CORNELL UNIVERSITY MATHEMATICS DEPARTMENT SENIOR THESIS

Mathematical Models for Salmonella Transmission Dynamics

A THESIS PRESENTED IN PARTIAL FULFILLMENT
OF CRITERIA FOR HONORS IN MATHEMATICS

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1 Introduction

Salmonella is a major zoonot ic disease that is transmitted from cattle to humans in beef [1], milk and other dairy products [2][3], or through direct contact with sick animals and their environment [4]. It accounts for approximately 1.4 million clinical cases, 16,000 hospitalizations and 600 deaths annually in the United States [5]. The recent emergence of multi-drug resistant *Salmonella* strains increases the mortality rate of the salmonellosis, and complicates the disease dynamics as well as the corresponding treatments and control strategies [6].

Mathematical models provide a comprehensive framework for understanding the disease transmission behaviors, as well as for evaluating the effectiveness of different intervention strategies [7]. These models have been widely used in studying diseases such as measles [8] [9], influenza[10][11] and cholera[12][13] . However, there are only three existing mathematical models of *Salmonella* transmission dynamics in dairy herds. Xiao et al. investigated the effects of demographic and epidemiologic factors on the transmission behavior and the threshold for invasion using theoretical deterministic [14] and stochastic [15] models. Chapagain et al. [16] fitted empirical data of a *Salmonella Cerro* outbreak in a dairy herd to an SIR model with multiple infectious stages. A lot of significant issues involved in *Salmonella* transmission dynamics were not addressed, such as the presence of subclinical cases as well as long-term shedders.

Empirical studies have found that subclinical shedding is more common than clinical disease[17]. Subclinical shedders are an important source of infection particularly in endemic herds but have not been incorporated into previous models of *Salmonella* transmission [16]. Long-term shedders play an important role in *Salmonella* disease dynamics as they transmit infection without showing any visible signs[18]. This makes detection and diagnosis difficult and poses a challenge for control. The long-term shedders may be shedding the organism undetected at slaughter, and therefore, pose a risk to human health. A US study found that 14.9% of 2287 culled dairy cows at market were tested fecal positive for *Salmonella*[19]. *Salmonella* has been isolated from ground beef in the US[20] and the consumption of beef has been associated with a number of *Salmonella* outbreaks [1][?] illustrating that the presence of infected cattle and consequent risk of cross-contamination during processing represents a significant food safety hazard.

The objective of this study is to show, through model simulations, how heterogeneity in infectious period and contagiousness is demonstrated in the different infectious stages, and how it relates to the prevalence of salmonellosis in dairy herds. In particular, the study aims at showing the relative importance of clinical and subclinical cases in the transmission of the infection, the role of long-term shedders, as well as the impact of heterogeneity in host infectiousness on the efficiency of control strategies such as vaccination. To address these questions we developed a series of state transition models, in which model parameters were estimated from literature and field outbreak data. Different infectious states representing current knowledge were included.

2 Methods

2.1 Construction of the Models

Systems of ordinary differential equations (ODEs) are used to represent the changes of the state variables in the compartmental flow models, derived from the Kermack and McKendrick SIR model[22]. Two models are modified from the basic SIR model to incorporate multiple infectious stages, each of which has a different force of infection as well as the infectious period.

    The systems of ODEs for Models 1 and 2 are shown below. Figures 1 and 2 display the compartmental flow diagrams of the two models.

Model 1

$$
\begin{aligned}
\frac{dS}{dt} &= \mu N + rR - (\beta_c I_c + \beta_s I_s + \mu)S \\
\frac{dI_c}{dt} &= f(\beta_c I_c + \beta_s I_s)S - (e + m + \mu)I_c \\
\frac{dI_s}{dt} &= (1 - f)(\beta_c I_c + \beta_s I_s)S + eI_c - (h + \mu)I_s \\
\frac{dR}{dt} &= hI_s - (r + \mu)R
\end{aligned}
$$

Model 2

$$
\begin{aligned}
\frac{dS}{dt} &= \mu N + rR - (\beta_c I_c + \beta_s I_s + \beta_{lt} I_{lt} + \mu)S \\
\frac{dI_c}{dt} &= f(\beta_c I_c + \beta_s I_s + \beta_{lt} I_{lt})S - (e + m + \mu)I_c \\
\frac{dI_s}{dt} &= (1 - f)(\beta_c I_c + \beta_s I_s + \beta_{lt} I_{lt})S + eI_c - (h + \mu)I_s \\
\frac{dI_{lt}}{dt} &= f_{lt} h I_s - (h_{lt} + \mu)I_{lt} \\
\frac{dR}{dt} &= (1 - f_{lt})h I_s + h_{lt} I_{lt} - (r + \mu)R
\end{aligned}
$$

    Model 1 consists of individuals which belong to one of the following compartments at each time step: susceptible (S), clinically infected (I_c), subclinically infected (I_s), and recovered (R). Model 2 is modified from Model 1, with a long-term shedding (I_{lt}) compartment incorporated after I_s to investigate the impact of long-term shedders. Note that latent state is not included in any of the models, because the latent period in Salmonella infections is thought to be very short (24-48 hours), and hence it has little impact on the infection dynamics[7]. Also note that in the above diagrams, λ denotes the force of infection, defined as (βI). This represents the density-dependence of the *Salmonella* transmission, which means the prevalence of infection increases with the population size[23][24].
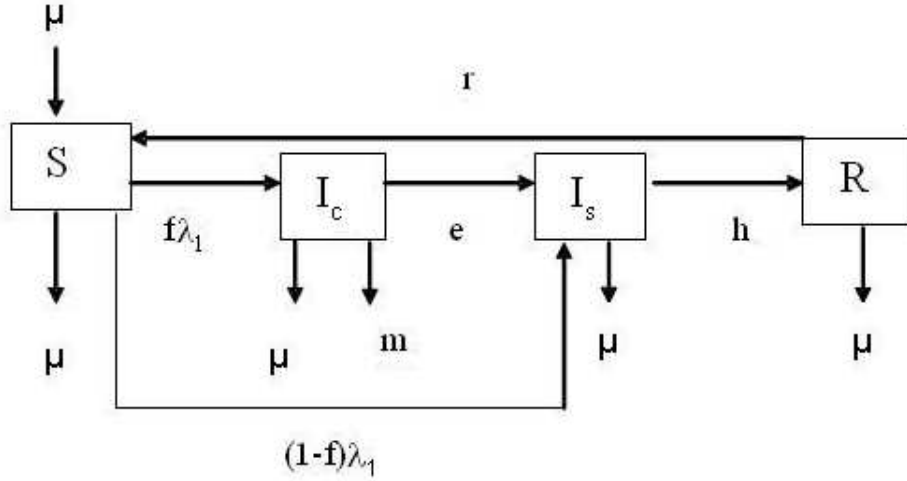
Figure 1: Compartmental Flow Diagram of Model 1

In Model 1, a fraction of the infected animals was assumed to become subclinically infected (I_s) immediately following infection, and all clinically infected animals (I_c) will go to the subclinical before full recovery. These states reflect the observed disease behavior that not all infected animals develop clinical salmonellosis[27], and that individuals which have recovered from clinical disease can continue to shed Salmonella, and hence infect other susceptible animals[28]. It was found in previous studies that exposure to cattle with clinical salmonellosis is a risk factor for development of salmonellosis[24][29], as individuals in I_c tend to shed larger quantities of bacteria in their feces than individuals in I_s. Therefore, the transmission coefficient for I_c is assumed to be 0.0016, almost 27 times than that of I_s, which is 0.000016.

