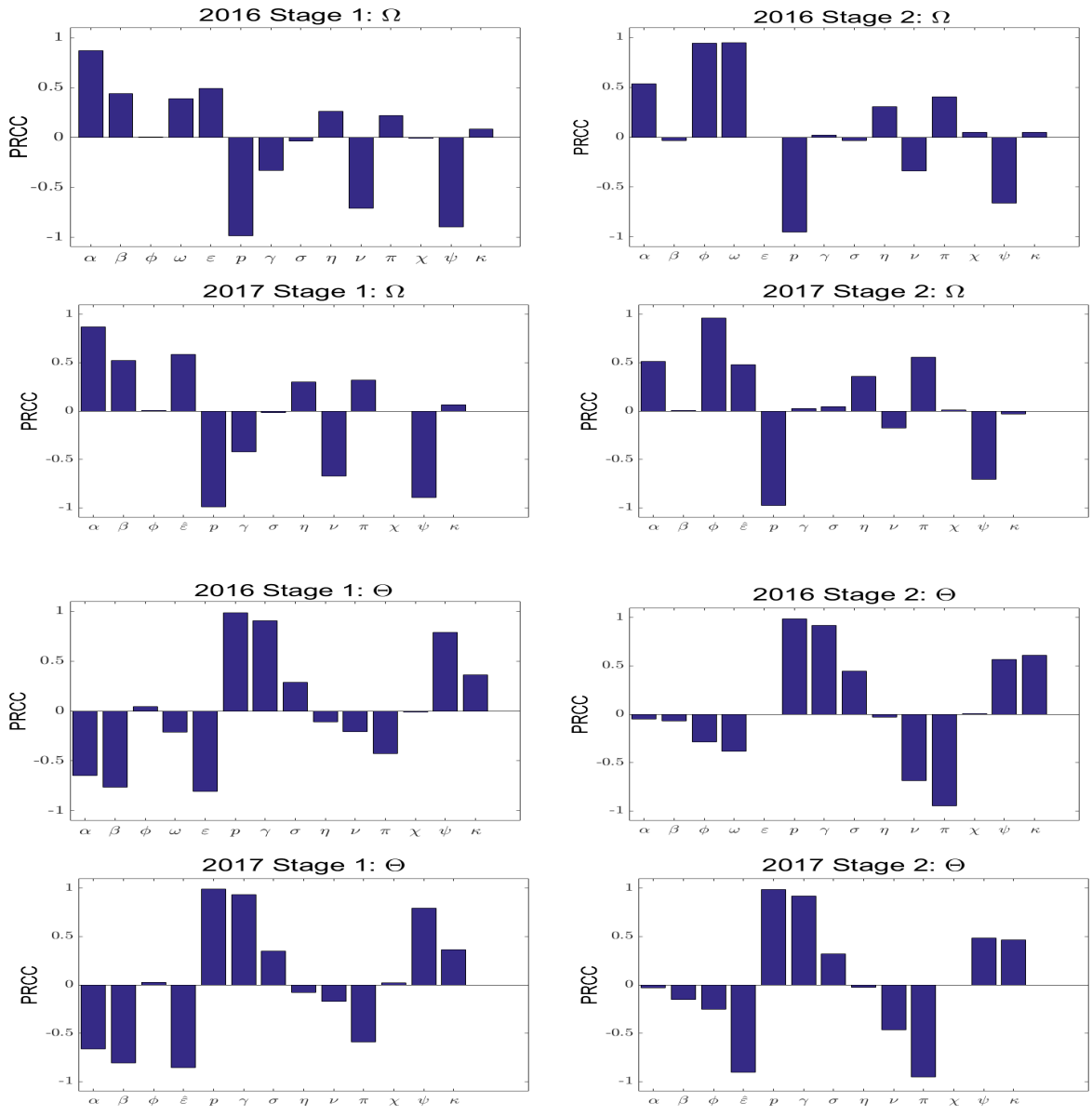

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Figure 7: Uncertainty Quantification for Ω and Θ for 2016 and 2017, specific PRCC values can be found in the Appendix in Tables 5, 6, 7, and 8

Normalized Sensitivity Analysis (SA) shows changes in the output's sensitivity over time as a result of a 1% change in one input parameter. Observed parameters include: $\varepsilon, \phi, \psi, \chi$ and κ (Fig. 8). These values were selected due to their ability to be biologically manipulated through sanitation, changes in quarantine rates or capacity, as well as culling rates. SA values show at what point measures to reduce ABR would be most effective. In Stage 1, environment (ε) and quarantine (ψ) have the largest impact on Ω. After the 2017 legislation is put into place, ε is predicted to influence the cattle earlier and with greater impact. Therefore, efforts to decrease rates of ABR from the environment via sanitation should be directed towards cow-calf operations, especially after 2017. In Stage 2, ABR bacteria from the environment (ϕ) and quarantine (ψ) have the largest impact on Ω.

