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# From Big Farm to Big Pharma: A Differential Equations Model of Antibiotic-Resistant Salmonella in Industrial Poultry Populations

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# From Big Farm to Big Pharma:
# A Differential Equations Model of Antibiotic-Resistant *Salmonella* in Industrial Poultry Populations

by

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# Chapter 1

# Background

## 1.1 Introduction

The emergence of antibiotic resistance in bacterial pathogens presents a great challenge to public health. Antibiotic resistance occurs when a bacterial infection is no longer effectively treated by a particular class of antibiotics, or when that strain of bacteria has evolved mechanisms of avoiding the action of the antibiotic. This leads to longer treatment periods or higher dosages of drugs becoming necessary to treat such antibiotic-resistant infections [31],[33]. Bacteria can become resistant to multiple classes of antibiotics, and infections caused by multidrug-resistant bacteria are even harder to treat. This results in higher treatment costs and higher mortality associated with antibiotic-resistant infections as compared to infections by antibiotic-susceptible bacteria, as the standard antibiotics can not be used to combat these antibiotic-resistant infections. Estimates for the yearly cost of treating antibiotic-resistant infections in the U.S. range from $100 million to $34 billion [14],[22],[29],[32].

The use of antibiotics for growth promotion and prophylactic, or preventative, treatment in industrial livestock production has been linked with the increasing prevalence of antibi-

otic resistance [4],[15],[17],[22],[23],[28],[39]. About 80% of antibiotics sold in the United States are used in livestock production, and 70% of the antibiotics given to food animals are classified as medically important for humans [29]. These medically important antibiotics are used to treat human diseases as well, so if resistance to them arises from agricultural antibiotic use, it will be harder to use these drugs to treat human illness. In industrial livestock production, antibiotics are used as growth promoters, as prophylactic treatment of bacterial infections, and as therapeutic agents for active bacterial infections. First, administering sub-therapeutic levels of antibiotics in animal feed has been shown to lead to weight gain [2] which translates to a higher profit per animal produced. Giving antibiotics as preventative treatment for common livestock diseases is also profitable, as it allows more animals to be raised in confined spaces while maintaining overall herd health. However, in both growth promotion and prophylactic uses of antibiotics, bacteria populations within the animals and their environment are exposed to consistent levels of the antibiotic, and resistance to the antibiotic is therefore selected for in these populations. Concern for the development of antibiotic resistance through antibiotic growth promotion is so great that many nations, including the U.S. and much of the E.U., have banned the use of antibiotics as growth promoters [11]. Enforcement of these laws is somewhat difficult, however, given that it is hard to tell whether antibiotics are being used to promote growth or reduce disease [11].

Once resistant infections develop in animal populations, they can spread to humans through contact between animals and farm workers, through individuals handling or consuming raw or under-cooked meat products carrying drug-resistant bacteria, or through environmental exposure to the antibiotic-resistant bacteria in the farm [11]. The last few decades have seen a rise in antibiotic resistance among pathogens of particular concern, including food-borne illnesses such as *Salmonella* spp., *Campylobacter* spp., *Listeria* spp., and *E. Coli*, all of which likely stem from animal agriculture [11],[22].

Our goal for this project is to use differential equations to model the development of antibiotic resistance in *Salmonella enterica* in concentrated animal feeding operation (CAFO) chicken populations, and how this antibiotic resistance affects human consumers of chicken products. More specifically, we are interested in modeling and comparing the financial burden on the human health sector for treating antibiotic resistant infections of *Salmonella* to the financial benefit to the farmers of using antibiotics, either for growth promotion or prophylaxis. *Salmonella* is one of the most common causes of food-borne infections and has been documented developing resistance to several classes of antibiotics, so it was a natural choice to focus our model around this particular bacteria. Chicken populations were chosen because they are the most common source of the infection in humans. It is our hope that the general principles of this model could be applied to other bacterial infections or other industrial livestock populations.

In Chapter 1 of this thesis, we will explore the biological motivation for our project: how antibiotic resistance is acquired and amplified in a population, and how antibiotic resistance in *Salmonella* affects human health. We will also briefly discuss the SIR model and the previous work in mathematical modeling of Salmonellosis infections. In Chapter 2, we will explain and present our model: a series of two interrelated modified SIR models of the spread of antibiotic-resistant *Salmonella* in chicken and human populations. Chapter 3 will consist of analysis of and numerical experiments on our model. In Chapter 4, we will present a discussion of our results on the costs and benefits of using antibiotics in poultry farming, particularly with respect to the development of antibiotic-resistant Salmonellosis infections. Finally, in Chapter 5, we will conclude the thesis with a brief exploration of potential future extensions of our work.

## 1.2 What is Antibiotic Resistance?

Bacteria can evolve mechanisms of avoiding antibiotics through random mutation or horizontal gene transfer. Throughout the course of bacteria reproduction, random mistakes can occur in DNA replication, and some of these mistakes may confer resistance to a particular antibiotic. This is the process of antibiotic resistance through random mutation. Horizontal gene transfer occurs when bacteria pass plasmids containing resistance genes to each other, either through direct contact between two bacteria cells, transfer via bacteriophage, or uptake of the resistance-containing plasmids from the environment [4],[31]. Resistance is specific to a particular antibiotic or class of antibiotics. Antibiotic resistant genes encode for proteins that help the bacteria evade the action of a particular type of antibiotic, often by building a protein with a slightly altered shape that prevents binding of the antibiotic or by preventing the antibiotic from entering the cell [31]. These changes to the proteins must incur resistance but still allow the proteins to function as they would normally. Because of this, advantageous random mutations are rare.

Though development of resistance in an individual bacterium is random, resistance can be amplified in a population through the use of antibiotics. If an antibiotic is applied to a population of bacteria – whether that population is in the environment, in a hospital, or in an individual patient – the antibiotic will kill or stunt the growth of only those bacteria which are susceptible to the antibiotic. The remaining bacteria have resistance to the antibiotic and are able to reproduce, resulting in a population that is more resistant to the antibiotic [32]. This can occur when the antibiotic treatment is not strong enough to kill or diminish the growth of the entire population of bacteria, as is the case when a patient does not finish their antibiotic treatment, or when bacterial populations are consistently exposed to a low concentration level of antibiotics, as is the case with antibiotic use in animal agriculture.

## 1.3 Antibiotic Use in Poultry Production

Antibiotics are used in poultry production as prophylaxis, curative treatment, and growth promotion. The first use is as prophylaxis, or prevention of common bacterial diseases. The crowded conditions in concentrated animal feeding operations necessitate management of infectious disease to ensure overall animal health and the profitability of such operations. In these farms, between 20,000 and 125,000 birds are raised in shed-like enclosures [3], with an average of less than one square foot of space per chicken [34]. Antibiotics are currently used in chicken farms to manage and prevent common bacterial diseases such as respiratory and digestive tract infections, as well as more serious and life threatening infections such as necrotic enteritis, coccidiosis, and infections caused by some strains of *Salmonella* and *Escherichia coli* [15]. Prophylactic antibiotics are usually added to the water supply [22], [15] and taken by all chickens in the farm. Since the purpose of these antibiotics is prevention rather than treatment, they are administered at lower levels than antibiotics used for treatment and are deemed sub-therapeutic, meaning they are below the dose required to kill or stop the growth of most bacteria [40]. Using antibiotics in this way helps keep the large and concentrated populations of chickens healthy for their 48-day life before slaughter, but it also contributes to the problem of antibiotic resistance, as sub-therapeutic doses of antibiotics select for increased resistance [40]. Unlike the use of antibiotics for growth promotion, using antibiotics as prophylaxis is legal and widely practiced.

A second use of antibiotics in poultry production is for treatment of disease. Antibiotics are used in this way when disease is identified in a chicken population by a veterinarian. Antibiotic use for this purpose makes up a minority of the total antibiotic use in poultry production [22], [40]. In most instances, the whole flock is given antibiotic treatment through the water supply, as the farmer will want to protect other chickens from contracting the

infection [40], [15]. Therapeutic levels of antibiotic treatment are less likely to cause antibiotic resistance, as they eliminate bacteria with higher levels of resistance as well. However, with some infections, such as those caused by *E. coli*, there are few treatment options, so development of resistance can occur [40].

The final, and most controversial, use of antibiotics in poultry production is for growth promotion. The exact mechanism of why some antibiotics promote growth in livestock is unclear, but it has been demonstrated that sub-therapeutic doses of antibiotics such as penicillin and tetracycline enhance growth in livestock animals, which correspondingly leads to more profit for the poultry producer [15]. Since these doses are sub-therapeutic, they select for antibiotic resistance in a population. The connection between the use of growth promoting antibiotics and the development of antibiotic resistance is so strong that it has been illegal to use growth-promoting antibiotics in the European Union since 2007 and in the United States since 2017 [15].

## 1.4 Antibiotic resistance in Salmonella

*Salmonella enterica* is the bacteria responsible for salmonellosis infections. It is a food-borne pathogen most frequently acquired from consumption of chicken and turkey products. Chicken are a natural host for *Salmonella enterica*, and they often display no symptoms when infected. The infection is transmitted through a fecal-oral route – chickens infected with *Salmonella* shed bacteria through their feces and susceptible chickens can acquire the infection from contact with the infected feces. Around 20% of *Salmonella* isolates from poultry products have been found to be resistant to many medically-important antibiotics, including tetracycline, streptomycin, sulfamethoxazole, and ampicillin [1],[41]. Humans can become infected through consuming infected chicken products or other food products containing traces of contaminated chicken feces. Salmonellosis infections cause symptoms such

as stomach aches, diarrhea and fever [21]. The infection usually clears on its own, but it can be life-threatening if it causes severe dehydration [9].

Antibiotic-resistant *Salmonella* has a great health and economic impact in the United States. It is the most common foodborne infection in the U.S. Annually, there are 1,200,000 *Salmonella* infections in the U.S., and at least 100,000 infections are caused by antibiotic-resistant bacteria [14]. Of the 1,200,000 total infections per year, around 19,000 result in hospitalization and 380 in death [24]. The total annual cost associated with *Salmonella* infections is $3.7 billion [24]. Antibiotics are the primary route of treating *Salmonella* infections in hospitalized patients; thus, antibiotic-resistant infections are more difficult and more expensive to treat. Estimates have found that antibiotic-resistant infections cost on average $400 more and require one extra day of hospital care per patient [16]. These economic and health impacts give us further reason to study antibiotic resistance in *Salmonella* specifically.

## 1.5 The Basic SIR model

In this project, we construct a modified SIR model to represent the epidemiology of *Salmonella* infections. We will briefly present the well-known SIR model which serves as the basis for our model. For further discussion, see [25],[27],[43]. In a simple SIR model, the population is divided into three disjoint groups: susceptible individuals (S), infected individuals (I), and recovered individuals (R). The movement from S to I depends on the number of susceptible people one infected person can infect per unit of time; denote this parameter $\beta$. More specifically, $\beta$ is the number of susceptible people infected by one infected individual under the assumption that only one person is infected and all others are susceptible, such that the movement from S to I can be represented as $-\beta SI$. Individuals move from I to R when they recover, which is dependent on the amount of time they have been infected. The movement from I to R is only dependent on the size of I and $\gamma$, where $\frac{1}{\gamma}$

is the average recovery time. So the movement from I to R is represented as $-\gamma I$ [25]. This is all summarized in the diagram below (Figure 1.1).


Figure 1.1: A sketch of the basic SIR model. Individuals move from S to I at a rate of $\beta SI$ and they move from I to R at a rate of $\gamma I$.

The system is therefore governed by the following differential equations,

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

where the dependent variable $t$ is time measured in a chosen unit [25].

Using this model, we can learn some useful things about the epidemiology of the system. First, we can easily see that the number of susceptible individuals declines monotonically since $\beta$, $S$, and $I$ must always be positive. Similarly, since $\gamma$ and $I$ are always positive, we can see that the number of recovered individuals will increase monotonically. Furthermore, since $\frac{dI}{dt} = \beta SI - \gamma I$, we can see that the population of infected individuals will increase while $\beta SI > \gamma I$, reach a peak when $\beta SI = \gamma I$, and decrease while $\beta SI < \gamma I$. These relationships can be seen in the figure below (Figure 1.2).

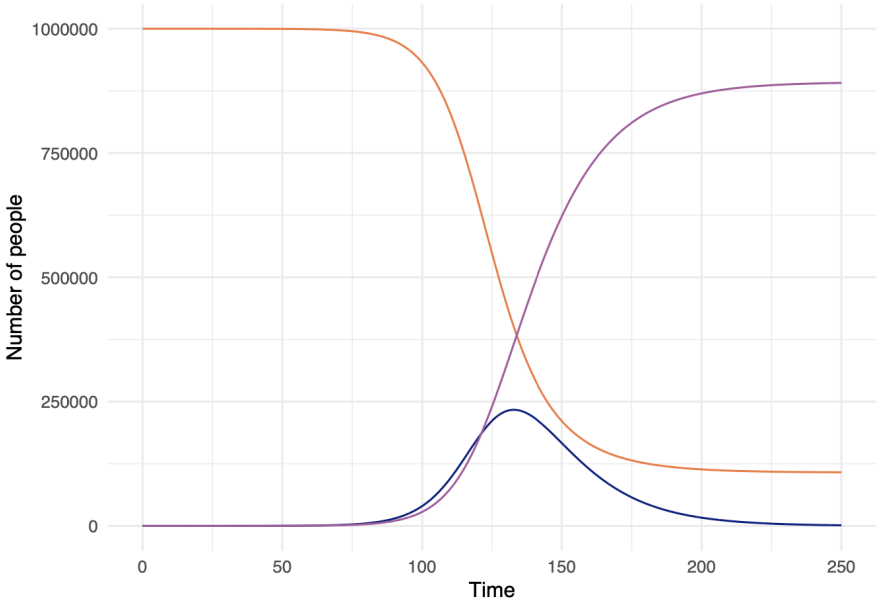


Figure 1.2: The graph above is an example of a numerical solution for an SIR system. The orange curve represents the susceptible population (S), the blue curve represents the infected population (I), and the purple curve represents the recovered population (R).