For Model 2, the addition of a I_{lt} compartment reflects the long-term persistence of Salmonella at farm level observed for several serotypes, including multi-drug resistant S. Newport[25] and S. Dublin [26]. On farms with persistent cases of salmonellosis, there are always animals without clinical signs reported to shed Salmonella persistently or intermittently. These animals belong to the I_{lt} compartment in Model 2. Since individuals at the long-term shedding stage do not show clinical signs, the transmission coefficient of I_{lt} is assumed to be equivalent to that of I_s.

The models assume that the population size stays constant. The exit rate of individuals due to natural death and also disease-induced mortality is balanced by the replacement rate. This assumption is in fact a common management practice in dairy herds, as farmers tend to keep the number of animals in a herd constant for efficient utilization of resources. It is also assumed that all animals entering the system are susceptible, and that animals can die from salmonellosis at any point during clinical disease.
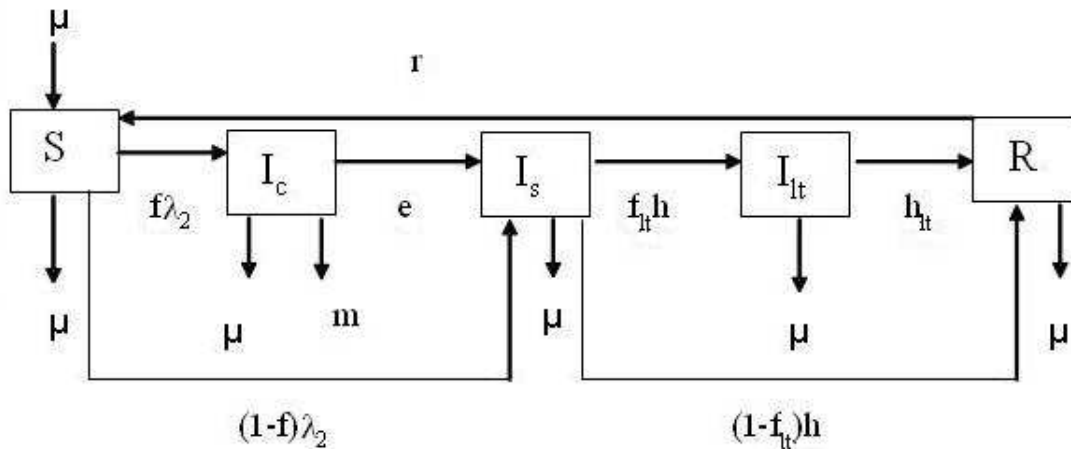
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Figure 2: Compartmental Flow Diagram of Model 2

We further assume that the only route of *Salmonella* infection is direct fecal-oral transmission. Indirect transmission routes such as the influence of the environment are not taken into account, since the contribution of different types of infected animals to transmission would remain unchanged whether or not the indirect routes of infection are included.

2.2 Estimation of Parameter Values

The descriptions and mean values of the parameters of Models 1 and 2 are listed in Table 1 below. The values of the parameters are obtained from several sources, including recent field data, existing literature and assumptions based on biological knowledge of the disease dynamics. The field data used was collected by in a longitudinal study performed by the College of Veterinary Medicine of Cornell University between February 2004 and September 2005[30]. The longitudinal study aimed at determining the incidence of salmonellosis in dairy cattle in the northeastern United States. Of the 34 herds enrolled in the study, 22 of them had at least 2 laboratory-confirmed cases of salmonellosis. These 22 farms were then enrolled in a prospective follow-up study to determine the duration of fecal shedding following clinical salmonellosis. Fecal samples from *Salmonella* culture-positive cases were collected at approximately monthly intervals until 3 consecutive negative samples were obtained, or the animal was lost to follow-up.

The mean replacement and exit rates (μ) for the models are read off directly from the data set of the longitudinal study. The transmission coefficients could not be calculated directly from the data because non-clinical cases (subclinical and long-term shedders) could not be diagnosed on field. Hence the values of the transimission coefficients are estimated

Parameters	Description	Mean Value	Reference
μ	Replacement and exit rate	0.0011	1
β_c	Transmission coefficient for clinical animals	0.0016	n/a
β_s	Transmission coefficient for subclinical animals	0.00006	n/a
β_{lt}	Transmission coefficient for long-term shedders	0.00006	n/a
f	Proportion of infected animals that develop clinical case	0.5	n/a
f_{lt}	Proportion of subclinical cases that become long-term shedders	0.14	2
e	Rate of clinical cases that become subclinical	0.25	1,3
h	Recovery rate for subclinical case	0.041/ 0.057	2
h_{lt}	Recovery rate for long-term shedders	0.01	2
m	Disease-induced induce mortality rate	0.011	2
r	Immunity loss rate	0.01	1

Table 1: List of parameter values Note: 1 - From literature; 2 - From data obtained in the longitudinal study; 3 - From expert opinion; n/a - Assumed value.

based on theoretical assumptions and previous models[**?**]. The recovery rate for I_c is defined as reciprocal of the duration of the clinical signs. The duration of clinical signs was estimated to be 4 days based on literature[27] and the consensus of a panel of experts (T. Divers, C. Guard and L. Warnick, personal communication). Data from the two enrolled herds with the largest outbreaks were used to estimate the remaining recovery rates (h, h_{lt}), fraction of long term shedders (f_{lt}) and diseased induced mortality rates (m):

The recovery rate from subclinical salmonellosis is defined as the reciprocal of the duration of shedding the bacteria. The proportion of animals shedding after clinical salmonellosis follows an exponential decay function. For Model 1, since all infected animals pass from I_c to I_s , the proportion of animals shedding at time t $(P(t))$ was is given by the function[7]:

$$P(t) = e^{-ht}$$

In model 2, there are two populations of animals shedding sequentially. All animals in I_s shed at rate h, and a fraction of $I_s(f_{lt})$ continues to shed at a rate h_{lt}. Solving the corresponding system of differential equations gives the solution $P(t)$[7]:

$$P(t) = (1 - \frac{h}{h - h_{lt}} f_{lt})e^{-ht} + \frac{h}{h - h_{lt}} f_{lt} e^{-h_{lt}t}$$

The decay functions were fitted to the data by nonlinear regression, using the NLIN procedure of SAS (SAS Institute, Cary, NC). The Levenberg-Marquard algorithm [31] was used. Salmonella-induced mortality rate (m) is defined as

$$m = \frac{\text{number of death due to salmonellosis}}{(\text{number of days at risk of death})(\text{number of cows at risk})}$$

Since disease-induced mortality is only possible when the individual is clinically infected, the number of cows at risk is defined as the animals with clinical signs, and the number of days at risk of death is the mean duration of clinical signs.