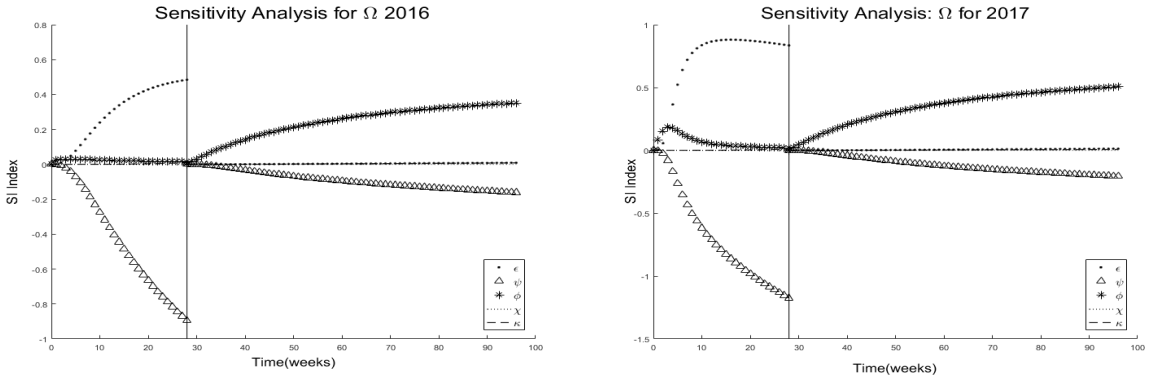

Figure 8: Sensitivity analysis for Ω in both 2016 and 2017

Parameter Perturbation

The practice of quarantine and culling are arguably the most simple parameters to alter as both are already in practice at cow-calf operations and feedlots. In order to examine their influence on the system, parameters ψ and χ are varied while numerically analyzing the changes in Ω and Θ. The minimum value of each function is then estimated to find the rates of ψ and χ that result in the most ideal outputs.

Figure 9 reveals that culling and quarantine rates have an effect on reducing Ω. The proportion of slaughtered cattle with ABR decreases as ψ increases; for values of $\psi < 0.5$ per week a sharp decrease is observed. The decrease is less dramatic for $\psi > 1$ per week. Similar patterns are observed for χ. Therefore, values between 0.5 and 1 per week would be ideal for maximizing efficiency in reducing incidences of ABR in cattle.

After new legislation is enacted, parameter perturbations predict an overall drop in Ω. Values between 0.5 and 1 per week are still most efficient for ψ and χ. However, values below 0.5 per week show marked improvement over current scenarios. This is beneficial because risk of infection with antibiotic susceptible *M. haemolytica* is increased without suppression of bacterial growth by antibiotics. Therefore, while increased rates of quarantine or culling may not

be realistic, the ratio of cattle with latent ABR bacteria at slaughter should still decrease in comparison to current practices.