The SIR model can also tell us about the potential for an outbreak to occur and the proportion of the population that will evenutally be infected. One of the most important results of the SIR model is the basic reproductive number ($R_0$), which gives an idea of how fast the disease is spreading and how fast people are recovering from it. $R_0 = \frac{\beta}{\gamma}$, and if $R_0 > 1$, it indicates that the disease is spreading faster than people can recover from it, causing an epidemic [25]. The SIR model can also be solved numerically to predict what proportion of a population will become infected over a period of time given different values for $\beta$ and $\gamma$. This is a useful result, as it allows the modeler to predict the magnitude of the outbreak and find ways to minimize the damaging results.

The accuracy of the SIR model to a situation is limited by the key assumptions it makes. First, the SIR model assumes a homogeneous population, that is, no individuals are more or less affected than others. This assumption also means individuals are assumed to be evenly dispersed, not clumped in groups of family and friends. Infected individuals are also

assumed to be infectious immediately upon infection, when the reality of some diseases is that there is an incubation period before the individual becomes infectious. Additionally, in the traditional SIR model, once an individual is recovered, they cannot become infected again. This assumption is fine for diseases which confer life-long immunity, but it does not hold true for diseases one can contract repeatedly. Finally, the model assumes a large population. Because these assumptions are not always satisfied, many modified SIR models have been developed to more accurately model a particular situation, such as by including a category for incubating infections or allowing individuals to return to a susceptible state [25]. Our model, too, is a modified SIR model.

## 1.6 Literature Review

Some work has been done to model, separately, the disease dynamics of *Salmonella* and the impact of antibiotic use in animal agriculture on human health. The existing models range in focus from the microbiome interactions of food-borne illness within poultry populations [42] to the spread of *Salmonella* within livestock populations [18] to the human impact of antibiotic resistance in food-borne diseases [13],[45]. While models exist for both *Salmonella* spread within a poultry population and the disease burden of *Salmonella* in human populations, to our knowledge ours is the first model which attempts to model the dynamics of both populations simultaneously, linked through the food supply.

Rawson, Dawkins, and Bonsall developed a model of Campylobacter dynamics in Broiler flocks in 2019 [42]. Though this model is not focused on *Salmonella* specifically, it is still relevant to this project because *Campylobacter* is also a foodborne disease spread through a fecal-oral transmission route. Their model demonstrated the relationships between Campylobacter and other bacterial species at a gut microbiome level within a single chicken using a system of differential equations. One element that is similar to our model is the inclusion

of an environment variable, which keeps track of the concentration of *Campylobacter* in the chicken's environment. This also facilitates spread of the disease among multiple chickens through a fecal-oral route. Our model differs in that ours is a modified SIR model, includes development of antibiotic resistance, and includes a human population as well as a poultry population.

Rihan, Baleanu, Lakshmanan and Rakkiyappan developed what they call a "SIRC" model of *Salmonella* infection within a generic livestock population (either chickens, pigs, or cows) in 2014 [18]. Theirs is a modified SIR model with an added compartment for cross-immune individuals, who are neither fully susceptible nor fully protected from the disease. Their model is somewhat similar to ours in that it uses a modified SIR model, but it does not measure antibiotic resistance or keep track of the environmental *Salmonella* populations. Their model also only focuses on livestock populations, not human populations as well.

In 2002, Smith, Harris, Johnson, Silbergeld, and Morris developed a model of the impact of animal antibiotic use on antibiotic resistance present in human populations [13]. This model included differential equations corresponding to three groups within the human population: exposed, amplified, and colonized with antibiotic resistant bacteria. The researchers compared the prevalence of antibiotic resistant bacteria, defined as the sum of the above sub-populations, when animal antibiotics were used (and hence antibiotic resistance transferred to the human population through consumption of contaminated animal products) and when they were not. They also compared the impacts of animal antibiotic use and medical antibiotic use. This model focuses on the human population, and differs from our model in that it allows person-to-person transmission of antibiotic resistant bacteria, while our model only allows for transmission through food (as *Salmonella* is not generally transmitted from person to person, assuming proper hygiene). Their model also treats animal antibiotic use as a binary (either fully on or off), while our model allows for a range of antibiotic use.

In 2017, van Bunnik and Woolhouse developed an interconnected systems of differential

equations model representing the development of antibiotic resistance through interactions between human and livestock populations [45]. Their model includes only two equations, one for the fraction of humans colonized by antibiotic resistant bacteria and one for the fraction of livestock animals colonized with antibiotic resistant bacteria. With this model, they compared the impact of various factors, including development of antibiotic resistance from exposure to infected humans and animals, to see which had the greatest impact on the fraction of humans with antibiotic resistant bacteria. This model differs from ours because, while it is a connected system of the two populations, it is much simpler, and does not model spread of disease within a population in the same SIR format. The researchers also only compared two levels of animal antibiotic use (high and low), while our model allows for a range of antibiotic use.

While previous models have investigated the complicated relationships between antibiotic use, *Salmonella* disease dynamics, and the disease burden for human populations, we have not encountered a model that uses a system of differential equations to model antibiotic-resistant *Salmonella* dynamics in both populations. Additionally, none of the models mentioned have attempted to quantify the economic costs and benefits of antibiotic use in addition to modeling disease dynamics. For these reasons, we believe our model presents an interesting and useful addition to the existing literature.

# Chapter 2

# The Model

Our model consists of two interconnected sets of differential equations. One set of equations models the spread of *Salmonella* around the chicken farm, and the other models the spread of *Salmonella* around a human population which buys chicken sourced from the chicken farm. We will focus on each part of the model in turn, starting with the chicken farm and then moving to the human population, and then end with an explanation of the connection between the two models and the economic quantification of the system.

## 2.1 *Salmonella* on an Industrial Chicken Farm

Our industrial chicken farm model is a modified SIR model (see Figure 2.1). In order to use such a model, we have made several simplifying assumptions. First, we are assuming a homogeneous population of chickens which vary only in their disease status and not in other factors of health. We also assume the chickens are relatively well mixed spatially and that the bacteria populations are evenly distributed across the barn and not clumped in one or another spot. These assumptions follow from the standard SIR model assumptions [25]. Our model does not assume a constant population, as chickens may die from various

bacterial diseases. No chickens may enter or leave the population during the 48-day life cycle of the chickens, except through death, and all chicken deaths are from diseases other than Salmonellosis.

The model includes four categories of chicken: susceptible chicken ($S_c$) who do not have *Salmonella*, high antibiotic-resistant *Salmonella*-infected chicken ($I_{Hc}$), medium antibiotic-resistant *Salmonella*-infected chicken ($I_{Mc}$), and low antibiotic-resistant *Salmonella*-infected chicken ($I_{Lc}$). The model also keeps track of the concentrations of three populations of Salmonella in the chicken's environment: high antibiotic-resistant *Salmonella* ($I_{He}$), medium antibiotic-resistant *Salmonella* ($I_{Me}$), and low antibiotic-resistant *Salmonella* ($I_{Le}$). The different levels of infections and *Salmonella* populations correspond to higher concentrations of antibiotics being required to eliminate the bacteria in that class. We distinguish these classes quantitatively by assigning a different MIC to each. MICs, or minimum inhibitory concentrations, are the minimum concentration of antibiotic required to halt or reverse growth of a bacterial population. For ampicillin, our test antibiotic of choice, the MIC for bacteria with low resistance is $64\frac{\mu g}{mL}$, $128\frac{\mu g}{mL}$ for medium resistance and $256\frac{\mu g}{mL}$ for high resistance [26].

Since *Salmonella* spreads through interactions with feces, rather than by contact with infected individuals, chickens move from susceptible to infected by interacting with the *Salmonella* in the environment. We represent the rates of moving from susceptible to infections of high, medium, and low antibiotic resistance as $f_{IHc}, f_{IMc}$, and $f_{ILc}$, respectively. Chickens can also recover from infection by *Salmonella* if certain concentrations of antibiotics are administered, which would cause them to move from infected back to susceptible. For high, medium, and low resistance infections, these rates are governed by $f_{rHc}, f_{rMc}$ and $f_{rLc}$, respectively. Chickens in any category can die from other diseases. For susceptible chickens, high resistance infected chickens, medium resistance infected chickens, and low resistance infected chickens, the death rates are $f_{dSc}, f_{dHc}, f_{dMc}$, and $f_{dLc}$, respectively. Chickens in our model die from various diseases, including those caused by *E. coli*, *Clostridium spp.* and

some strains of *Salmonella*. The strains of *Salmonella* which make chicken sick, however, are not the same as those that make humans sick. The strains of *Salmonella* which infect humans do not generally harm chickens themselves [35]. Therefore, the death rates for each class of chicken are the same regardless of *Salmonella* infection status.

Our *Salmonella* populations also change over time as bacteria are born, die, shed from infected chickens through feces, and mutated to different levels of resistance. The reproduction rates for high, medium, and low resistance bacteria are $f_{bHe}$, $f_{bMe}$, and $f_{bLe}$, respectively; the death rates are $f_{dHe}$, $f_{dMe}$, and $f_{dLe}$, respectively; and the shedding rates are $f_{sHe}$, $f_{sMe}$, and $f_{sLe}$, respectively. Finally, $f_{muMe}$ refers to the rate of mutation from medium to high resistance, $f_{mdHe}$ is the rate of mutation from high to medium resistance, $f_{muLe}$ refers to the rate of mutation from low to medium resistance, and $f_{mdMe}$ is the rate of mutation from medium to low resistance. These relationships are summarized in (Figure 2.1).

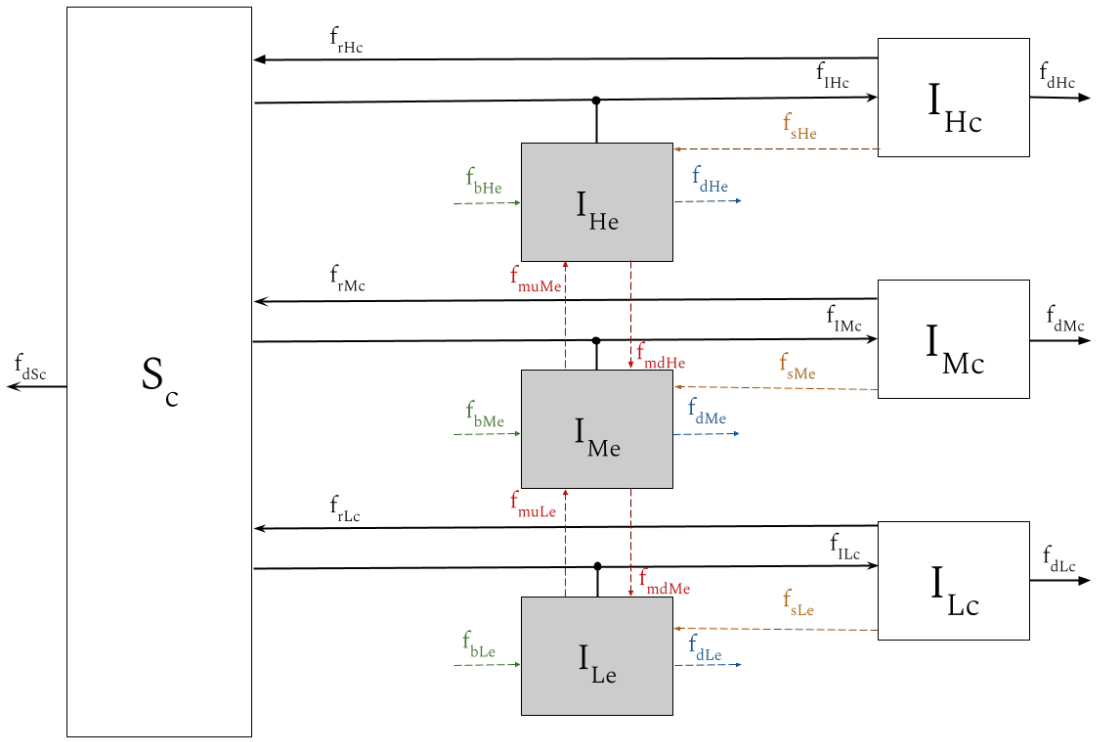


Figure 2.1: Compartment diagram for the spread of *Salmonella* on an industrial chicken farm. Solid lines denote rates for chicken populations, while dashed lines indicate rates for bacteria populations. Green dashed lines denote bacterial reproduction rates, blue dashed lines are bacterial death rates, red dashed lines are mutation rates, and orange dashed lines are shedding rates. Note that *Salmonella* bacteria can only move from compartment to compartment along dashed lines and chicken can only move along solid lines. For example, $f_{sHe}$ is the rate of *Salmonella* shedding from infected chickens, and does not represent a movement of chickens themselves.