2.3 Derivation of the R_0 Formula

R_0, the basic reproductive ratio, is defined as the average number of secondary infections produced when one infected individual is introduced into a host population where the rest of the population is susceptible. R_0 is the threshold parameter that determines the existence and local stability of the disease-free equilibrium of a compartmental infectious disease model[32]. If $R_0 < 1$, there exists a locally asymptotically stable equilibrium. In biological terms, it means that on average an infected individual produces less than one new infected individual over the course of its infectious period. Hence the infection cannot persist, and the model will eventually reach a locally stable disease-free equilibrium [33]. Conversely, if $R_0 \geq 1$, the disease-free equilibrium is locally unstable, and the infection will persist because each newly infected individual will spread the disease to at least one susceptible individual on average[33]. The R_0 expressions for Models 1 and 2 are formulated using the 'Next Generation Method'as shown below. Detailed explanation and proofs of the method were developed by van den Driessche and Watmough, 2002 [32].

First we enumerate the compartments in our models from left to right, ie Susceptible $(S) = \text{Compartment1}, \text{Clinically infected}(I_c) = \text{Compartment2}$, and so on. Then let

$$F = \left(\frac{\partial F_i(x)}{\partial x_j}\right)_{x=x_0} \text{ and } V = \left(\frac{\partial V_i(x)}{\partial x_j}\right)_{x=x_0}$$

where $F_i(x)$ denote the rate of appearance of new infections in compartment i, and $V_i(x)$is the net transfer rate (other than infections) of compartment i. The net transfer rate is given by $V_i = V_i^- - V_i^+$, where V_i^- is the rate of transfer of individuals out of compartment i, and V_i^+ is the rate of transfer of individuals into compartment i by means other than infection.

Therefore, in Model 1,

$$F = \begin{pmatrix} f\beta_c S(0) & f\beta_s S(0) \\ (1-f)\beta_c S(0) & (1-f)\beta_s S(0) \end{pmatrix}$$

$$V = \begin{pmatrix} e + \mu + m & 0 \\ -e & h + \mu \end{pmatrix}$$

$S(0)$ is the initial value of compartment S. Note that both F and V are 2×2 square matrices, because there are two infectious stages, I_c and I_s. Further, note that F is non-negative, and V is non-singular. Hence we can compute V^{-1} and FV^{-1}, which are both non-negative:

$$V^{-1} = \begin{pmatrix} \frac{1}{e+\mu+m} & 0 \\ \frac{e}{(e+\mu+m)(h+\mu)} & \frac{1}{h+\mu} \end{pmatrix}$$

$$FV^{-1} = \begin{pmatrix} \frac{f\beta_c S(0)}{e+\mu+m} + \frac{fe\beta_s S(0)}{(e+\mu+m)(h+\mu)} & \frac{f\beta_s S(0)}{h+\mu} \\ \frac{(1-f)\beta_c S(0)}{e+\mu+m} + \frac{(1-f)e\beta_s S(0)}{(e+\mu+m)(h+\mu)} & \frac{(1-f)\beta_s S(0)}{h+\mu} \end{pmatrix}$$

Now we solve the characteristic equation of the matrix FV^{-1} and find its eigenvalues. The (i,j)-th entry of FV^{-1} denotes the expected number of new infections in compartment i, produced by an infected individual in compartment k. Hence FV^{-1} is referred as the "Next Generation Matrix", and R_0 is given by the spectral radius (dominant eigenvalue) of the next generation matrix[34]:

$$\det \begin{pmatrix} \frac{f\beta_c S(0)}{e+\mu+m} + \frac{fe\beta_s S(0)}{(e+\mu+m)(h+\mu)} - \Lambda & \frac{f\beta_s S(0)}{h+\mu} \\ \frac{(1-f)\beta_c S(0)}{e+\mu+m} + \frac{(1-f)e\beta_s S(0)}{(e+\mu+m)(h+\mu)} & \frac{(1-f)\beta_s S(0)}{h+\mu} - \Lambda \end{pmatrix} = 0$$

i.e.

$$\Lambda \left(\Lambda - \frac{f\beta_c S(0)}{e+\mu+m} - \frac{(1-f)\beta_s S(0)}{h+\mu} - \frac{fe\beta_s S(0)}{(e+\mu+m)(h+\mu)} \right) = 0$$

Hence,

$$R_0 = \frac{f\beta_c S(0)}{e+\mu+m} + \frac{(1-f)\beta_s S(0)}{h+\mu} + \frac{fe\beta_s S(0)}{(e+\mu+m)(h+\mu)}$$

Similarly, for Model 2,

$$F = \begin{pmatrix} f\beta_c S(0) & f\beta_s S(0) & f\beta_{lt} S(0) \\ (1-f)\beta_c S(0) & (1-f)\beta_s S(0) & (1-f)\beta_{lt} S(0) \\ 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} e+\mu+m & 0 & 0 \\ -e & h+\mu & 0 \\ 0 & -f_{lt}h & h_{lt}+\mu|| \end{pmatrix}$$

Note that there are 3 infectious stages in Model 2, hence the dimension of F and V is 3×3.

$$V^{-1} = \begin{pmatrix} \frac{1}{e+\mu+m} & 0 & 0 \\ \frac{e}{(e+\mu+m)(h+\mu)} & \frac{1}{h+\mu} & 0 \\ \frac{ef_{lt}h}{(e+\mu+m)(h+\mu)(h_{lt}+\mu)} & \frac{f_{lt}h}{(h+\mu)(h_{lt}+\mu)} & \frac{1}{h_{lt}+\mu} \end{pmatrix}$$

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Hence the next generation matrix is

$$FV^{-1} = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ 0 & 0 & 0 \end{pmatrix}$$

where

$$a_{11} = \frac{f\beta_c S(0)}{e+\mu+m} + \frac{fe\beta_s S(0)}{(e+\mu+m)(h+\mu)} + \frac{fef_{lt}h\beta_{lt}S(0)}{(e+\mu+m)(h+\mu)(h_{lt}+\mu)}$$

$$a_{12} = \frac{f\beta_s S(0)}{h+\mu} + \frac{ff_{lt}h\beta_{lt}S(0)}{(h+\mu)(h_{lt}+\mu)}$$

$$a_{13} = \frac{f\beta_{lt}S(0)}{h_{lt}+\mu}$$

$$a_{21} = \frac{(1-f)\beta_c S(0)}{e+\mu+m} + \frac{(1-f)e\beta_s S(0)}{(e+\mu+m)(h+\mu)} + \frac{(1-f)ef_{lt}h\beta_{lt}S(0)}{(e+\mu+m)(h+\mu)(h_{lt}+\mu)}$$

$$a_{22} = \frac{(1-f)\beta_s S(0)}{h+\mu} + \frac{(1-f)f_{lt}h\beta_{lt}S(0)}{(h+\mu)(h_{lt}+\mu)}$$

$$a_{23} = \frac{(1-f)\beta_{lt}S(0)}{h_{lt}+\mu}$$

On solving the characteristic equation of FV^{-1}, we have

$$R_0 = \Lambda_{\max} = \frac{f\beta_c S(0)}{e+\mu+m} + \frac{(1-f)\beta_s S(0)}{h+\mu} + \frac{fe\beta_s S(0)}{(e+\mu+m)(h+\mu)}$$

$$+\frac{(1-f)f_{lt}h\beta_{lt}S(0)}{(h+\mu)(h_{lt}+\mu)} + \frac{fef_{lt}h\beta_{lt}S(0)}{(e+\mu+m)(h+\mu)(h_{lt}+\mu)}$$

Note that from our model assumptions, all the individuals enter the system as susceptible. Hence the R_0 expression only depend on the initial condition of the susceptible compartment $(S(0))$.