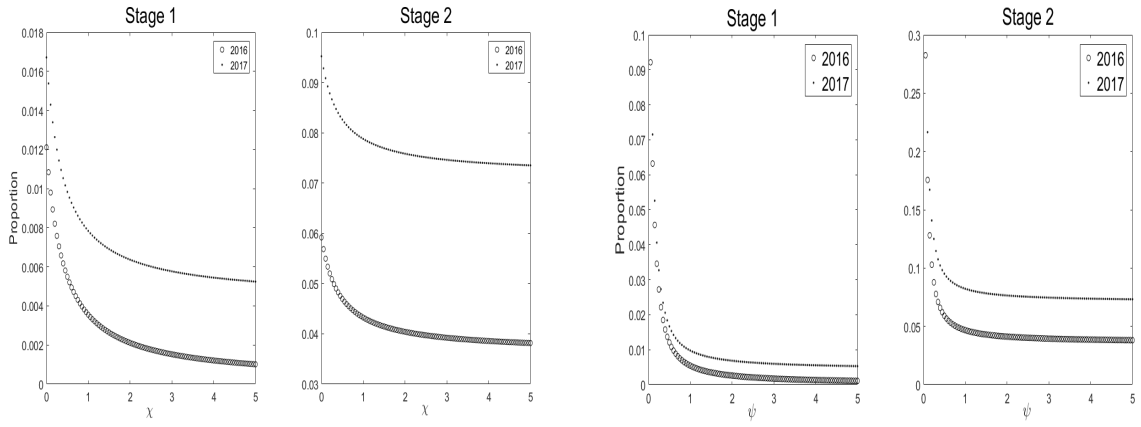

Figure 9: Parameter perturbations and changes in Ω over time

SDE Results

Cattle are often exposed to the elements; thus, changes in weather and seasons affect the health of the cattle. To account for this variation in circumstances, and therefore to ensure that the differences in results obtained using the ODE system are meaningful, and not due to random chance, an SDE system is employed. The model is run through both stages for each iteration of the stochastic process, and the initial conditions for the second stage are obtained via the same method used for the ODE system. The distribution of both outputs at t_2 (Fig. 10) allows for assessment of the difference between outputs before and after new legislation. Along with the distribution of Ω and Θ, Table 3 gives the summary statistics for each output for both years. The Kolmogorov-Smirnov (KS) two-sample test is employed to test the differences [13]. The difference between the distributions Ω before and after 2017 legislation significantly differ ($D = 1, p =$ 2.2E-16). However, for Θ, no statistical or practical differences are found ($D = 0.12, p = .8693$). Similar results can be obtained through other statistical tests such as a t-test for differences between the means of each distribution.

The proportion of slaughtered cattle with antibiotic resistant (ABR) bacteria (Ω) significantly decreased from 2016 to 2017. The model also predicts that the proportion of observably healthy cattle does not decrease after legislation is implemented, and thus profit may not decrease due to health of cattle.

Variable	Year	Mean	Std. Dev.	Min.	Med.	Max.
Ω	2016	0.0847	0.0031	0.0747	0.0847	0.0928
	2017	0.0524	0.0027	0.0433	0.0523	0.0605
Λ	2016	0.0886	0.0032	0.0779	0.0886	0.0974
	2017	0.0558	0.0029	0.0457	0.0558	0.0656
Θ	2016	0.9919	0.0009	0.9889	0.9920	.9955
	2017	0.9917	0.0010	0.9883	0.9917	0.9943
N			1000			

Table 3: SDE output summary statistics for 2016 and 2017, where N is the number of different stochastic runs.

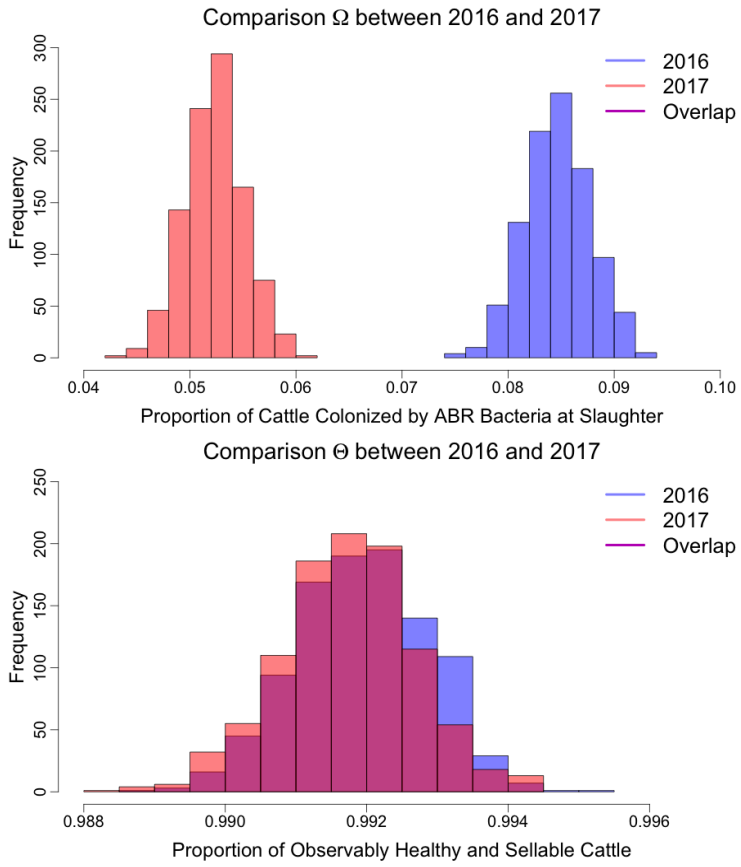

Figure 10: Comparison of distributions of Ω, and Θ at t_2 between 2016 and 2017.