Our industrial chicken farm model ultimately consists of a system of seven differential equations, one for each compartment. The first four equations measure change in chickens in the corresponding compartment over time, and hence have units $\frac{chickens}{days}$. The last three equations measure change in concentration of bacteria over time, and therefore have units $\frac{CFUs/mL}{days}$. The system of differential equations is as follows:

$$\frac{dS_c}{dt} = f_{rHc} + f_{rMc} + f_{rLc} - f_{dSc} - f_{IHc} - f_{IMc} - f_{ILc}$$

$$\frac{dI_{Hc}}{dt} = f_{IHc} - f_{rHc} - f_{dHc}$$

$$\frac{dI_{Mc}}{dt} = f_{IMc} - f_{rMc} - f_{dMc}$$

$$\frac{dI_{Lc}}{dt} = f_{ILc} - f_{rLc} - f_{dLc}$$

$$\frac{dI_{He}}{dt} = f_{bHe} + f_{muMe} - f_{mdHe} - f_{dHe}$$
$$\frac{dI_{Me}}{dt} = f_{bMe} + f_{muLe} + f_{mdHe} - f_{mdMe} - f_{muMe} - f_{dHe}$$
$$\frac{dI_{Le}}{dt} = f_{bLe} + f_{mdMe} - f_{muLe} - f_{dLe}$$

### 2.1.1 Rate Functions

In this section, we will introduce and explain the rate functions for the chicken farm system of differential equations. We will start first with the infection rates. Each infection rate is the product of an infection constant, called $\beta_c$, the population of susceptible chickens ($S_c$) and the *Salmonella* bacterial concentration with that resistance level ($I_{Xe}$ with $X \in \{H, M, L\}$). This is consistent with the assumption that *Salmonella* spreads through a fecal-oral route. The infection rate $\beta_c$ is the same for all levels of antibiotic resistance, as having antibiotic resistance does not affect the infectiousness of *Salmonella*. The infection rate equations are below:

$$f_{IHc}(I_{He}, S_c) = \beta_c I_{He} S_c$$
$$f_{IMc}(I_{Me}, S_c) = \beta_c I_{Me} S_c$$
$$f_{ILc}(I_{Le}, S_c) = \beta_c I_{Le} S_c$$

Next, we will explore the recovery rate equations. We assume that chicken recover from *Salmonella* infections only after antibiotic treatment, so the recovery rate for each class of infected chickens is dependent on the concentration of antibiotics administered. The concentration of antibiotics administered to the flock is included in our model as the parameter $A$. If the concentration of antibiotics exceeds the MIC for a particular resistance class of *Salmonella* (called $A_L, A_M$ and $A_H$ for low, medium, and high resistance infections, respectively), some of the chickens infected with that class of bacteria will be able to recover. The number of chickens recovering is proportional to the difference in the administered antibiotic

concentration and the MIC for a particular antibiotic class. This relationship is summarized in the recovery rate equations below, where $k$ is a constant:

$$f_{rHc}(A, I_{Hc}) = \begin{cases} k(A - A_H)I_{Hc} & \text{if } A \geq A_H \\ 0 & \text{if } A < A_H \end{cases}$$

$$f_{rMc}(A, I_{Mc}) = \begin{cases} k(A - A_M)I_{Mc} & \text{if } A \geq A_M \\ 0 & \text{if } A < A_M \end{cases}$$

$$f_{rLc}(A, I_{Lc}) = \begin{cases} k(A - A_L)I_{Lc} & \text{if } A \geq A_L \\ 0 & \text{if } A < A_L \end{cases}$$

For ampicillin, $A_L = 64\frac{\mu g}{mL}$, $A_M = 128\frac{\mu g}{mL}$ and $A_H = 256\frac{\mu g}{mL}$.

The final rate equations applying to categories of chickens are the chicken death functions. These too are a function of antibiotic use, but they do not vary based on the MIC of each infection class, as the resistance for different infection classes apply only to *Salmonella* resistance, and chickens can die from a variety of different diseases. We assume that increasing antibiotic usage decreases death from these other causes until a maximum reduction in death is achieved. The death rate for all classes of chickens is the same, and thus is represented by the following, where $d_c$ is the base chicken death rate with no antibiotic use and $\sigma_{Max}$ is the maximum proportion of deaths reduced by antibiotic use:

$$f_{dSc}(A, S_c) = d_c(1 - \tfrac{\sigma_{Max} \cdot A}{1+A})S_c$$
$$f_{dHc}(A, I_{Hc}) = d_c(1 - \tfrac{\sigma_{Max} \cdot A}{1+A})I_{Hc}$$
$$f_{dMc}(A, I_{Mc}) = d_c(1 - \tfrac{\sigma_{Max} \cdot A}{1+A})I_{Mc}$$
$$f_{dLc}(A, I_{Lc}) = d_c(1 - \tfrac{\sigma_{Max} \cdot A}{1+A})I_{Lc}$$

Now we will move on to discussing the rate equations governing our bacterial populations. The reproduction, mutation, and death rates for each class of bacteria are interconnected.

Recall that mutation occurs when a bacterium undergoes binary fission and mistakes occur in the DNA replication. Under our model which classifies three levels of antibiotic resistance, the newly resistant bacterium would be born into that new resistance class. We define $q$ as the proportion of each class of bacteria that are born into either the higher or lower resistance class. The proportion of bacteria born into the same resistance class as their parents is then $(1-q)$ for high and low resistance bacteria and $(1-2q)$ for medium resistance bacteria (as medium resistance bacteria can mutate to high or low resistance). The total reproduction rate of each class is represented by the constant $b_{Xe}, X \in \{H, M, L\}$. The birth of new bacteria is also limited by a collective carrying capacity, which we call $C_e$. The bacterial reproduction rate equations are then as follows:

$$f_{bHe}(I_{He}, I_{Me}, I_{Le}) = (1-q)b_{He}(1 - \tfrac{I_{He}+I_{Me}+I_{Le}}{C_e})I_{He}$$
$$f_{bMe}(I_{He}, I_{Me}, I_{Le}) = (1-2q)b_{Me}(1 - \tfrac{I_{He}+I_{Me}+I_{Le}}{C_e})I_{Me}$$
$$f_{bLe}(I_{He}, I_{Me}, I_{Le}) = (1-q)b_{Le}(1 - \tfrac{I_{He}+I_{Me}+I_{Le}}{C_e})I_{Le}$$

The mutation rates follow a similar pattern to the reproduction rates, and are merely the proportion of bacteria mutating multiplied by the total reproduction rate and the population of bacteria for each resistance category. The mutation rates are:

$$f_{mdHe}(I_{He}) = q \cdot b_{He} \cdot I_{He}$$
$$f_{muMe}(I_{Me}) = q \cdot b_{Me} \cdot I_{Me}$$
$$f_{mdMe}(I_{Me}) = q \cdot b_{Me} \cdot I_{Me}$$
$$f_{muLe}(I_{Le}) = q \cdot b_{Le} \cdot I_{Le}$$

The bacterial death rates for bacteria in the environment are the same for each class of resistance. Our model does not have a mechanism by which antibiotics act on bacteria in the environment – the antibiotics only act to help infected chickens recover and do not kill bacteria in the environment. Therefore the death rates for each class of bacteria are simply

a common death rate ($d_e$) multiplied by the concentration of bacteria in that class. They are as follows:

$$f_{dHe}(I_{He}) = d_e \cdot I_{He}$$
$$f_{dMe}(I_{Me}) = d_e \cdot I_{Me}$$
$$f_{dLe}(I_{Le}) = d_e \cdot I_{Le}$$

Finally, we shall discuss the shedding rates. These equations describe the rate at which infected chickens shed *Salmonella* through their feces. This rate is simply the shedding rate ($s$), which is a product of how much feces a chicken sheds in one day and how much bacteria is contained within each unit of feces, multiplied by the number of infected chickens in each category. This relationship is summarized in the following rate equations:

$$f_{sHe}(I_{Hc}) = s \cdot I_{Hc}$$
$$f_{sMe}(I_{Mc}) = s \cdot I_{Mc}$$
$$f_{sLe}(I_{Lc}) = s \cdot I_{Lc}$$

With these rate equations, and parameter values, which we will explore in the following section, we can solve our system of differential equations. The numerical solutions to the differential equations give the number of individual chickens in each category at time $t$. The solution also gives the concentration of environmental *Salmonella* bacteria in each level of resistance at time $t$. We are particularly interested in the number of chickens infected with *Salmonella* at the end of 48 days, which is approximately the length of time broiler chickens are raised before slaughter, as this informs how much of the resulting meat supply may be contaminated with *Salmonella*.

### 2.1.2 Parameter Values and Estimation

Parameter values were taken from relevant primary literature when possible, and estimated when not possible. The parameters we could find values for include the maximum

reduction in chicken death rate from antibiotic use ($\sigma_{Max}$), which we found to be 40% based on the difference in mortality on antibiotic-free and standard industrial chicken farms [10]. We found the low antibiotic resistance *Salmonella* reproduction rate constant ($b_{Le}$) to be $72/day$ based on a 20 minute doubling time [12]. Reproduction rate constants for medium and high resistance were based on this reproduction rate with a slight penalty to make up for the assumption that maintaining resistance genes is energetically expensive. The *Salmonella* carrying capacity was chosen to be $10^8 CFUs/mL$ based on [8]. Finally, the shedding rate constant ($s$) was based on the concentration of *Salmonella* bacteria shed per gram of feces, multiplied by the average feces load per chicken per day, which was found to be $2128.125 \frac{CFUs/mL}{chickens*days}$ [46].

Some parameters, such as *Salmonella* death rate ($d_e$) or the infection rate constant ($\beta_c$), were difficult to find in primary literature, as they are difficult to estimate in a laboratory setting. For this reason, we used values we could find, such as the percentage of chickens who were infected with *Salmonella* or the percentage of chickens infected with high antibiotic-resistant *Salmonella* by the end of the 48 day growing period, to estimate the values of parameters we could not find. Estimations were done by systematically computing numerical solutions to the system of differential equations with different values for the chosen parameter using the NDSolve[] command in Wolfram Mathematica and comparing the model outputs to known values.

Since we were estimating several parameters at once, the choice of which parameter to estimate first was somewhat arbitrary. We chose to start by estimating $\beta_c$ and $d_e$ simultaneously, as we wanted to compare the solutions under each of these parameters to the proportion of chickens infected with *Salmonella* at the end of the 48 day growing cycle. According to the U.S. Food Safety and Inspection Service (FSIS) and Pew, approximately 5% of whole chicken carcasses inspected test positive for the presence of *Salmonella* [38],[44]. To find the proportion of chickens infected at the end of the 48 day growing period in our

model, we found numerical solutions to the differential equations and divided the number of *Salmonella*-infected chickens (the sum of $I_{Hc}, I_{Mc}$ and $I_{Lc}$) by the total number of chickens (the sum of $S_c, I_{Hc}, I_{Mc}$ and $I_{Lc}$) at $t = 48$. We call this value *propSick*. The formula for *propSick* can be seen below.

$$propSick = \frac{\text{number of } Salmonella \text{ infected chickens}}{\text{total number of chickens}} = \frac{I_{Hc}(48)+I_{Mc}(48)+I_{Lc}(48)}{S_c(48)+I_{Hc}(48)+I_{Mc}(48)+I_{Lc}(48)}$$

We iterated over combinations of values of $\beta_c$ ranging from 0 to $10^{-8}$ and values of $d_e$ ranging from 0 to 100, with all other parameters kept constant. The potential values of $\beta_c$ are small because they represent the number of chickens infected by $1\frac{CFU}{mL}$ of *Salmonella*, which is a very low concentration of *Salmonella*. Correspondingly, $\beta_c$ is quite small. For each combination of $\beta_c$ and $d_e$, *propSick* was computed and compared to 0.05. The parameter values which minimized the difference $|propSick - 0.05|$ were $\beta_c = 3.91 \times 10^{-9}$ and $d_e = 36$.

Next, we estimated the chicken death rate constant $d_c$. To estimate this parameter, we computed solutions to the differential equations with the values for $d_c$ ranging from 0 to 0.001. For each solution, we calculated the proportion of chickens still alive at the end of the 48 day growing period (called *propSurvived*) by dividing the sum of all chicken categories $(S_c + I_{Hc} + I_{Mc} + I_{Lc})$ at $t = 48$ by the initial number of chickens $(S_c(0))$. The formula for *propSurvived* can be seen below.

$$propSurvived = \frac{\text{total number of chickens at 48 days}}{\text{total number of chickens at 0 days}} = \frac{S_c(48)+I_{Hc}(48)+I_{Mc}(48)+I_{Lc}(48)}{S_c(0)+I_{Hc}(0)+I_{Mc}(0)+I_{Lc}(0)}$$

We then found the relationship between $d_c$ and the proportion of chickens surviving using the LinearModelFit[] function in Wolfram Mathematica, which was found to be $propSurvived = 0.9998 - 45.9217(d_c)$. We solved for the value of $d_c$ that corresponded with a *propSurvived* equal to 0.958, as it has been found in farms with no antibiotic input, there is an average chicken mortality of 4.2% [10]. The best value of $d_c$ for was found to be $0.00091/days$. The relationship between $d_c$ and *propSurvived* can be seen in Figure 2.2.