2.4   Model Simulation

The models are coded and simulated using MATLAB 6.5. The source code can be found in the Appendix. The total population is taken to be 345, which is the mean value of the herd sizes involved in the longitudinal study described in Section 2.2. The numerical simulation is started by introducing one clinically infected individual into the otherwise completely susceptible population. Hence, the initial conditions are $S(0) = 344$, $I_c(0) = 1$, and $I_s(0) = I_{lt}(0) = R(0) = 0$. Parameter values used are listed in Table 1. The epidemic curves of the two systems with variable parameters are studied. The sensitivities of R_0 with respect to the transimission coefficients (β) and recovery rates are also investigated.

In order to determine how heterogeneity in infectiousness affect vaccination programs, we need to calculate the critical proportion of the population (p_c) to be immunized so to make $R_0 < 1$. Since the efficacy for *Salmonella* vaccines is highly variable[35], p_c is calculated for different vaccination efficacies (Φ). The formula of p_{c_1} is obtained from [7]:

$$p_{c_1} = \frac{1}{\Phi}\left(1 - \frac{1}{R_0}\right)$$

Here we are assuming that the population is homogeneously mixed, and that the vaccine is equally effective across all infectious stages. The value of p_c should be less than or equal to 1, as the critical proportion to be vaccinated cannot exceed the entire population. The vaccine is said to be not feasible if $p_c > 1$.

In reality, however, a vaccine may not be able to prevent infection due to clinically infected animals. It is only capable of reducing the transmission of clinically infected animals in a homogeneously mixed population. In this case, p_{c_2} is calculated as shown in [7]:

$$p_{c_2} = \frac{1}{\Phi}\left(1 - \frac{1 - R^*}{R_{cl}}\right)$$

where R_{cl} is the contribution of the clinically infected compartment to the R_0 expression, and R^* is the contribution of other infectious stages, i.e. $R_0 = R_{cl} + R^*$. If $R^* > 1$, $p_{c_2} > 1$, and hence the vaccine is not feasible, because the reduction of the transmission from the clinically infected animals would not be enough to prevent an epidemic, or eliminate an endemic infection.

3 Results

Numerical methods are used to analyze the two systems of higher-order ordinary differential equations. The dynamics of each compartment of the two models are plotted against time in Figures 3 and 4. Figure 5 verifies that the total population of the system stays constant over the course of simulation. The effect of a change in proportion of the infected stages on the disease prevalence is studied. The relative contribution of each stage to new infections is also assessed. Figure 6 shows the change in prevalence for Model 1 against different values of f, the fraction of newly infected individuals that develop clinical diseases. The expected value of f is 0.5, and we run the simulation using $f = 0.5$ as well as $f = 0.5 \pm 0.35$. When $f = 0.15$, subclinically infected animals dominate the infectious population. However, they are not able to sustain the infection, because with the given parameter values, $R_0 < 1$, and hence an epidemic outbreak did not take place. On the other hand, when f is large ($f = 0.85$), it results in a well-defined epidemic that peaks early, and is followed by damped oscillations before reaching the steady state. Predicted endemic prevalence was greater for larger f.

The early stages (before Day 100) of the epidemic in Model 2 is similar to that of Model 1, because the early contribution of the long-term shedders is relatively low (Figure 3,4). We vary f_{lt}, that is the fraction of subclinically infected individuals that become long term shedders in Model 2. Notice that the disease prevalence, while very sensitive to the change in f (Figure 6), is not sensitive to the change in f_{lt}, as shown in Figure 7. The value of the basic reproductive number, R_0, is plotted against different values of the transmission coefficients β_c, β_s and β_{lt} in Figure 8. R_0 is also plotted against e, h and $h_l t$ in Figure 9. R_0 increases linearly with the transmission coefficients, as suggested by the positively sloped parallel lines observed in Figure 8. However, note that when $\beta_c < 0.8x10^{-3}$ in Model 1, R_0 is less than 1. In Model 2, when β_c is less than approximately $0.45x10^{-3}$, $R_0 < 1$. On the other hand, for all values of β_s, given the values of $\beta_c = 0.0016$ and $\beta_{lt} = 0.00006$, the value of R_0 is always greater than 1. Moreover, R_0 is sensitive to the value of e, especially when $e < 0.25$, which is its mean value. Similarly, R_0 is also very sensitive to the change in h, when h is less than its expected value 0.041. When $h > 0.041$, the sensitivity of R_0 to h decreases, and finally shows no change in value when h ranges from 0.25 to 1.

The values p_{c_1} and p_{c_2} are calculated for the vaccine efficacies $\Phi = (0.25, 0.5, 0.75, 1)$. Results are shown in Table 2.

	Φ							
	$\phi = 0.25$		$\phi = 0.50$		$\phi = 0.75$		$\phi = 1.0$	
Model	p_{c_1}	p_{c_2}	p_{c_1}	p_{c_2}	p_{c_1}	p_{c_2}	p_{c_1}	p_{c_2}
1	nf	nf	0.70	nf	0.46	0.68	0.35	0.51
2	nf	nf	0.76	nf	0.51	0.78	0.38	0.58

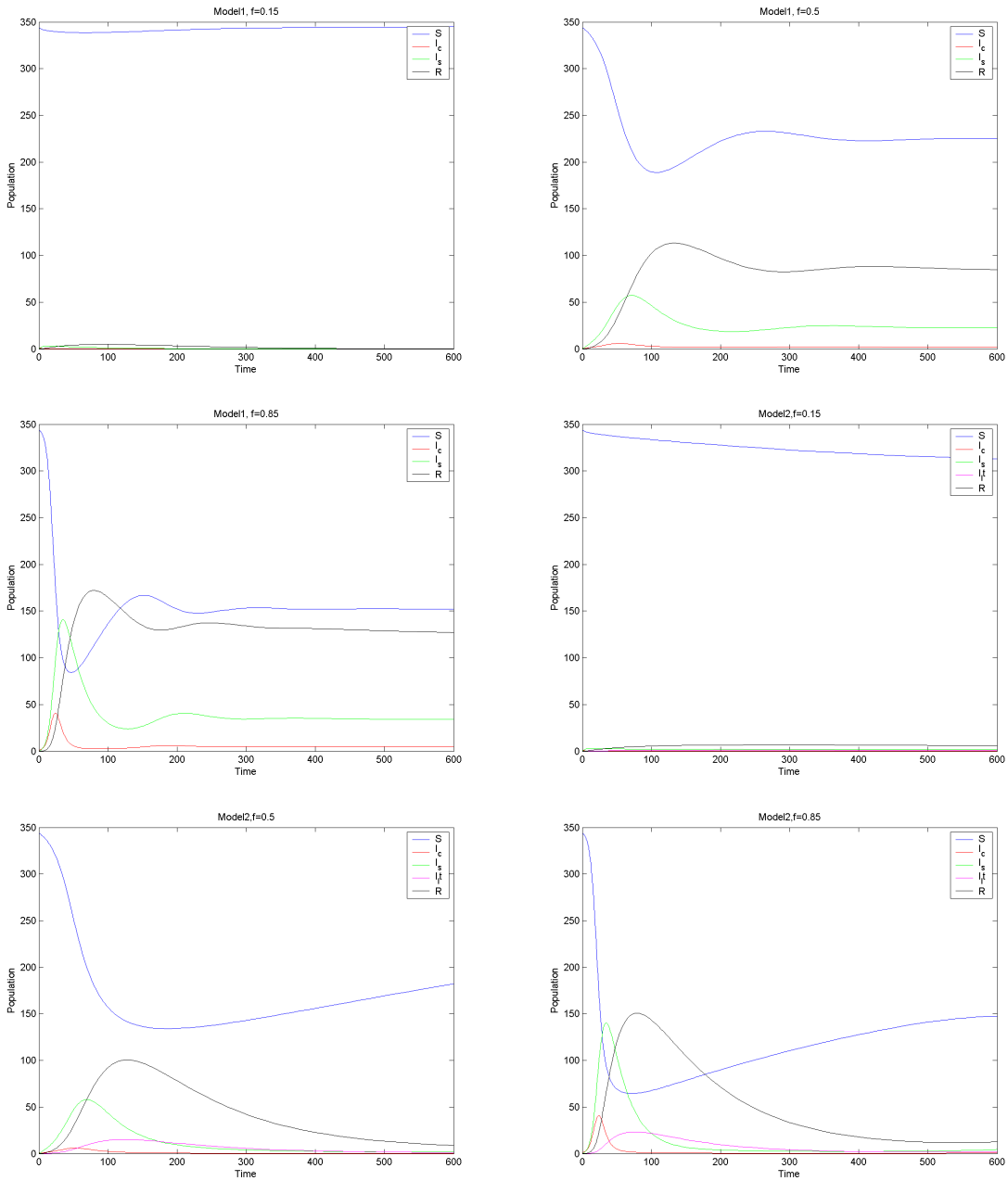Table 2: List of parameter values. Here nf stands for non-feasible.