6 Discussion

Antibiotic resistance and the potential spread of ABR bacteria between humans and animals is an important but complex issue. ABR *M. haemolytica* in beef cattle is just one small part of the issue. However, using mathematical models, it is possible to better understand the spread of resistance and formulate targeted strategies to combat the issue. After January 1, 2017, the Veterinary Feed Directive (VFD) will restrict the use of antibiotics to prescription by a veterinarian. This model shows that decreasing or eliminating antibiotics in cattle feed will successfully reduce the proportion of cattle with ABR at slaughter by an average of 3.2%. However, this change comes with the possibility of increased levels of infection throughout the cattle population. This model predicts that after 2017, efforts to reduce ABR in cattle will be most effectively placed in improving successful treatment rates, detecting infectious cattle earlier, and increasing sanitation of the environment.

The ideal rate of isolation occurs within two weeks of cattle showing symptoms. After the VFD is put into place, ideal quarantine rates will continue to be 0.5 to 1 per week, with an overall drop in the proportion of cattle with ABR at slaughter. Distributions of the proportions of cattle with ABR at slaughter in 2016 and 2017 are statistically different, with 2017 being visibly lower. Our model predicts that not only will the VFD significantly reduce the spread of ABR bacteria within a cattle population, but that overall health of herd will not significantly decline.

Accuracy of this model could be improved by better parameter estimations. Biological accuracy of parameters were affected by the lack of data. Inclusion of a spontaneous recovery rates could help provide a more accurate picture. Because cattle spend a majority of their lives outdoors, environmental factors such as weather and seasonal conditions play a major role in BRD. Additionally, the majority of cattle with asymptomatic BRD are not discovered until after slaughter. While current options are cost prohibitive, testing cattle for ABR periodically during the two stages of life would provide a basis for understanding the progression of resistance through the cohort. Future directions may include incorporating reinfection history as well as profit according to the number of times cattle have been infected.

Although this model is a simplification of reality, results indicate that isolation and culling, as well as early detection of disease and sanitation, are effective in slowing ABR in beef cattle. These strategies make a significant difference, not just in the cattle population, but in the environment which affects humans. This conclusion provides motivation to continue efforts to better understand and address BRD and antibiotic use in cattle. By diligent and deliberate care of food animals, the spread of antibiotic resistant bacteria can be slowed, saving antibiotics for the life-saving measures for which they were first designed.

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Appendix

Event	Transition	Rate	Wiener Trajectory
$H \to L_r$	(-1 1 0 0 0 0)	$\alpha \frac{I_r}{N}$	W_1
$H \to L_r$	(-1 1 0 0 0 0)	$\phi + \omega$	W_2
$H \to L_w$	(-1 0 1 0 0 0)	$\eta \frac{I_w}{N}$	W_3
$H \to L_w$	(-1 0 1 0 0 0)	ε	W_4
$I_w \to H$	(1 0 0 0 -1 0)	$p\gamma$	W_5
$Q \to H$	(1 0 0 0 -1 0)	σ	W_6
$L_w \to L_r$	(0 1 -1 0 0 0)	$\beta \frac{I_r}{N}$	W_7
$L_w \to L_r$	(0 1 -1 0 0 0)	$\phi + \omega$	W_8
$L_w \to I_w$	(0 0 -1 0 1 0)	π	W_9
$L_r \to I_r$	(0 -1 0 1 0 0)	ν	W_{10}
$I_w \to I_r$	(0 0 0 1 -1 0)	$(1-p)\gamma$	W_{11}
$I_r \to Q$	(0 0 0 -1 0 1)	ψ	W_{12}
$I_r \to out$	(0 0 0 -1 0 0)	χ	W_{13}
$Q \to out$	(0 0 0 0 0 -1)	κ	W_{14}
	$(H\ L_r\ L_w\ I_r\ I_w\ Q)$		