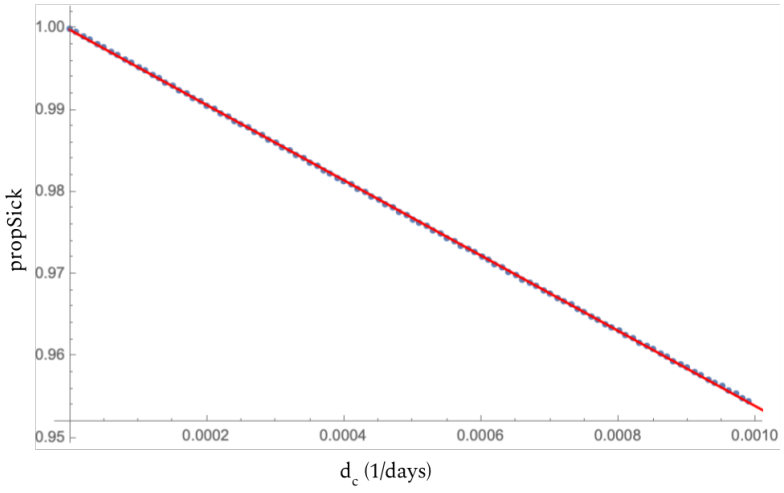


Figure 2.2: The relationship between $d_c$ and $propSurvived$ is approximated by the linear relationship $propSurvived = 0.9998 - 45.9217(d_c)$. The blue points are the $propSurvived$ values generated for each value of $d_c$ and the red line is the best-fit curve.

Finally, we estimated the value of the proportion of *Salmonella* mutating to other categories, $q$. We computed solutions to the differential equations for values of $q$ ranging from 0 to 0.005 in intervals of $5 \times 10^{-5}$ and calculated the proportion of infected chickens infected with high antibiotic-resistant *Salmonella* (called $propIHc$). This was computed by the quotient $\frac{I_{Hc}}{S_c+I_{Hc}+I_{Mc}+I_{Lc}}$, with all values taken at time $t = 48$, corresponding to the end of the growing period. We then fit several functions to the data to estimate the value of $q$ that corresponds to a $propIHc$ of 0.15, which is the approximate proportion of chicken products infected with ampicillin-resistant *Salmonella* [19]. Exponential, logarithmic, logistic, and linear curves were fit to the data using NonlinearModelFit[] in Mathematica, and all functions fit the data reasonably well. A value of $q = 0.0012$ was chosen, as it agreed with the results from the best fit curves. The relationship between $q$ and $propIHc$ can be seen in Figure 2.3

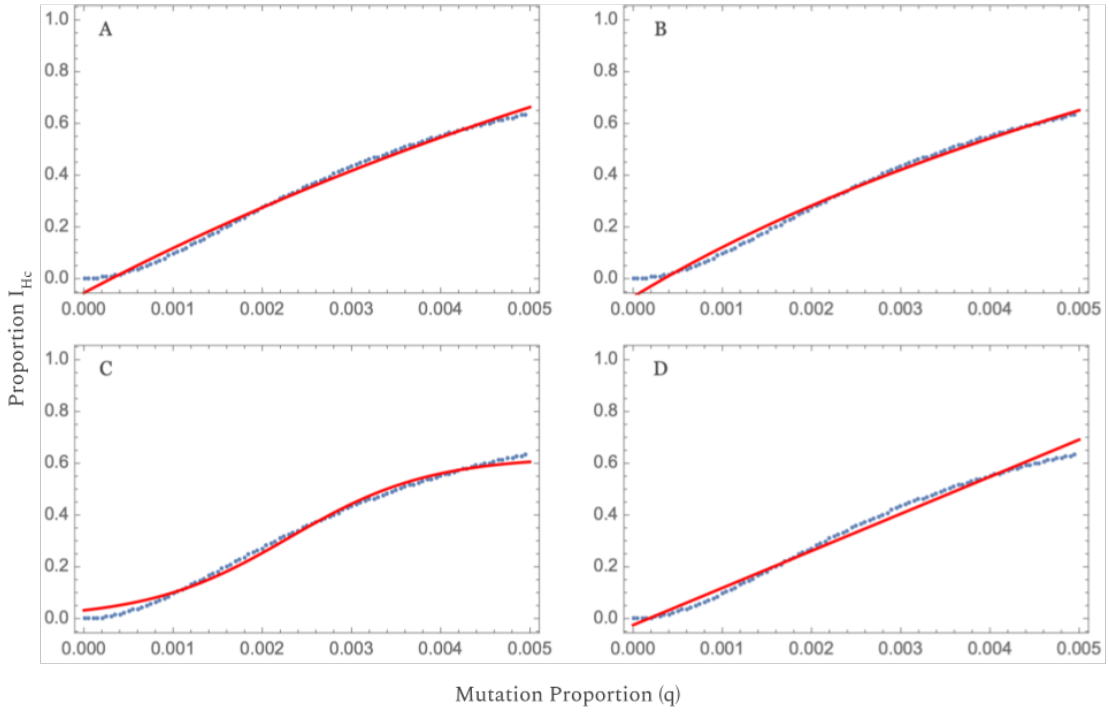


Figure 2.3: The relationship between $q$ and $propIHc$ is approximated by four different best-fit curves: exponential (A), logarithmic (B), logistic (C), and linear (D) The blue points on each plot are the $propIHc$ values generated for each value of $q$ and the red line is the best-fit curve.

The chicken model parameter values are summarized in Table 2.1.

| Parameter | Description | Units | Value [Source] |
|---|---|---|---|
| $\beta_c$ | Infection rate constant | $\frac{1}{days*CFU/mL}$ | $3.91 \times 10^{-9}$ [Estimated] |
| $k$ | Recovery rate constant | $\frac{1}{days*CFU/mL}$ | 0.1 [Estimated] |
| $d_c$ | Chicken death rate constant with no antibiotics | $\frac{1}{days}$ | 0.00091 [Estimated] |
| $\sigma_{Max}$ | Maximum proportion of chicken deaths prevented by antibiotic use | N/A | 0.4 [10] |
| $A$ | Concentration of antibiotics administered to chicken population | $\frac{\mu g}{mL}$ | Manipulated in various experiments |
| $b_{Le}$ | Low antibiotic-resistant *Salmonella* reproduction rate constant | $\frac{1}{days}$ | 72 [12] |
| $b_{Me}$ | Medium antibiotic-resistant *Salmonella* reproduction rate constant | $\frac{1}{days}$ | 68.4 [Estimate based on [12]] |
| $b_{He}$ | High antibiotic-resistant *Salmonella* reproduction rate constant | $\frac{1}{days}$ | 65 [Estimate based on [12]] |
| $C_e$ | *Salmonella* carrying capacity | $\frac{CFUs}{mL}$ | $10^8$ [8] |
| $q$ | *Salmonella* mutation proportion | N/A | 0.0012 [Estimated] |
| $d_e$ | *Salmonella* death rate | $\frac{1}{days}$ | 36 [Estimated] |
| $s$ | Concentration of *Salmonella* shed per chicken per day | $\frac{CFUs/mL}{chickens*days}$ | 2128.125 [46] |

Table 2.1: Model parameters, descriptions, and values.

## 2.2 *Salmonella* in a Human Population

The second major part of our model is the sub-model of *Salmonella* spread in a human population. For simplicity, we assume a homogeneous human population who differ only in their *Salmonella* infection status and no other underlying health factors, and who also purchase chicken in stores and restaurants who source their chicken meat from the chicken farm modeled above. The humans in our model can become infected by consuming chicken meat infected with *Salmonella*, and they can either seek treatment in a hospital or self-treat. Consequently, there are seven disjoint compartments representing the disease states of the human population (see Figure 2.4). They are susceptible humans ($S_h$), high antibiotic-resistant *Salmonella*-infected patients seeking treatment in a hospital ($I_{Hht}$), high antibiotic-resistant *Salmonella*-infected patients not seeking treatment in a hospital ($I_{Hhnt}$), medium antibiotic-resistant *Salmonella*-infected patients seeking treatment in a hospital ($I_{Mht}$), medium antibiotic-resistant *Salmonella*-infected patients not seeking treatment in a hospital ($I_{Mhnt}$), low antibiotic-resistant *Salmonella*-infected patients seeking treatment in a hospital ($I_{Lht}$), and low antibiotic-resistant *Salmonella*-infected patients not seeking treatment in a hospital ($I_{Lhnt}$). The human population model consists of seven differential equations, one for each compartment. Humans move from susceptible to infected compartments based on their consumption of meat infected with either high, medium, or low antibiotic-resistant *Salmonella*, and based on the severity of their illness, which dictates whether or not they seek treatment. The rates of susceptible humans becoming infected with high antibiotic-resistant *Salmonella* are $f_{IHht}$ and $f_{IHhnt}$, for those seeking treatment and not seeking treatment, respectively. The rates of susceptible humans becoming infected with medium antibiotic-resistant *Salmonella* are $f_{IMht}$ and $f_{IMhnt}$, for those seeking treatment

and not seeking treatment, respectively. Finally, the rates of susceptible humans becoming infected with low antibiotic-resistant *Salmonella* are $f_{ILht}$ and $f_{ILhnt}$, for those seeking treatment and not seeking treatment, respectively. Humans infected with Salmonella recover (and return to the $S_h$ compartment) at a rate governed by the average recovery time corresponding to the level of antibiotic resistance of the infection and whether or not the patient seeks treatment. The recovery rate equations for people infected with high antibiotic-resistant *Salmonella* are $f_{rHht}$ and $f_{rHhnt}$ for those seeking treatment and not seeking treatment, respectively. The recovery rate equations for people infected with medium antibiotic-resistant *Salmonella* are $f_{rMht}$ and $f_{rMhnt}$ for those seeking treatment and not seeking treatment, respectively. And finally, the recovery rate equations for people infected with low antibiotic-resistant *Salmonella* are $f_{rLht}$ and $f_{rLhnt}$, respectively. These relationships are summarized in Figure 2.4.

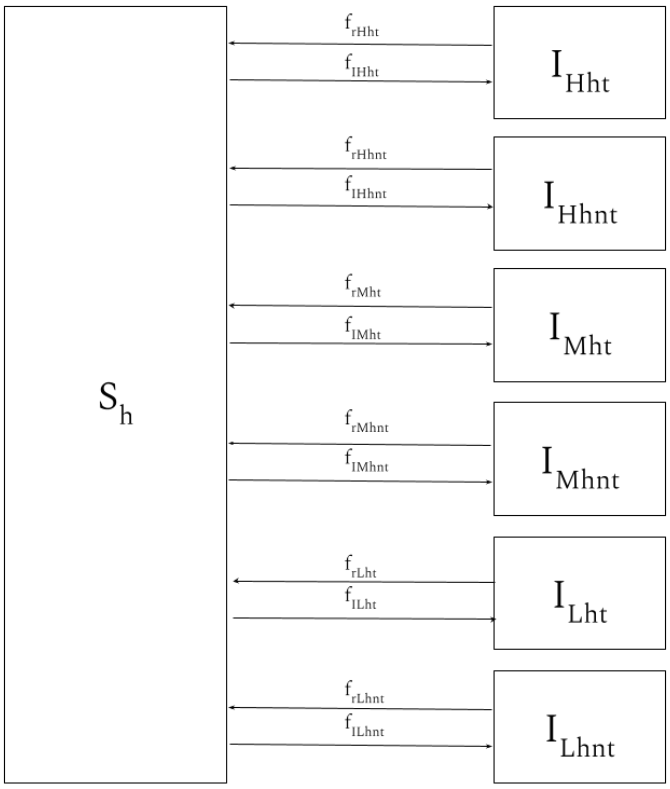


Figure 2.4: Compartment diagram for the spread of *Salmonella* in a human population. This model consists of humans becoming sick and recovering from *Salmonella*

The system of differential equations governing the human population model is as follows:

$$\frac{dS_h}{dt} =$$

$$f_{rHht} + f_{rHhnt} + f_{rMht} + f_{rMhnt} + f_{rLht} + f_{rLhnt} - f_{IHht} - f_{IHhnt} - f_{IMht} - f_{IMhnt} - f_{ILht} - f_{ILhnt}$$

$$\frac{dI_{Hht}}{dt} = f_{IHht} - f_{rHht}$$

$$\frac{dI_{Hhnt}}{dt} = f_{IHhnt} - f_{rHhnt}$$

$$\frac{dI_{Mht}}{dt} = f_{IMht} - f_{rMht}$$

$$\frac{dI_{Mhnt}}{dt} = f_{IMhnt} - f_{rMhnt}$$

$$\frac{dI_{Lht}}{dt} = f_{ILht} - f_{rLht}$$

$$\frac{dI_{Lhnt}}{dt} = f_{ILhnt} - f_{rLhnt}$$

### 2.2.1 Rate Functions

The rate equations for the human model include the infection rates and the recovery rates. The infection rates are based on the size of the susceptible population and the proportion of the meat which is infected with *Salmonella* of each resistance level, which is represented by $I_{Xf}, X \in \{L, M, H\}$. They are scaled by the infection rate constant $\beta_h$, which is the same for all levels of resistance, and by the proportion of people with infections of each resistance-level seeking treatment in a hospital, represented by $p_{Xht}, X \in \{L, M, H\}$. The infection rate equations are thus as follows:

$$f_{IHht} = p_{Hht}\beta_h S_h I_{Hf}$$
$$f_{IHhnt} = (1 - p_{Hht})\beta_h S_h I_{Hf}$$
$$f_{IMht} = p_{Mht}\beta_h S_h I_{Mf}$$
$$f_{IMhnt} = (1 - p_{Mht})\beta_h S_h I_{Mf}$$
$$f_{ILht} = p_{Lht}\beta_h S_h I_{Lf}$$
$$f_{ILhnt} = (1 - p_{Lht})\beta_h S_h I_{Lf}$$

The recovery rate equations are based on the average recovery time for each compartment. The recovery rate parameters $k_{Xht}$ and $k_{Xhnt}, X \in \{L, M, H\}$ are equal to the reciprocal of the average recovery time for hospital treated and non-hospital treated infections, respectively. The recovery rate equations are simply the product of these parameters and the population in each compartment.

$$f_{rHht} = k_{Hht}I_{Hht}$$
$$f_{rHhnt} = k_{Hhnt}I_{Hhnt}$$
$$f_{rMht} = k_{Mht}I_{Mht}$$
$$f_{rMhnt} = k_{Mhnt}I_{Mhnt}$$
$$f_{rLht} = k_{Lht}I_{Lht}$$
$$f_{rLhnt} = k_{Lhnt}I_{Lhnt}$$

The solution to this system of differential equations gives the number of susceptible people and the number of people in each category of *Salmonella* illness at time $t$. We now must find values for the parameters in order to compute numerical solutions to the system of differential equations.