Figure 3: Distribution of the compartments of Model 1 and Model 2 with respect to different values of f. The susceptible curves (S) are drawn in blue, I_c in red, I_s in green, I_{lt} in magenta, R in black.
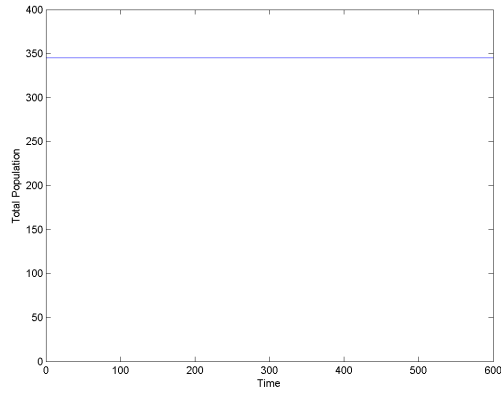
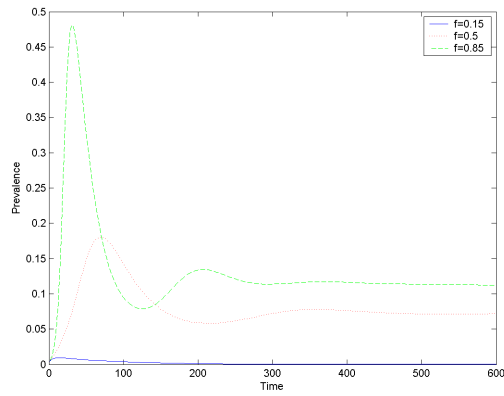Figure 4: Constant total population for Models 1 and 2.

Figure 5: Impact of the fraction of clinically infected animals (f) on the prevalence of infection in Model 1.
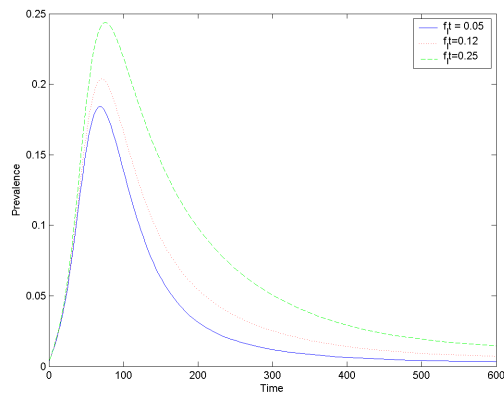

Figure 6: Impact of the fraction of subclinically infected animals that become long-term shedders (f_{lt}) on the prevalence of infection in Model 2.

Figure 7: Sensitivity of R_0 with respect to the transmission coefficients. Blue lines stand for R_0 of Model 1, red lines stand for R_0 of Model 2. Horizontal black line indicates the threshold value $R_0 = 1$.
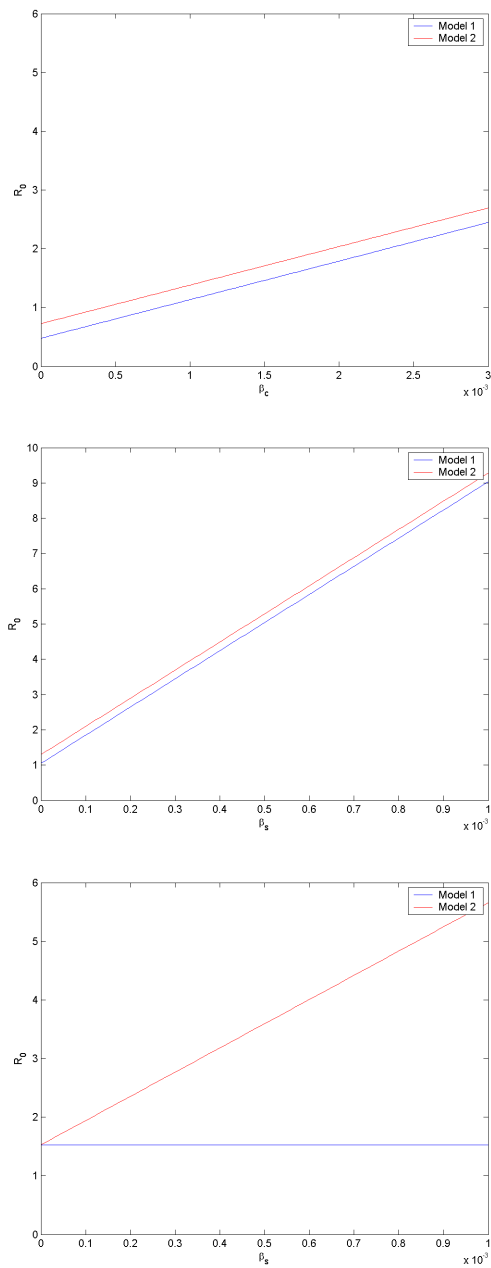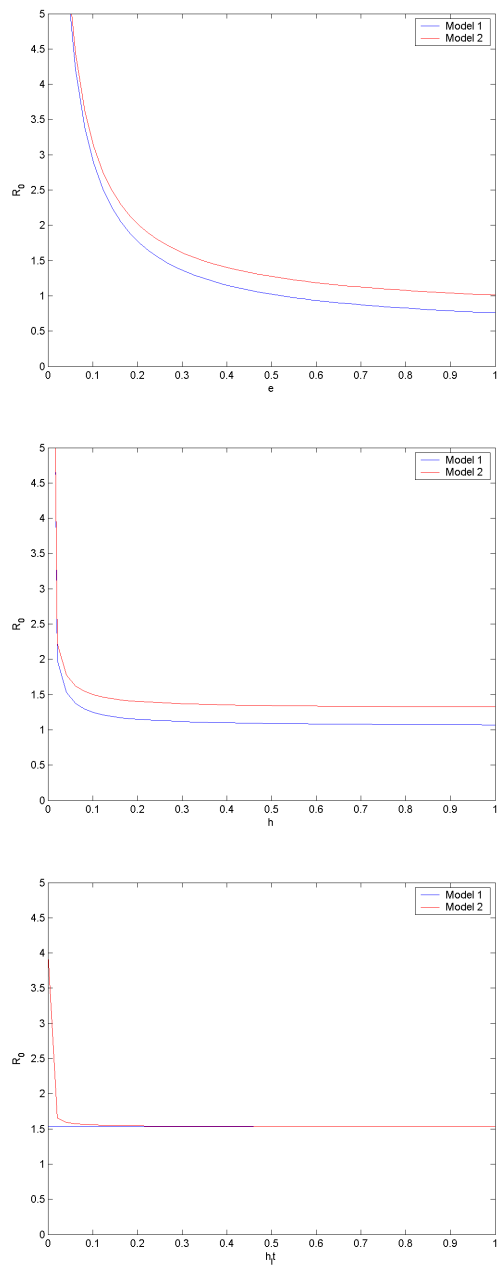
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Figure 8: Sensitivity of R_0 with respect to the recovery rates. Blue lines stand for R_0 of Model 1, red lines stand for R_0 of Model 2. Horizontal black line indicates the threshold value $R_0 = 1$.