Table 4: Description of transitions including rates and random Wiener trajectory used in the stochastic differential equations. For a more theoretical discussion of the transitions and breakdown of the stochastic process, look to Allen et al. (2008) [2]

Ω			Λ			Θ		
Par.	PRCC	P-Value	Par.	PRCC	P-Value	Par.	PRCC	P-Value
α	-0.6497	$1.9920e-119$	α	0.8556	$5.3596e-284$	α	0.8733	$6.3284e-310$
β	-0.7676	$1.7584e-192$	β	0.5634	$9.6252e-84$	β	0.4420	$1.8414e-48$
ϕ	0.0430	$1.7679e-01$	ϕ	-0.0089	$7.7908e-01$	ϕ	0.0050	$8.7570e-01$
ω	-0.2127	$1.4501e-11$	ω	0.3630	$4.2024e-32$	ω	0.3894	$4.3109e-37$
ϵ	-0.8080	$1.4052e-228$	ϵ	0.6109	$5.1195e-102$	ϵ	0.4940	$7.4433e-62$
p	0.9849	$0.0000e+00$	p	-0.9908	$0.0000e+00$	p	-0.9846	$0.0000e+00$
γ	0.9036	$0.0000e+00$	γ	-0.4695	$2.9209e-55$	γ	-0.3297	$1.8908e-26$
σ	0.2889	$1.9747e-20$	σ	-0.2307	$2.1457e-13$	σ	-0.0349	$2.7308e-01$
η	-0.1084	$6.4638e-04$	η	0.2380	$3.5642e-14$	η	0.2650	$2.4920e-17$
ν	-0.2085	$3.6791e-11$	ν	-0.3799	$3.1217e-35$	ν	-0.7114	$4.6930e-153$
π	-0.4263	$7.5035e-45$	π	0.2893	$1.7797e-20$	π	0.2200	$2.7549e-12$
χ	-0.0123	$6.9996e-01$	χ	0.0086	$7.8698e-01$	χ	-0.0073	$8.1883e-01$
ψ	0.7903	$9.7871e-212$	ψ	-0.9047	$0.0000e+00$	ψ	-0.8974	$0.0000e+00$
κ	0.3623	$5.6053e-32$	κ	-0.2358	$6.1072e-14$	κ	0.0865	$6.5486e-03$

Table 5: Uncertainty quantification for Stage 1 in 2016

Ω			Λ			Θ		
Par.	PRCC	P-Value	Par.	PRCC	P-Value	Par.	PRCC	P-Value
α	-0.6650	$3.7333e-127$	α	0.8469	$1.1728e-272$	α	0.8708	$2.6626e-306$
β	-0.8101	$7.5661e-231$	β	0.6125	$8.6387e-103$	β	0.5233	$1.5171e-70$
ϕ	0.0281	$3.7833e-01$	ϕ	0.0176	$5.7982e-01$	ϕ	0.0074	$8.1584e-01$
ϵ	-0.8564	$2.2181e-285$	ϵ	0.6842	$2.5185e-137$	ϵ	0.5862	$2.9639e-92$
p	0.9902	$0.0000e+00$	p	-0.9935	$0.0000e+00$	p	-0.9900	$0.0000e+00$
γ	0.9336	$0.0000e+00$	γ	-0.5407	$4.3898e-76$	γ	-0.4219	$6.4494e-44$
σ	0.3510	$4.9933e-30$	σ	-0.2332	$1.1512e-13$	σ	-0.0162	$6.1126e-01$
η	-0.0804	$1.1518e-02$	η	0.2605	$8.7320e-17$	η	0.3011	$3.8018e-22$
ν	-0.1727	$4.6647e-08$	ν	-0.3583	$2.7200e-31$	ν	-0.6731	$2.4827e-131$
π	-0.5896	$1.5381e-93$	π	0.3878	$8.3678e-37$	π	0.3187	$9.2152e-25$
χ	0.0214	$5.0080e-01$	χ	-0.0047	$8.8190e-01$	χ	-0.0014	$9.6569e-01$
ψ	0.7936	$5.5007e-215$	ψ	-0.8992	$0.0000e+00$	ψ	-0.8971	$0.0000e+00$
κ	0.3629	$3.9900e-32$	κ	-0.2382	$3.2646e-14$	κ	0.0668	$3.5843e-02$