### 2.2.2 Parameter Values and Estimation

The human parameters for which we want to find values are the infection rate parameter $\beta_h$, the proportion of individuals seeking treatment $p_{Xht}, X \in \{L, M, H\}$, and the recovery rate parameters $k_{Xht}$ and $k_{Xhnt}, X \in \{L, M, H\}$. The infection rate parameter was estimated against known values for the proportion of humans infected with *Salmonella*, and the other parameter values were found in the relevant literature.

The infection rate parameter was estimating by systematically finding solutions to the system of differential equations (using NDSolve[] in Mathematica) with $\beta_h$ varying from 0 to 0.05 in intervals of 0.0005. All other parameters were fixed at the values in Table 2.2. On each iteration the proportion of humans who were sick at the end of the simulation was calculated by taking the sum of all compartments corresponding to humans infected with *Salmonella* ($I_{Hht}, I_{Hhnt}, I_{Mht}, I_{Mhnt}, I_{Lht}$ and $I_{Lhnt}$) and dividing it by the sum of all compartments, or the total human population. The relationship between $\beta_h$ and the proportion of humans sick, which we called $propSick_h$, was then plotted and seen to be approximately linear. The formula for $propSick_h$ can be seen below, with each function evaluated at its end time point.

$$propSick_h = \frac{\text{number of sick humans}}{\text{total number of humans}} = \frac{I_{Hht}+I_{Hhnt}+I_{Mht}+I_{Mhnt}+I_{Lht}+I_{Lhnt}}{S_c+I_{Hht}+I_{Hhnt}+I_{Mht}+I_{Mhnt}+I_{Lht}+I_{Lhnt}}$$

We then used the function LinearModelFit[] to quantify this relationship, and we solved for the value of $\beta_h$ which corresponded to a $propSick_h$ value of 0.004 [20]. This value of $\beta_h$ was found to be 0.019. The relationship between $\beta_h$ and $propSick_h$ can be seen in Figure 2.5

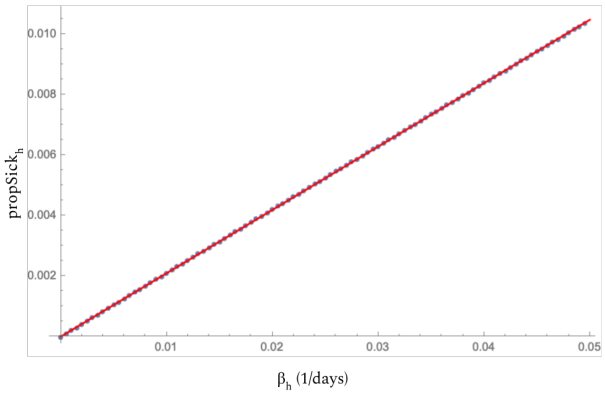


Figure 2.5: The relationship between $\beta_h$ and $propSick_h$ is approximated by the linear relationship $propSick_h = 1.793 \times 10^{-5} + 0.2097(\beta_h)$. The blue points are the $propSick_h$ values generated for each value of $\beta_h$ and the red line is the best-fit curve.

The proportion of people seeking treatment is set at $\frac{1}{6}$ based on a study which shows that out of 1200 *Salmonella* cases linked to poultry in 2021, 200 resulted in hospitalization [5].

The recovery rate parameters are based on the average time to recover from *Salmonella* infections of varying degrees of severity. The average time to recover from *Salmonella* infections ranges from $4 - 7$ days [21], and antibiotic-resistant infections last one to two day(s) longer than non-resistant infections [16], [37] Additionally, infections severe enough to warrant a hospital visit last longer on average than those which can be treated at home [21],[36]. Based on this, we set the average recovery times for infections of each level of resistance and treatment type. The recovery rate parameters are the reciprocals of the average time to recovery for each compartment. These and the other parameter values for the human model are summarized in Table 2.2.

| Parameter | Description | Units | Value [Source] |
|---|---|---|---|
| $\beta_h$ | Infection rate constant | $\frac{1}{days}$ | 0.019 [Estimated] |
| $p_{Hht}$ | Proportion of high-resistance *Salmonella* infected individuals choosing treatment | N/A | 0.167 [5] |
| $p_{Mht}$ | Proportion of medium-resistance *Salmonella* infected individuals choosing treatment | N/A | 0.167 [5] |
| $p_{Lht}$ | Proportion of low-resistance *Salmonella* infected individuals choosing treatment | N/A | 0.167 [5] |
| $k_{Hht}$ | Recovery rate constant for $I_{Hht}$ | $\frac{1}{days}$ | $\frac{1}{7.6}$ [36] |
| $k_{Hhnt}$ | Recovery rate constant for $I_{Hhnt}$ | $\frac{1}{days}$ | $\frac{1}{5}$ [Estimate based on [21],[36]] |
| $k_{Mht}$ | Recovery rate constant for $I_{Mht}$ | $\frac{1}{days}$ | $\frac{1}{6}$ [37] |
| $k_{Mhnt}$ | Recovery rate constant for $I_{Mhnt}$ | $\frac{1}{days}$ | $\frac{1}{4}$ [Estimate based on [21]] |
| $k_{Lht}$ | Recovery rate constant for $I_{Lht}$ | $\frac{1}{days}$ | $\frac{1}{5}$ [Estimate based on [16],[37]] |
| $k_{Lhnt}$ | Recovery rate constant for $I_{Lhnt}$ | $\frac{1}{days}$ | $\frac{1}{3}$ [Estimate based on [21]] |

Table 2.2: Model parameters, descriptions, and values.

## 2.3 Connecting the two sub-models

The two sub-models (the chicken farm and human population) are connected by the chicken meat contaminated with *Salmonella* coming from the chicken farms to human con-

sumers. From the chicken sub-model, we learn how many of the chickens are infected with each level of antibiotic-resistant *Salmonella* at the end of a 48 day growing period. We can use this information to compute how much of the meat supply is contaminated by dividing the ending population of each *Salmonella*-infected compartment by the total ending population of chickens:

$$I_{Hf} = \frac{I_{Hc}}{S_c+I_{Hc}+I_{Mc}+I_{Lc}}$$
$$I_{Mf} = \frac{I_{Mc}}{S_c+I_{Hc}+I_{Mc}+I_{Lc}}$$
$$I_{Lf} = \frac{I_{Lc}}{S_c+I_{Hc}+I_{Mc}+I_{Lc}}$$

These proportions are then used in the human model. The number of farms ($\Lambda$) supplying the human population with chicken meat and the number of 48-day growing cycles in the simulation (called $\epsilon$) can be manipulated by the user of the model. Growing cycles are staggered to start $\frac{48}{\Lambda}$ days after the previous cycle so that chicken meat enters the human food supply every $\frac{48}{\Lambda}$ days. The arrival of meat from the farms is accounted for in the human model by changing the proportion of meat which is contaminated with *Salmonella* ($I_{Hf}, I_{Mf}$, and $I_{Lf}$). Each arrival of meat corresponds to a new solution to the human model differential equations using NDSolve[]. Farms are assumed to not be thoroughly disinfected between 48-day growing cycles, so the *Salmonella* present in the environment in each farm will stay there for the next growing cycle. The proportion of *Salmonella* that are within each resistance class also carry over from one growing cycle to the next. The connection between the two sub-models can be seen in Figure 2.6

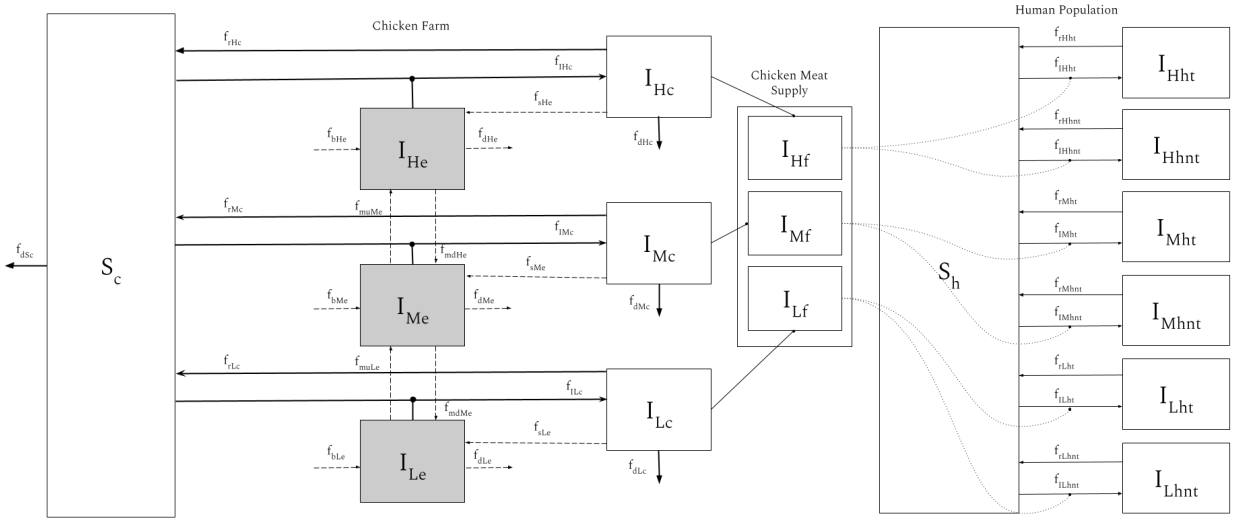


Figure 2.6: The connection between the two sub-models is facilitated by the proportion of meat that is infected, $I_{Hf}, I_{Mf}$, and $I_{Lf}$ for high, medium, and low antibiotic resistance, respectively. The curved dotted lines between these compartments and the rates of infection represent the role of these proportions in these rate equations and serve to represent the connection between the two models.

## 2.4 Economic Quantification

Since one of the major goals of constructing this model is to compare economic gain by the agriculture industry to healthcare costs of antibiotic resistant infections, it is necessary to quantify the costs and benefits of several steps of our model. First, we are interested in the economic gain of farmers using antibiotics derived from healthier flocks and larger chickens. We calculate the profit to the agriculture system as the product of the profit per pound of chicken (represented by $c_c$) and the pounds of chicken produced (represented by $w_c$). The pounds of chicken produced depends on the number of chickens alive at the end of the 48 day growing period and the amount of antibiotics used, as antibiotic use can lead to up to a 5% increase in weight. The base weight of chickens without any antibiotic input is 4.5 lbs, and antibiotics can increase the weight per chicken up to 4.725 pounds. The function for the pounds of chicken produced as a function of antibiotic use ($A$) and number of chickens ($S_c + I_{Hc} + I_{Mc} + I_{Lc}$) is consequently as follows:

$$w_c = 4.5(1 + \frac{0.05A}{1+A})(S_c + I_{Hc} + I_{Mc} + I_{Lc})$$

And the total profit to the agriculture sector is calculated by:

$$\text{Total agriculture profit} = c_c w_c = c_c(4.5(1 + \frac{0.05A}{1+A})(S_c + I_{Hc} + I_{Mc} + I_{Lc}))$$

We calculate the cost to the healthcare system as the sum of the cost for each level of antibiotic-resistant *Salmonella* infection. The cost for each level of infection is equal to the product of the number of people sick with each infection level times the number of days they are sick (represented as $n_{Xht}$ and $n_{Xhnt}$ for those seeking treatment and not, respectively) and the cost to treat each person with the infection (represented as $c_{Xht}$ and $c_{Xhnt}, X \in \{L, M, H\}$, for those seeking treatment and not, respectively). The number of people sick times how long they are sick can be computed by integrating each function of number of people in each category over the simulation time period ($t_{start}$ to $t_{end}$), as seen below:

$$\begin{aligned}
n_{Hht} &= \int_{t_{start}}^{t_{end}} I_{Hht}(t)dt \\
n_{Hhnt} &= \int_{t_{start}}^{t_{end}} I_{Hhnt}(t)dt \\
n_{Mht} &= \int_{t_{start}}^{t_{end}} I_{Mht}(t)dt \\
n_{Mhnt} &= \int_{t_{start}}^{t_{end}} I_{Mhnt}(t)dt \\
n_{Lht} &= \int_{t_{start}}^{t_{end}} I_{Lht}(t)dt \\
n_{Lhnt} &= \int_{t_{start}}^{t_{end}} I_{Lhnt}(t)dt
\end{aligned}$$

The total cost to the healthcare sector can be seen by the following sum:

Total healthcare cost = $\sum_{\text{all } Y} c_Y n_Y$ where $Y \in \{Hht, Hhnt, Mht, Mhnt, Lht, Lhnt\}$.