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4   Discussion

To study the impact of heterogeneity of infectiousness in contagiousness and infectious period, two deterministic compartmental flow models are constructed. Heterogeneity is added to these models by incorporating different homogeneous infected stages into the models. After estimating the parameters from field data and statistical analysis, the systems of ordinary differential equations corresponding to the two models are solved numerically using MATLAB. The dynamics displayed by the models and the thresholds quantities are studied.

The two models exhibited different qualitative dynamic patterns. First, it is obvious that it takes a shorter time for Model 1 to reach an endemic equilibrium than Model 2. Over the course of simulation of 600 days with the parameter values in Table 1, Model 1 is able to reach its endemic state after damped oscillation, while Model 2 still demonstrates significant fluctuations. By extending the simulation time, it is found that Model 2 takes approximately 2000 days to reach its endemic equilibrium. It is noted that Model 1 is more prone to damped oscillations, especially when there is a high fraction of clinically infected animals, high transmission coefficients or fast recovery rates. The prevalence of infection in Model 2 tends to increase until it reaches the endemic prevalence, and the epidemic curve of Model 2 is less defined. Here the significance of the additional long-term shedders stage is illustrated: when the long-term shedding compartment is incorporated, the prevalence of infection sustains at a higher level, and it takes more than six times longer to reach the equilibrium state.

Clinically infected animals are the main force of transmission for both models. Increasing the number of clinically infected individuals results in larger outbreaks as well as a larger equilibrium value, that is, a higher prevalence at endemic stage. The relevance of clinical cases on *Salmonella* persistence has been outlined in previous studies. In a case study, the prevalence was higher for the two herds that had a previous history of clinical salmonellosis[36]. Exposure to cattle with clinical salmonellosis has been described as a risk factor for development of salmonellosis[24][29]. In order to simulate the high prevalence of subclinical infection displayed by some serotypes (e.g. S. Cerro) in the absence of clinically infected animals ($f = 0$), slower recovery rates for subclinically infected animals and long term shedders than the values reported in Table 1 are necessary.

Although heterogeneity in transmission has not been previously addressed for *Salmonella*, extensive work has been undertaken to investigate sources of heterogeneity for another foodborne bacteria, *Escherichia coli* O157 [37][38]. Matthews et al.[38] evaluated several stochastic SIS models that included different sources of heterogeneity. They found that models which included between-animal variability of infectious period in the same infectious compartment failed to explain the observed data. Similarly to the case of *E. coli*, Model 2 shows that $R_0 > 1$ can be achieved if and only if the long-term shedders have a very slow recovery rate, given that only 14% of the subclinically infected individuals move into the I_{lt} compartment. This suggests that the few individuals with unusually long infectious period but low contagiousness do not play an important role on the persistence and transmission of the infection.

It is a new concept in understanding the Salmonella transmission dynamics, as the role of long-term shedders has long been overestimated.

Heterogeneity in the transmission of any disease is known to have the implication that individual-specific control measures designed to target the most infectious individuals (e.g. isolation) are more efficient in eradicating the disease than population-wide control measures (e.g. vaccination at random)[39][40]. However, in our environment of study, targeting specific subgroups to control *Salmonella* transmission in dairy herds is very challenging. It is because there are difficulties in identifying persistently infectious individuals without clinical signs. For example, the reported sensitivity of bacterial culture of *S. Dublin* from feces may be as low as 6-14 % in animals without clinical symptoms[41]. Furthermore, the isolation of clinically ill cows in sick pens has been reported to favor *Salmonella* persistence as well as the emergence of multi-drug resistance[25]. Therefore, in this study, the impact of heterogeneity on population-wide control measures is evaluated. The aim of carrying out a vaccination program is to eradicate an endemic *Salmonella* infection, or to prevent *Salmonella* introduction into a completely susceptible population.

The critical proportion of individuals that must be vaccinated in order to eliminate the infection (p_c) is correlated to both R_0 and the vaccine efficacy (Φ). Results shown in Table 2 indicate that vaccines with low efficacy ($\Phi = 0.25$) are rather ineffective at providing protection against persistent or invasive *Salmonella* infection. High efficacy vaccines ($\Phi \geq 0.75$) that either reduce transmission from clinically infected animals or from all infectious individuals are feasible, since both (p_{c_1}) and (p_{c_2}) are less than 1. They are predicted to aid in eradicating infection for Models 1 and 2. However, in most cases, more than 50% of the individuals has to be vaccinated in order to protect the population from *Salmonella* outbreak. The cost of such a vaccination program versus its actual effectiveness has to be evaluated.

5   Conclusion

The impact of individual heterogeneity on *Salmonella* transmission dynamics and eradication thresholds has been evaluated. Infected individuals with clinical signs are the main force of infection and the transmission for both models. Hence, it is suggested that reducing transmission coefficient of I_c could be an effective way to reduce *Salmonella* prevalence, or even prevent the outbreak of salmonellosis epidemic in dairy herds. Long-term shedders have an unexpectedly small impact on the transmission of the infection as well as the estimated vaccination thresholds. Model 1 and 2 are appropriate to describe *Salmonella* transmission dynamics of different serotypes as well as different farm management practices. However, the specific conditions applicable for each model remain contingent upon future findings. Further work can be focused on other possible infectious stages, such as having a superspreading class that develops from the clinically infected individuals, with the superspreaders being several times more infectious than the normal clinical animals. With more extensive empirical data, such as the fecal analysis of the animals without clinical signs, the final size distribution of an *Salmonella* outbreak can be determined. Stochastic models can also be constructed to help elucidate the relative contribution of the infected stages to transmission and would move forward modeling efforts to address *Salmonella* spread.