Table 6: Uncertainty quantification for Stage 1 in 2017

Ω			Λ			Θ		
Par.	PRCC	P-Value	Par.	PRCC	P-Value	Par.	PRCC	P-Value
α	-0.0519	$1.0288e-01$	α	0.5103	$1.5036e-66$	α	0.5363	$1.3418e-74$
β	-0.0712	$2.5373e-02$	β	-0.0375	$2.3974e-01$	β	-0.0356	$2.6355e-01$
ϕ	-0.2879	$2.7304e-20$	ϕ	0.9374	$0.0000e+00$	ϕ	0.9454	$0.0000e+00$
ω	-0.3832	$6.9694e-36$	ω	0.9400	$0.0000e+00$	ω	0.9478	$0.0000e+00$
ϵ	NaN	NaN	ϵ	NaN	NaN	ϵ	NaN	NaN
p	0.9880	$0.0000e+00$	p	-0.9663	$0.0000e+00$	p	-0.9514	$0.0000e+00$
γ	0.9170	$0.0000e+00$	γ	0.0105	$7.4160e-01$	γ	0.0220	$4.9037e-01$
σ	0.4479	$7.2597e-50$	σ	-0.0967	$2.3661e-03$	σ	-0.0351	$2.7070e-01$
η	-0.0316	$3.2097e-01$	η	0.2841	$8.7907e-20$	η	0.3055	$8.9933e-23$
ν	-0.6870	$8.9231e-139$	ν	-0.1858	$4.0672e-09$	ν	-0.3372	$1.1473e-27$
π	-0.9470	$0.0000e+00$	π	0.4613	$3.6316e-53$	π	0.4037	$5.6643e-40$
χ	0.0085	$7.8980e-01$	χ	0.0524	$9.9931e-02$	χ	0.0482	$1.3043e-01$
ψ	0.5674	$3.6619e-85$	ψ	-0.6776	$1.3282e-133$	ψ	-0.6646	$8.5915e-127$
κ	0.6120	$1.7853e-102$	κ	-0.0639	$4.4734e-02$	κ	0.0479	$1.3303e-01$

Table 7: Uncertainty quantification for Stage 2 in 2016

Ω			Λ			Θ		
Par.	PRCC	P-Value	Par.	PRCC	P-Value	Par.	PRCC	P-Value
α	-0.0322	$3.1213e-01$	α	0.4988	$2.8516e-63$	α	0.5151	$4.6606e-68$
β	-0.1525	$1.4580e-06$	β	0.0119	$7.0938e-01$	β	0.0089	$7.7944e-01$
ϕ	-0.2540	$5.1392e-16$	ϕ	0.9565	$0.0000e+00$	ϕ	0.9603	$0.0000e+00$
ϵ	-0.9056	$0.0000e+00$	ϵ	0.5419	$1.7617e-76$	ϵ	0.4783	$1.2856e-57$
p	0.9889	$0.0000e+00$	p	-0.9853	$0.0000e+00$	p	-0.9774	$0.0000e+00$
γ	0.9210	$0.0000e+00$	γ	0.0276	$3.8585e-01$	γ	0.0274	$3.8989e-01$
σ	0.3228	$2.1557e-25$	σ	-0.0313	$3.2532e-01$	σ	0.0474	$1.3651e-01$
η	-0.0249	$4.3349e-01$	η	0.3572	$4.2058e-31$	η	0.3601	$1.2654e-31$
ν	-0.4661	$1.9930e-54$	ν	-0.0706	$2.6511e-02$	ν	-0.1775	$1.9484e-08$
π	-0.9512	$0.0000e+00$	π	0.6391	$1.6253e-114$	π	0.5574	$1.0248e-81$
χ	-0.0026	$9.3533e-01$	χ	0.0079	$8.0442e-01$	χ	0.0105	$7.4277e-01$
ψ	0.4850	$1.9564e-59$	ψ	-0.7216	$1.1346e-159$	ψ	-0.7047	$3.9121e-149$
κ	0.4678	$7.2265e-55$	κ	-0.1362	$1.7318e-05$	κ	-0.0293	$3.5806e-01$

Table 8: Uncertainty quantification for Stage 2 in 2017