The cost values needed for these computations are summarized in Table 2.3

| Parameter | Description | Units | Value [Source] |
|---|---|---|---|
| $c_c$ | Profit per pound of chicken produced | $\frac{\$}{chicken}$ | 0.25 [30] |
| $c_{Hht}$ | Cost of $I_{Hht}$ infection per person per day | $\frac{\$}{person*days}$ | 2516.23 [Estimate based on [24],[16]] |
| $c_{Hhnt}$ | Cost of $I_{Hhnt}$ infection per person per day | $\frac{\$}{person*days}$ | 293.15 [Estimate based on [24],[16]] |
| $c_{Mht}$ | Cost of $I_{Mht}$ infection per person per day | $\frac{\$}{person*days}$ | 2375.46 [Estimate based on [24],[16]] |
| $c_{Mhnt}$ | Cost of $I_{Mhnt}$ infection per person per day | $\frac{\$}{person*days}$ | 276.75 [Estimate based on [24],[16]] |
| $c_{Lht}$ | Cost of $I_{Lht}$ infection per person per day | $\frac{\$}{person*days}$ | 1759.60 [Estimate based on [24],[16]] |
| $c_{Lhnt}$ | Cost of $I_{Lhnt}$ infection per person per day | $\frac{\$}{person*days}$ | 205.00 [Estimate based on [24],[16]] |

Table 2.3: Cost and profits parameters, descriptions, and values. Costs of each infection category include treatment and lost productivity due to illness.

# Chapter 3

# Numerical Experiments

## 3.1 Impact of Antibiotic Use on Chicken Population

As we are primarily interested in the impact of antibiotic use on incidence of antibiotic-resistant *Salmonella* in chicken and human populations, we will focus our experiments on manipulating the parameter $A$, representing the concentration of antibiotics administered to each chicken. For all experiments, all $20,000$ chickens begin as susceptible, and the concentration of low resistance *Salmonella* in the environment is set to $10,000\frac{CFU}{mL}$, while the concentration of medium and high resistance bacteria is set to $0\frac{CFU}{mL}$. The system of differential equations is solved over a 48 day time period, as this is approximately equal to the growing period of broiler chickens before slaughter.

First, we investigate the impact of different $A$-values on the incidence of *Salmonella* in a chicken population. We decided to investigate antibiotic use below all MICs ($0\frac{\mu g}{mL}$), between the low and medium MICs ($75\frac{\mu g}{mL}$), between the medium and high MICs (150 and $225\frac{\mu g}{mL}$) and above the high MIC ($300\frac{\mu g}{mL}$). When $A$ is set to $0\frac{\mu g}{mL}$, most chickens become infected with *Salmonella*, likely because there are no antibiotics present to combat the spread of the bacteria (see Figure 3.1). Most are infected with low antibiotic resistance *Salmonella*, which

may be because the low resistance *Salmonella* has a competitive advantage in the absence of antibiotics due to its higher reproduction rate constant ($b_{Le} > b_{Me} > b_{He}$).

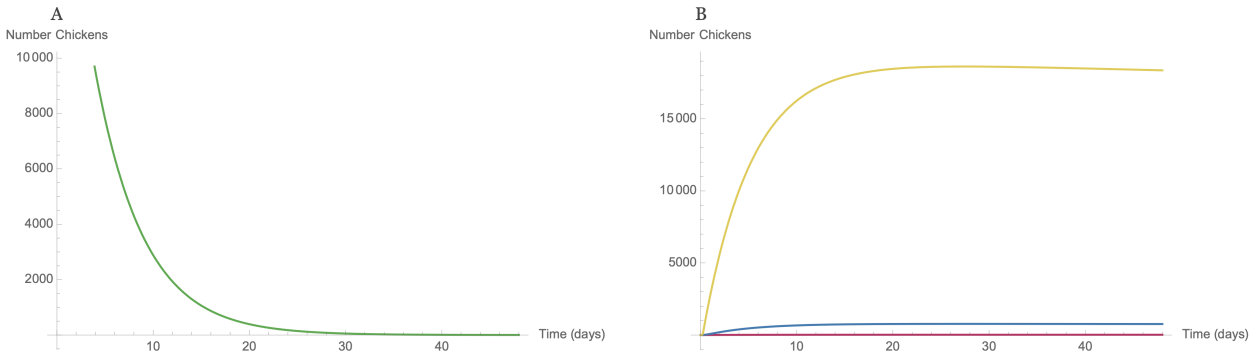


Figure 3.1: Chicken populations over time with $A = 0\frac{\mu g}{mL}$. (A) Susceptible chicken population ($S_c$) over the 48 day growing period. (B) High (pink), medium (blue), and low (yellow) antibiotic resistant *Salmonella*-infected chicken population over time in days. By the end of this simulation, 99.99% of all chickens were infected with *Salmonella*, and 95.8% of the original 20,000 chickens were still alive.

When the antibiotic concentration $A$ is increased to $75\frac{\mu g}{mL}$, a smaller proportion of chickens are infected with *Salmonella*, but more chickens are infected with medium resistance *Salmonella* than in the experiment without antibiotics (see Figure 3.2). Since $75\frac{\mu g}{mL}$ is greater than the MIC for low resistance *Salmonella* ($64\frac{\mu g}{mL}$), many of the chickens infected with low resistance *Salmonella* recovered with antibiotic treatment; however, $75\frac{\mu g}{mL}$ is below the MIC for medium resistance *Salmonella* infections, so chickens infected with medium resistance infections do not recover, leading to a higher prevalence of infections from this more resistant strain. It takes a few days for the medium-resistant infections to become dominant, since the initial population of bacteria is all low resistance *Salmonella*. In order for medium-resistant infections to become the most prevalent, there must be mutations to lead to birth of medium-resistant *Salmonella*, which then infect susceptible chickens who shed more medium resistance bacteria. Since most of the low resistance *Salmonella*-infected chickens recover with antibiotic treatment, there is less shedding of low resistance bacteria, and gradually the medium resistance bacteria come to dominate the infections.

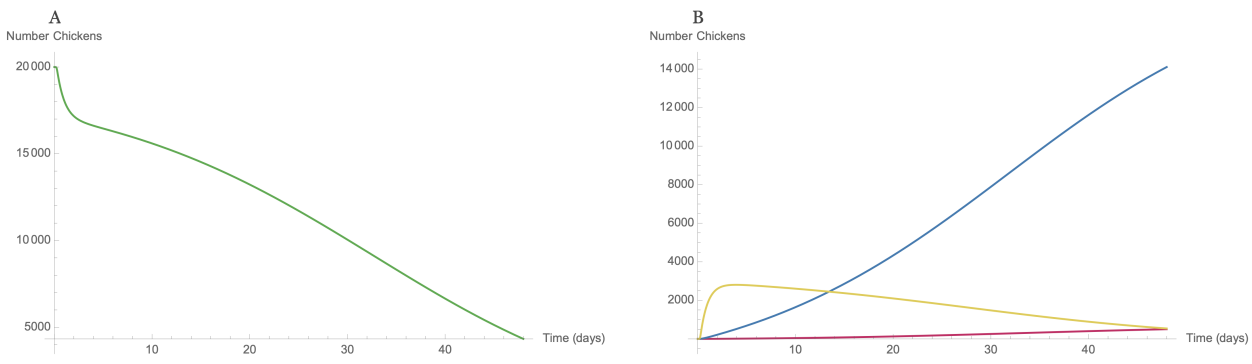


Figure 3.2: Chicken populations over time with $A = 75\frac{\mu g}{mL}$. (A) Susceptible chicken population ($S_c$) over the 48 day growing period. (B) $I_{Hc}$ (pink), $I_{Mc}$ (blue), and $I_{Lc}$ (yellow) population over time in days. By the end of this simulation, 73.22% of all chickens were infected with *Salmonella*, and 97.45% of the original $20,000$ chickens were still alive.

Next, we ran experiments with antibiotic concentrations above the MIC for medium resistance ($128\frac{\mu g}{mL}$) but below the MIC for high resistance ($256\frac{\mu g}{mL}$). With $A = 150\frac{\mu g}{mL}$ and $A = 225\frac{\mu g}{mL}$, we see a dramatic decrease in the number of chickens infected with *Salmonella* overall, but an increase in the proportion of infections which are at the highest antibiotic-resistance level (see Figure 3.3). The decrease in infections may be because low and medium resistance *Salmonella*-infected chickens recover at a higher rate, leading to less *Salmonella* in the environment and fewer infections overall. Most of the remaining infections are highly resistant to the antibiotic because the antibiotic is not administered at a high enough concentration to kill the highly resistant *Salmonella*. The number of chickens infected with high resistance *Salmonella* grows very rapidly in simulations for both $150\frac{\mu g}{mL}$ and $225\frac{\mu g}{mL}$ of ampicillin applied to the chicken population. This is particularly alarming given the fact that none of the initial population of *Salmonella* begins having a high level of ampicillin resistance. This means that in 48 days, the mutations to higher resistance were sufficiently amplified in the *Salmonella* population to become the dominant type of infection. If the simulation were run for longer than 48 days, we may have seen an even more dramatic increase in the high-resistant infections. Furthermore, in the combined model, the concentration of

bacteria remains the same for consecutive growing cycles within the same farm. This means that most of the *Salmonella* in the environment has high antibiotic resistance, so the next crop of chickens will likely have even more cases of high resistance infections. In the long run, the number of high resistance infections will likely increase.

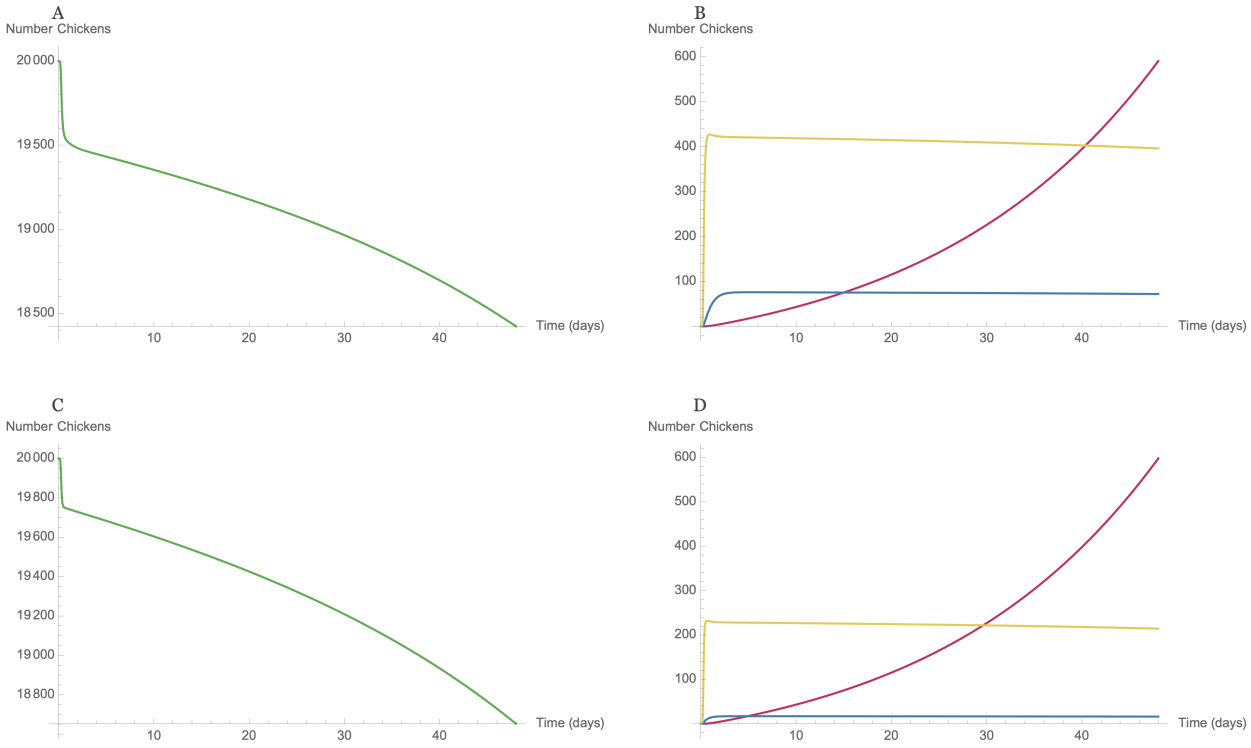


Figure 3.3: Chicken populations over time with $A = 150\frac{\mu g}{mL}$ and $225\frac{\mu g}{mL}$. (A) Susceptible chicken population ($S_c$) over the 48 day growing period, with $A = 150\frac{\mu g}{mL}$. (B) $I_{Hc}$ (pink), $I_{Mc}$ (blue), and $I_{Lc}$ (yellow) populations over time in days, with $A = 150\frac{\mu g}{mL}$. (C) Susceptible chicken population ($S_c$) over the 48 day growing period, with $A = 225\frac{\mu g}{mL}$. (D) $I_{Hc}$ (pink), $I_{Mc}$ (blue), and $I_{Lc}$ (yellow) populations over time in days, with $A = 225\frac{\mu g}{mL}$. 4.45% and 3.27% of chickens were infected with *Salmonella* at the end of the $A = 150\frac{\mu g}{mL}$ and the $225\frac{\mu g}{mL}$ experiments, respectively.

Finally, when $300\frac{\mu g}{mL}$ of antibiotics were given to the chicken populations, most chickens infected with *Salmonella* healed and the *Salmonella*-infected chicken populations declined overall (see Figure 3.4). The populations reached equilibrium pretty quickly, with most chickens still being infected with low resistance *Salmonella*, likely because of the higher reproduction rate associated with low resistance *Salmonella*. This concentration of antibiotics

exceeds even the highest MIC (the MIC associated with $I_{Hc}$ infections is $256\frac{\mu g}{mL}$), which is why most chickens recovered from their infections with the help of antibiotics.