6   Appendix

6.1   Source Code of Model 1

```
% Yancy Lo
% Senior Thesis
% Salmonella Model 1

N = 345; % total population

tmax = 600; % time (in days) that the model runs through

mu = 0.0011;        % replacement and exit rate
beta_c = 0.0016;    % transmission coefficient for clinical animals
beta_s = 0.00006;   % transmission coefficient for subclinical animals
f = 0.5;        % proportion of infected animals that develop clinical disease
e = 0.25;           % rate of clinical cases that become subclinical
h = 0.041;          % recovery rate for subclinical cases
m = 0.011;          % disease induced mortality rate
r = 0.01;           % immunity loss rate

figure;
S = N-1;
Ic = 1; Is = 0; R = 0;
R_0 = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
         + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)))

tspan = [0 tmax];
x0 = [S;Ic;Is;R];
para = [mu beta_c beta_s f e h m r N];
options = odeset('RelTol',1e-4,'AbsTol',1e-4);
[T,x] = ode23s(@SIcIsR,tspan,x0,options,para);

len = length(x);
sus = zeros(len,1);
clin = zeros(len,1);
subclin = zeros(len,1);
recover = zeros(len,1);
total = zeros(len,1);

for t = 1:len
    total(t) = x(t,1)+ x(t,2)+ x(t,3)+ x(t,4);
    sus(t) = x(t,1);
```

```
    clin(t) = x(t,2);
    subclin(t) = x(t,3);
    recover(t) = x(t,4);
end
plot(T,total);
AXIS([0 600 0 400]);
XLABEL('Time');
YLABEL('Total Population');
figure;
plot(T,sus,'b',T,clin,'r', T, subclin,'g',T,recover,'k');
legend('S', 'I_c', 'I_s', 'R');
XLABEL('Time');
YLABEL('Population');


--------------------


function dx=SIcIsR(t,x,p)
dx=zeros(4,1);
dx(1) = p(1)*p(9) + p(8).*x(4) - p(2).*x(2).*x(1)
            - p(3).*x(3).*x(1) - p(1).*x(1);
dx(2) = p(4)*p(2).*x(2).*x(1) + p(4)*p(3).*x(3).*x(1)
            - p(5).*x(2) - p(7).*x(2) - p(1).*x(2);
dx(3) = (1-p(4))*p(2).*x(2).*x(1) + (1-p(4))*p(3).*x(3).*x(1)
            + p(5).*x(2) - p(6).*x(3) -p(1).*x(3);
dx(4) = p(6).*x(3) - p(8).*x(4) - p(1).*x(4);
```

6.2   Source Code for Model 2

```
% Yancy Lo
% Senior Thesis
% Salmonella Model 2

N = 345; % total population

tmax = 600; % time (in days) that the model runs through

mu = 0.0011;        % replacement and exit rate
beta_c = 0.0016;    % transmission coefficient for clinical animals
beta_s = 0.00006;   % transmission coefficient for subclinical animals
beta_lt = 0.00006;  % transmission coefficient for long-term shedders
f = 0.5;            % proportion of infected animals that develop clinical
                    % disease
f_lt = 0.14;        % proportion of subclinical cases that become long-term
```

```
                          % shedders
e = 0.25;                 % rate of clinical cases that become subclinical
h = 0.041;                % recovery rate for subclinical cases
h_lt = 0.01;              % recovery rate for long-term shedders
m = 0.011;                % disease induced mortality rate
r = 0.01;                 % immunity loss rate


S = N-1;
Ic = 1; Is = 0; Ilt = 0; R = 0;
R_0 = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
          + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)))
          + ((1-f)*f_lt*h*beta_lt*S)/((h+mu)*(h_lt+mu))
          + (f*e*f_lt*h*beta_lt*S)/((e+mu+m)*(h+mu)*(h_lt+mu))


tspan = [0 tmax];
x0 = [S;Ic;Is;Ilt;R];
para = [mu beta_c beta_s beta_lt f f_lt e h h_lt m r N];
options = odeset('RelTol',1e-4,'AbsTol',1e-4);
[T,x] = ode23s(@SIcIsIltR,tspan,x0,options,para);


len = length(x);
sus = zeros(len,1);
clin = zeros(len,1);
subclin = zeros(len,1);
longterm = zeros(len,1);
recover = zeros(len,1);
total = zeros(len,1);

for t = 1:len
    total(t) = x(t,1)+ x(t,2)+ x(t,3)+ x(t,4)+ x(t,5);
    sus(t) = x(t,1);
    clin(t) = x(t,2);
    subclin(t) = x(t,3);
    longterm(t) = x(t,4);
    recover(t) = x(t,5);
end

plot(T,total);
figure;
plot(T,sus,'b',T,clin,'r', T, subclin,'g',T,longterm, 'm', T,recover,'k');
legend('S', 'I_c', 'I_s', 'I_lt', 'R');
XLABEL('Time');
```

```
YLABEL('Population');

--------------------

function dx=SIcIsIltR(t,x,p)
dx=zeros(5,1);
dx(1) = p(1)*p(12) + p(1).*x(5) - p(2).*x(2).*x(1)
            - p(3).*x(3).*x(1) - p(4).*x(4).*x(1) - p(1).*x(1);
dx(2) = p(5)*p(2).*x(2).*x(1) + p(5)*p(3).*x(3).*x(1)
            + p(5)*p(4).*x(4).*x(1) - (p(7)+p(10)+p(1)).*x(2);
dx(3) = (1-p(5))*p(2).*x(2).*x(1) + (1-p(5))*p(3).*x(3).*x(1)
            + (1-p(5))*p(4).*x(4).*x(1) + p(7).*x(2) - (p(8)+p(1)).*x(3);
dx(4) = p(6)*p(8).*x(3) - (p(9)+p(1)).*x(4);
dx(5) = (1-p(6))*p(8).*x(3) + p(9).*x(4) - (p(11)+p(1)).*x(5);
```

6.3   Varying f

```
% Yancy Lo
% Senior Thesis
% Salmonella Model 1 - Varying f

N = 345;

mu = 0.0011;
beta_c = 0.0016;
beta_s = 0.00006;
f = 0.15;
e = 0.25;
h = 0.041;
m = 0.011;
r = 0.01;

S = N-1;
Ic = 1; Is = 0; R = 0;
R_0 = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
        + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)))

tspan = [0 tmax];
x0 = [S;Ic;Is;R];
para = [mu beta_c beta_s f e h m r N];
options = odeset('RelTol',1e-4,'AbsTol',1e-4);
[T,x] = ode23s(@SIcIsR,tspan,x0,options,para);
```

```
len = length(x);
clin = zeros(len,1);
subclin = zeros(len,1);
prev = zeros(len,1);
for t = 1:len
    clin(t) = x(t,2);
    subclin(t) = x(t,3);
    prev(t) = (clin(t) + subclin(t))./N;
end

figure
plot(T,prev,'b-');
hold on

f = 0.5;
S = N-1;
Ic = 1; Is = 0; R = 0;
R_0 = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
        + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)))

tspan = [0 tmax];
x0 = [S;Ic;Is;R];
para = [mu beta_c beta_s f e h m r N];
options = odeset('RelTol',1e-4,'AbsTol',1e-4);
[T,x] = ode23s(@SIcIsR,tspan,x0,options,para);

len = length(x);
clin = zeros(len,1);
subclin = zeros(len,1);
prev = zeros(len,1);
for t = 1:len
 clin(t) = x(t,2);
 subclin(t) = x(t,3);
 prev(t) = (clin(t) + subclin(t))./N;
end
plot(T,prev,'r:');
hold on

f = 0.85;
S = N-1;
Ic = 1; Is = 0; R = 0;
R_0 = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
```

```
       + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)))

tspan = [0 tmax];
x0 = [S;Ic;Is;R];
para = [mu beta_c beta_s f e h m r N];
options = odeset('RelTol',1e-4,'AbsTol',1e-4);
[T,x] = ode23s(@SIcIsR,tspan,x0,options,para);

len = length(x);
clin = zeros(len,1);
subclin = zeros(len,1);
prev = zeros(len,1);
for t = 1:len
 clin(t) = x(t,2);
 subclin(t) = x(t,3);
 prev(t) = (clin(t) + subclin(t))./N;
end
plot(T,prev,'g--');
legend('f=0.15', 'f=0.5', 'f=0.85')
XLABEL('Time');
YLABEL('Prevalence');
```