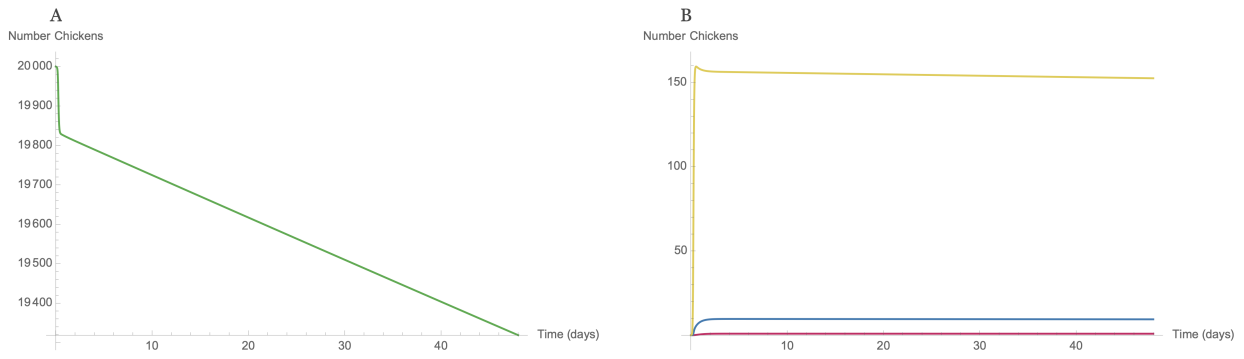


Figure 3.4: Chicken populations over time with $A = 300\frac{\mu g}{mL}$. (A) Susceptible chicken population ($S_c$) over the 48 day growing period. (B) $I_{Hc}$ (pink), $I_{Mc}$ (blue), and $I_{Lc}$ (yellow) populations over time in days. By the end of this simulation, 0.83% of all chickens were infected with *Salmonella*, and 97.46% of the original $20,000$ chickens were still alive.

The impact of antibiotic use on the proportion of chickens infected with *Salmonella* can further be seen after iterating through values of $A$ ranging from 0 to 300 and calculating the final proportion of chickens infected with *Salmonella*. The behavior of the resulting plot changes dramatically after each MIC ($64, 128$ and $256\frac{\mu g}{mL}$), with much higher rates of infection being observed below the lower MIC values. This is likely because the higher concentrations of antibiotics lead to most chickens recovering from their infections, leaving mostly those infected with high resistance *Salmonella*. We can also observe that the proportion of *Salmonella* infected chicken with high resistance infections changes after each MIC, with more high resistance infections occurring after the medium resistance MIC ($128\frac{\mu g}{mL}$) and before the high resistance MIC ($256\frac{\mu g}{mL}$). Both relationships can be seen in Figure 3.5.

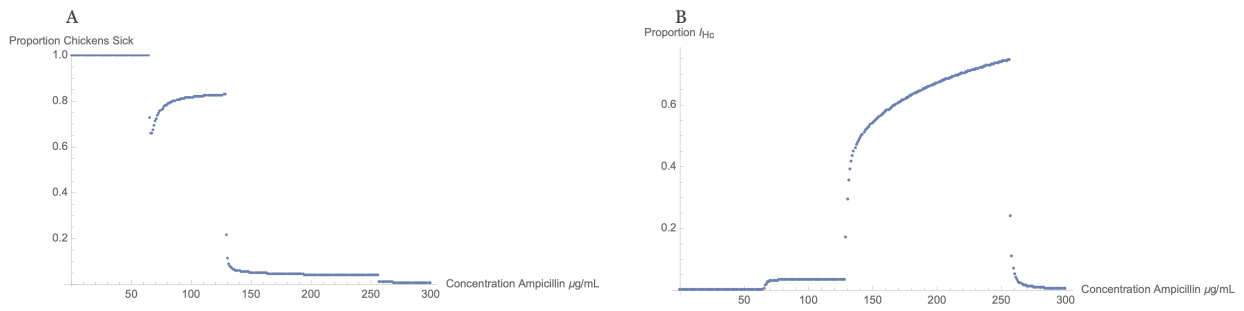


Figure 3.5: (A) Proportion of chickens with *Salmonella* infections by concentration of antibiotic applied (in $\frac{\mu g}{mL}$) (B) Proportion of *Salmonella*-infected chickens with high resistance infections by concentration of antibiotic applied (in $\frac{\mu g}{mL}$).

## 3.2 Impact of Antibiotic Use on Human Population

Next, we conducted experiments investigating the impact of changing the amount of antibiotics given to chicken on the spread of *Salmonella* in the human population. At the beginning of each experiment, the entire population of $10,000$ people is susceptible to *Salmonella*, meaning no humans start infected. The only source of *Salmonella* is the food supply, which is made of the infected chicken meat. Three 48 day cycles were run, with four different chicken suppliers, for a total of 12 deliveries over 148 days.

When no antibiotics are given to the chicken population, approximately 6.03% of the human population becomes infected with *Salmonella* (see Figure 3.6). Most of these infections have low resistance to antibiotics, and very few have high resistance. This makes sense considering the results presented in Figure 3.1, which shows that most of the chickens coming out of a farm using no antibiotics are infected with *Salmonella* with low antibiotic resistance. For each category of resistance, there were more infections treated at home than at a hospital. The total cost of treating all *Salmonella* infections in this experiment was $\$50,990,400$.

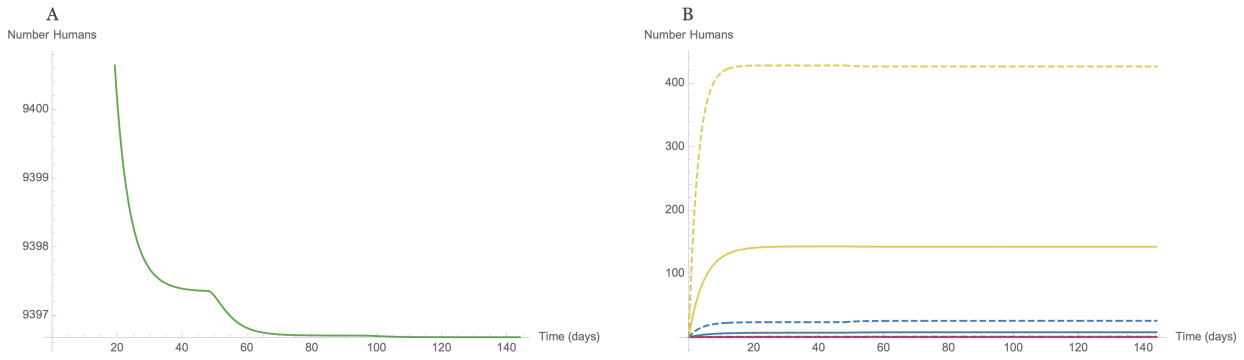


Figure 3.6: Human populations when chickens are given $0\frac{\mu g}{mL}$ of ampicillin (A) Number of susceptible (uninfected) humans over time (B) Number of humans with high (pink), medium (blue), and low (yellow) antibiotic-resistant *Salmonella* infections. Solid lines indicate humans whose infections were treated in a hospital and dashed lines indicate humans whose infections were treated at home.

When chickens are given $75\frac{\mu g}{mL}$ of ampicillin (which is greater than the MIC of $64\frac{\mu g}{mL}$ for low resistance infections), the number of infections in the human population is about the same. However, more of those infections were of medium antibiotic-resistant *Salmonella* (see Figure 3.7). This follows from the results presented in Figure 3.2, which show that that most chickens infected with *Salmonella* have medium resistance infections when $75\frac{\mu g}{mL}$ of antibiotics are administered. This higher proportion of medium resistance infections resulted in this set of infections being more expensive to treat, as reflected in the healthcare cost of $\$67,045,600$, which is $\$16,055,200$ higher than the cost when no antibiotics are given.

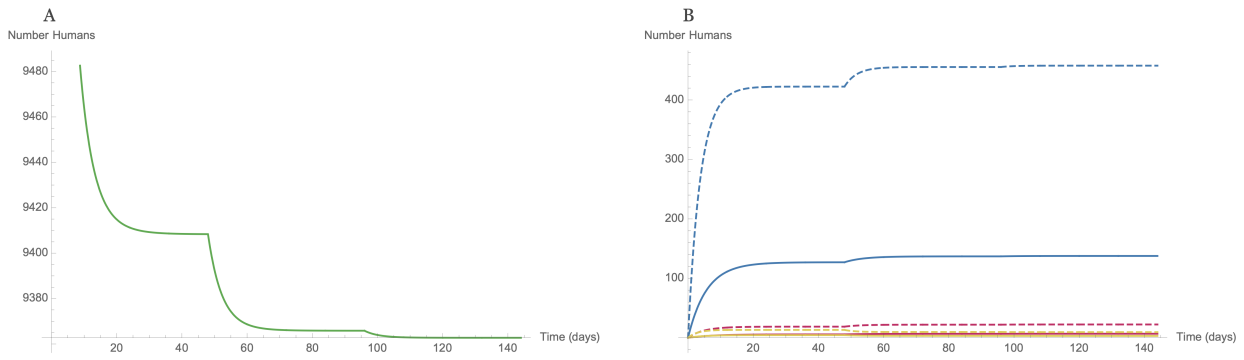


Figure 3.7: Human populations when chickens are given $75\frac{\mu g}{mL}$ of ampicillin (A) Number of susceptible (uninfected) humans over time (B) Number of humans with high (pink), medium (blue), and low (yellow) antibiotic-resistant *Salmonella* infections. Solid lines indicate humans whose infections were treated in a hospital and dashed lines indicate humans whose infections were treated at home. Unlike when $0\frac{\mu g}{mL}$ are administered, most of the infections are of medium antibiotic resistance.

We next tested the impact of administering $150\frac{\mu g}{mL}$ of ampicillin to the chicken population, as this is greater than the MICs of both low ($64\frac{\mu g}{mL}$) and medium ($128\frac{\mu g}{mL}$) resistance infections, but less than the MIC of high resistance infections ($256\frac{\mu g}{mL}$). In this simulation, there were far fewer infections, with only 0.50% of the human population becoming infected with *Salmonella*. However, most of the infections were of high antibiotic resistance *Salmonella* (see Figure 3.8). The number of infected individuals increases after each 48 day growing period, likely because the proportion of *Salmonella* that was high resistance increases in the chicken farm, and the chicken farm is not thoroughly disinfected after each growing cycle. Overall, the cost to treat these infections was lower, likely due to the smaller number of infections, at $\$6,162,120$.

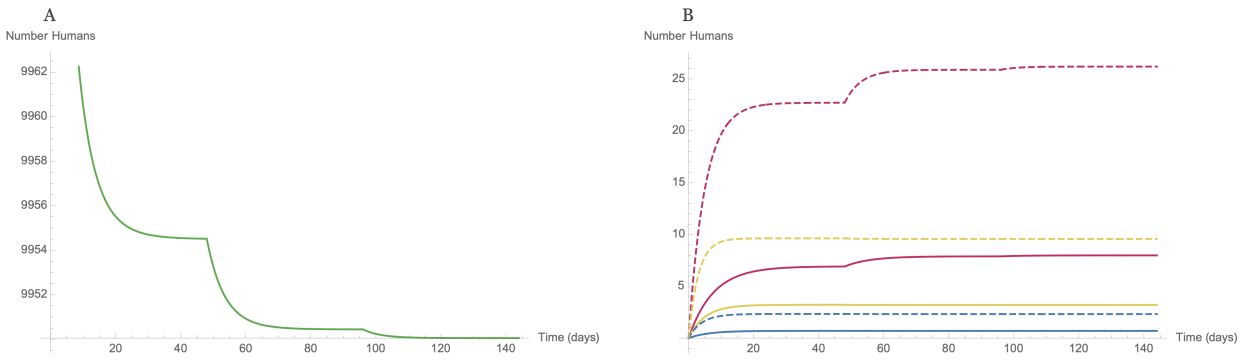


Figure 3.8: Human populations when chickens are given $150\frac{\mu g}{mL}$ of ampicillin (A) Number of susceptible (uninfected) humans over time (B) Number of humans with high (pink), medium (blue), and low (yellow) antibiotic-resistant *Salmonella* infections. Solid lines indicate humans whose infections were treated in a hospital and dashed lines indicate humans whose infections were treated at home. Though there are fewer infections in this simulation than when lower concentration of antibiotic are administered, most of these infections are of high resistance *Salmonella*.

Finally, we tested the impact of administering $300\frac{\mu g}{mL}$ of ampicillin to the chicken population. This concentration of ampicillin is greater than the MICs of all three resistance levels, and hence kills most of the *Salmonella* bacteria present in the infected chickens, allowing them to recover (see Figure 3.9). This results in a smaller proportion of the meat supply being contaminated with *Salmonella*. In this simulation, only 0.05% of the human population is infected with *Salmonella* and treating all of these infections costs only $\$462,091$.

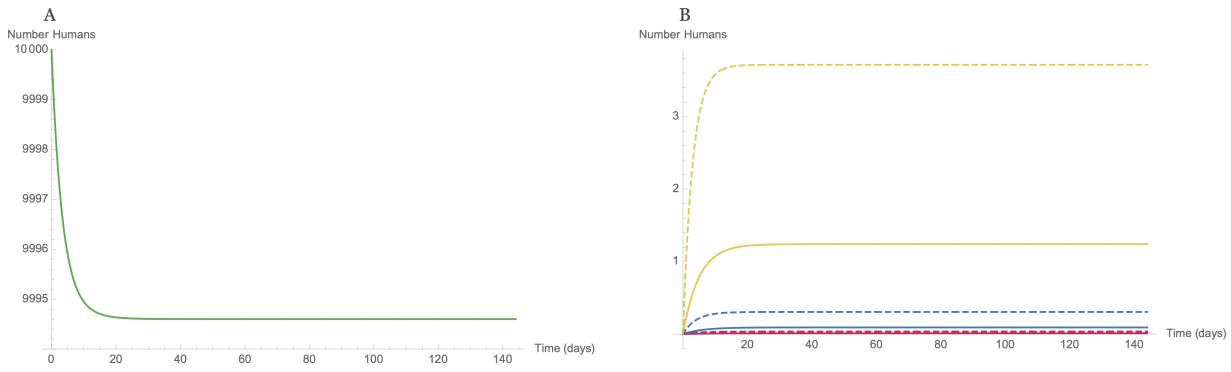


Figure 3.9: Human populations when chickens are given $300\frac{\mu g}{mL}$ of ampicillin (A) Number of susceptible (uninfected) humans over time (B) Number of humans with high (pink), medium (blue), and low (yellow) antibiotic-resistant *Salmonella* infections. Solid lines indicate humans whose infections were treated in a hospital and dashed lines indicate humans whose infections were treated at home. There were very few infections in this experiment.

## 3.3 Economic Quantification

A major goal of this model is to quantify both the costs to the healthcare system and the profit earned by the agriculture sector as a function of antibiotic use. To do this, we iterated over antibiotic concentrations from $0\frac{\mu g}{mL}$ to $300\frac{\mu g}{mL}$ and calculated both costs using the methods laid out in Section 2.4. The results can be seen in Figure 3.10. When antibiotic concentrations are below the lowest MIC ($64\frac{\mu g}{mL}$), healthcare costs well exceed agricultural profit, likely because the high prevalence of *Salmonella* in the chicken population leads to many cases in the human population. Healthcare cost increases when the concentration is between the MIC for low resistance ($64\frac{\mu g}{mL}$) and the MIC for medium resistance ($128\frac{\mu g}{mL}$), likely because in this range there are more cases of medium antibiotic resistant *Salmonella*, which cost more to treat than low resistance infections. When antibiotic concentration is between the MIC for medium resistance ($128\frac{\mu g}{mL}$) and the MIC for high resistance ($256\frac{\mu g}{mL}$), the healthcare costs are less than the agricultural profit, likely because there are fewer cases overall with higher antibiotic use. The cases that do occur are mostly of high resistance

*Salmonella*, but the increased price of treating these cases does not outweigh the reduction in cost due to fewer cases. Past $256\frac{\mu g}{mL}$, healthcare costs are even lower, due to most *Salmonella* being killed. Profit to the agriculture sector mostly increases linearly with increased antibiotic use, which makes sense, as in our model increased antibiotic use both helps chickens survive at a higher rate and increases their growth, providing the farmer with more pounds of meat to sell.

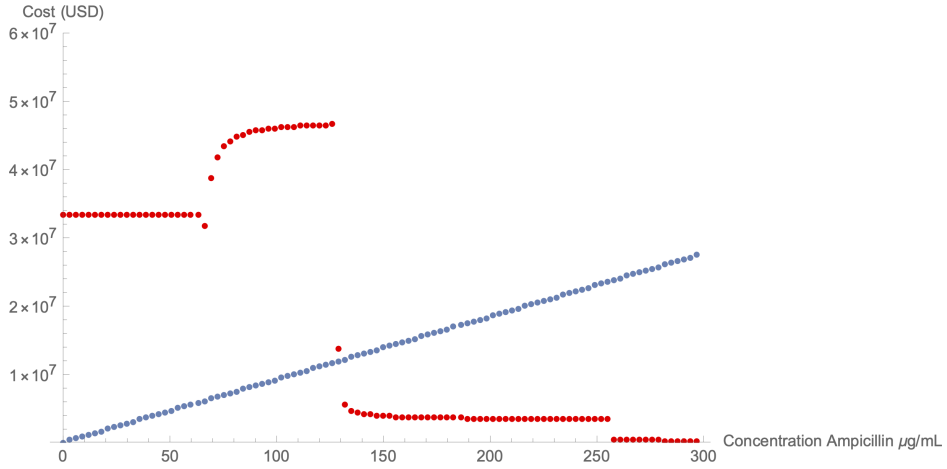


Figure 3.10: Monetary quantification (in USD) of cost of treating *Salmonella* infections (red) and profit to farmers (blue) against antibiotic concentration administered to chickens (in $\frac{\mu g}{mL}$). The difference between these two metrics is greatest when antibiotic concentration is between $64\frac{\mu g}{mL}$ and $128\frac{\mu g}{mL}$, or when the antibiotics can clear most low resistance infections but not medium resistance infections. When antibiotic use exceeds $128\frac{\mu g}{mL}$, agricultural profit exceeds healthcare costs.

# Chapter 4

# Discussion

With this model of antibiotic-resistant *Salmonella*, we hoped to explore disease dynamics in both commercial broiler chicken and human populations and to quantify the economic impact of antibiotic use. Though the accuracy of our model could be improved with access to more accurate parameter values or more precise parameter estimation (which we will discuss further in Chapter 5), the framework created by our model and general trends displayed still offer interesting insights. The model displays the distribution of infections between resistance levels changing as antibiotic use changes, with higher administered concentrations leading to a higher proportion of the infections being of higher resistance levels. This is consistent with the reality that antibiotic use amplifies the presence of antibiotic resistant bacteria. Additionally, our model shows that overall, infections decrease when higher concentrations of antibiotics are used. This too aligns with our biological motivation, as antibiotics are generally used to treat or prevent infections, and it provides financial incentive for the prophylactic use of antibiotics.

In terms of the economic impact of antibiotic use, our model both confirmed preconceptions about the harms of antibiotics and provided unexpected results. The greatest difference in costs to the healthcare system and farmer profits is observed when the antibiotic concen-

tration is just enough to kill the bacteria most susceptible to the drug (between 64 and $128\frac{\mu g}{mL}$. This could be described as a "sub-therapeutic" dose, as it does not clear the more resistant infections and thus amplifies their presence in a population. Use of antibiotics in these lower concentrations, such as for growth promotion in livestock, is warned against or banned for precisely this reason [28]. In demonstrating the economic detriment and the increase in resistance associated with such antibiotic use, our model affirms previously established knowledge on animal antibiotic use.

A more surprising result from our model is the prediction that healthcare costs dramatically decrease when antibiotic concentration is increased past $128\frac{\mu g}{mL}$ (Figure 3.10). Since $128\frac{\mu g}{mL}$ is the MIC for medium resistance *Salmonella*, this level of antibiotic use should amplify the presence of high resistance bacteria. While we do see a higher proportion of high resistance bacteria, the lower level of bacteria overall due to the high concentration of the antibiotic seems to have a stronger effect on the number of infected chickens and hence infected humans. In combination with higher income to farmers from increased chicken production and healthier chickens, this result seems to indicate that greater animal antibiotic use is the best option to maximize economic utility. However, the fact that $40 - 70\%$ of *Salmonella* infections are of high antibiotic resistance when a concentration $128 - 256\frac{\mu g}{mL}$ of ampicillin is administered should still give us pause (see Figure 3.5). Though the economic cost is still low in the model because of decreased number of cases, these high antibiotic resistance cases are likely to be more severe, harder to treat, and more likely to result in death. Additionally, the presence of more antibiotic resistance *Salmonella* has long term detriments that are hard to quantify on a short time frame. Other bacteria may gain access to antibiotic resistance genes in a hospital setting or within an individual human. This could result in more harmful species of bacteria becoming resistant to ampicillin, leading to a greater number of hard-to-treat infections. Finally, the rise in antibiotic resistance can reduce efficacy of drugs, increasing the cost of research and development to make new drugs and leading to

increased mortality from previously treatable conditions [33]. While our model does seem to indicate overall benefits to increased antibiotic use in poultry populations, it is important to interpret that result in the context of the more complicated long-term impacts of antibiotic resistance.

Our model presents the complex nature of antibiotic resistance resulting from antibiotic use in animal agriculture. While some antibiotic use greatly reduces the risk of livestock death from disease and decreases overall prevalence of *Salmonella*, sub-therapeutic doses of antibiotics lead to higher healthcare costs and higher prevalence antibiotic resistance. Higher antibiotic use reduces healthcare costs but increases the proportion of *Salmonella* which are of higher levels of antibiotic resistance. This complicated behavior does not give clear answers to policymakers and others looking to minimize the economic and health risks of antibiotic resistance in *Salmonella*. However, our model does serve as an interesting and useful basis upon which more complex and nuanced models could be built.

# Chapter 5

# Future Extensions and Conclusion

The accuracy of our model could be much improved with more accurate parameter values. In our model, many parameter values could not be found in the literature, and so these parameters were estimated one or two at a time. When estimating only one or two parameters at a time, however, we had to fix some of the unknown parameters at a random value and then estimate them after fixing the variables we estimated first. This process introduced the possibility that the order in which we estimated the parameters may have affected their values. Future studies could expand upon our work by implementing a parameter estimation method which more accurately estimate multiple parameters at once. An example of such a method is called genetic algorithms (GA) [6]. In this algorithm, a random sample of vectors of possible parameter values are selected, with each parameter value chosen between specified bounds. The solutions to the model generated with these parameters are then generated and compared to the expected results. The top 10% of the vectors will move to the next "step", where they can "mutate" – that is, their values change slightly – and the solutions are then run again and once again compared to the expected results. The algorithm continues until a stopping condition is met, that is, the estimation is good enough [6]. The algorithm is likened to biological evolution because the best parameter values emerge out of a process

where the best set of parameters performs better than the rest in a similar manner to how organisms with high fitness outperforms their peers in natural selection. Such an algorithm could perhaps help us to find parameter values which better represent the situation than can be accomplished through estimating only a few parameters at a time.

Another interesting extension would be to investigate the dynamics of *Salmonella* resistant to multiple drugs. Multi-drug resistance is particularly important to public health because bacterial infections that are resistant to multiple antibiotics are much harder and more expensive to treat than infections resistant to one or no drugs. In our model, we only measure resistance to ampicillin (though the model is generic enough to work for any single antibiotic at a time), and modeling multi-drug resistance with our compartment model would make the model more complicated. If we had two antibiotics, call them $A$ and $B$ applied to the chicken population, and two resistance levels, $H$ and $L$ for each, then we could subdivide our infected chicken population into four groups based on their resistance to both drugs. So the groups would be:

1. Susceptible (low resistance) to both drugs: $I_{AL,BL}$
2. Susceptible to A, resistant to B: $I_{AL,BH}$
3. Susceptible to B, resistant to A: $I_{AH,BL}$
4. Resistant to both A and B: $I_{AH,BH}$

Each of these groups would have its own compartment in the compartment diagram and corresponding differential equation. With only two levels of resistance and two drugs, this is not too complicated, but increasing either quickly adds many new compartments. Austin and Anderson explore methods of modeling the multi-drug resistance dynamics in their 1999 paper [7], and they arrive at a similar model to what is described above.

A third interesting extension of this work could focus on quantifying the risk of *Salmonella* infection originating in meat processing. Since *Salmonella* infects the gastrointestinal tract

in chickens, the bacteria are mostly contained within that part of the chicken carcass. When chicken meat is processed into different cuts, the bacteria in one part of the chicken carcass can spread to other parts. This leads to comminuted chicken meat (ground, minced, deboned, etc) and mechanically separated chicken meat having higher prevalence of *Salmonella*. According to the U.S. Food Safety and Inspection Service (FSIS), approximately 25% of comminuted chicken meat and 85% of mechanically separated chicken is infected with *Salmonella* [38]. This is much higher than the incidence of *Salmonella* in whole chicken carcasses (5%) [38], which is the metric we used to calibrate our model. Distinguishing between different cuts of meat and modeling the spread of *Salmonella* in meat processing could prove an interesting extension of this project which increases the accuracy of the model. Furthermore, it would be interesting to study the effect of this processing step under different levels of antibiotic use. In the situation of low antibiotic use, a larger proportion of the population is already infected with *Salmonella*, so the processing would have a weaker impact on spreading *Salmonella* from infected chicken carcasses to previously uninfected carcasses. However, when more antibiotics are used, a smaller proportion of the chicken population is infected with *Salmonella*, so the spread of *Salmonella* by the processing would have a stronger effect. This would also mean that more of the chicken would be infected with high resistance *Salmonella* in this case, as with higher antibiotic use (between the medium and high MICs), most of the infected chickens are infected with high antibiotic resistant *Salmonella*.

A final extension of this work would be to randomize the proportion of *Salmonella* which mutate to different resistance classes at each time step. In our current model, the rate of *Salmonella* mutating to a different resistance class is controlled by a fixed proportion, namely, the parameter $q$. In the future, we would like to have the mutation rate pulled from a binomial distribution with $p$ equal to the average mutation rate and $n$ equal to the number of bacteria born into each bacterial class during that time interval. Including an element of randomness in our model would increase its complexity as well as making it more accurate.

In this project, we have developed an interconnected differential equations model of antibiotic-resistant *Salmonella* in both a commercial broiler chicken population and a human population. We demonstrated how this model can be used to run several experiments which can predict both incidence of illness and economic costs associated with treatment. The accuracy of our results could be improved with more accurate parameter values or systematic parameter estimation techniques, but overall our model still yields interesting results on the impact of antibiotics on our study populations and on healthcare costs. Furthermore, our model is relatively generic, that is, the parameter values can easily be adjusted to instead model a different fecal-oral route food borne illness and a different antibiotic. While our current model is limited to modeling resistance to a single antibiotic, relatively simple, though perhaps tedious, adjustments could be made to study multi-drug resistance. This flexibility allows variations of our analysis to be applied to a wide variety of public health questions.

# Acknowledgements

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