6.4   Varying f_{lt}

```
% Yancy Lo
% Senior Thesis
% Salmonella Model 2 - Varying f_lt

N = 345;

mu = 0.0011;
beta_c = 0.0016;
beta_s = 0.00006;
beta_lt = 0.00006;
f = 0.5;
f_lt = 0.05;
e = 0.25;
h = 0.041;
h_lt = 0.01;
m = 0.011;
r = 0.01;
```

```
S = N-1;
Ic = 1; Is = 0; Ilt = 0; R = 0;
R_0 = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
        + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)))
        + ((1-f)*f_lt*h*beta_lt*S)/((h+mu)*(h_lt+mu)))
        + (f*e*f_lt*h*beta_lt*S)/((e+mu+m)*(h+mu)*(h_lt+mu)))

tspan = [0 tmax];
x0 = [S;Ic;Is;Ilt;R];
para = [mu beta_c beta_s beta_lt f f_lt e h h_lt m r N];
options = odeset('RelTol',1e-4,'AbsTol',1e-4);
[T,x] = ode23s(@SIcIsIltR,tspan,x0,options,para);

len = length(x);
clin = zeros(len,1);
subclin = zeros(len,1);
longterm = zeros(len,1);
prev = zeros(len,1);

for t = 1:len
    clin(t) = x(t,2);
    subclin(t) = x(t,3);
    longterm(t) = x(t,4);
    prev(t) = (clin(t)+subclin(t)+longterm(t))./N;
end

figure;
plot(T, prev, 'b-');
hold on

f_lt = 0.12;
S = N-1;
Ic = 1; Is = 0; Ilt = 0; R = 0;

tspan = [0 tmax];
x0 = [S;Ic;Is;Ilt;R];
para = [mu beta_c beta_s beta_lt f f_lt e h h_lt m r N];
options = odeset('RelTol',1e-4,'AbsTol',1e-4);
[T,x] = ode23s(@SIcIsIltR,tspan,x0,options,para);

len = length(x);
clin = zeros(len,1);
```

```
subclin = zeros(len,1);
longterm = zeros(len,1);
prev = zeros(len,1);

for t = 1:len
    clin(t) = x(t,2);
    subclin(t) = x(t,3);
    longterm(t) = x(t,4);
    prev(t) = (clin(t)+subclin(t)+longterm(t))./N;
end

plot(T, prev, 'r:');
hold on

f_lt = 0.25;
S = N-1;
Ic = 1; Is = 0; Ilt = 0; R = 0;

tspan = [0 tmax];
x0 = [S;Ic;Is;Ilt;R];
para = [mu beta_c beta_s beta_lt f f_lt e h h_lt m r N];
options = odeset('RelTol',1e-4,'AbsTol',1e-4);
[T,x] = ode23s(@SIcIsIltR,tspan,x0,options,para);

len = length(x);
clin = zeros(len,1);
subclin = zeros(len,1);
longterm = zeros(len,1);
prev = zeros(len,1);

for t = 1:len
    clin(t) = x(t,2);
    subclin(t) = x(t,3);
    longterm(t) = x(t,4);
    prev(t) = (clin(t)+subclin(t)+longterm(t))./N;
end

plot(T, prev, 'g--');
hold on
legend ('f_lt = 0.05', 'f_lt=0.12', 'f_lt=0.25');
XLABEL('Time')
YLABEL('Prevalence')
```

6.5 Sensitivity of R_0 with respect to transmission coefficients

```
%Yancy Lo
%Senior Thesis
%R_0 Sensitivity wrt Betas

N = 345;

mu = 0.0011;
beta_c = linspace(0,0.003,100);
beta_s = 0.00006;
beta_lt = 0.00006;
f = 0.5;
e = 0.25;
h = 0.041;
h_lt = 0.01;
m = 0.011;
r = 0.01;

S = N-1;
for i = 1: 100
    R_01(i) = ((f*beta_c(i)*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
                  + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)));
    R_02(i)= ((f*beta_c(i)*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
                  + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)))
                  + ((1-f)*f_lt*h*beta_lt*S)/((h+mu)*(h_lt+mu))
                  + (f*e*f_lt*h*beta_lt*S)/((e+mu+m)*(h+mu)*(h_lt+mu));
end
plot(beta_c,R_01,'b-',beta_c,R_02,'r-');
LEGEND('Model 1', 'Model 2');
AXIS([0 0.003 0 6]);
XLABEL('\beta_c');
YLABEL('R_0');

%%%Vary beta_S%%%
beta_c = 0.0016;
beta_s = linspace(0,0.001,100);
for i = 1: 100
    R_01(i) = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s(i)*S)/(h+mu))
                  + ((f*e*beta_s(i)*S)/((e+mu+m)*(h+mu)));
    R_02(i) = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s(i)*S)/(h+mu))
              + ((f*e*beta_s(i)*S)/((e+mu+m)*(h+mu)))
              + ((1-f)*f_lt*h*beta_lt*S)/((h+mu)*(h_lt+mu))
```

```
                    + (f*e*f_lt*h*beta_lt*S)/((e+mu+m)*(h+mu)*(h_lt+mu));
end
figure;
plot(beta_s,R_01,'b-',beta_s,R_02,'r-');
LEGEND('Model 1', 'Model 2');
AXIS([0 0.001 0 10]);
XLABEL('\beta_s');
YLABEL('R_0');


%%%Vary beta_lt%%%
beta_s = 0.00006;
beta_lt = linspace(0,0.001,100);
for i = 1: 100
    R_01(i) = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
                    + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)));
    R_02(i)= ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
                    + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)))
                    + ((1-f)*f_lt*h*beta_lt(i)*S)/((h+mu)*(h_lt+mu))
                    + (f*e*f_lt*h*beta_lt(i)*S)/((e+mu+m)*(h+mu)*(h_lt+mu));
end
figure;
plot(beta_lt,R_01,'b-',beta_lt,R_02,'r-');
LEGEND('Model 1', 'Model 2');
AXIS([0 0.001 0 6]);
XLABEL('\beta_s');
YLABEL('R_0');
```

6.6   Sensitivity of R_0 with respect to recovery rates

```
% Yancy Lo
% Senior Thesis
% R_0 Sensitivity wrt Recovery Rates

N = 345;

mu = 0.0011;
beta_c = 0.0016;
beta_s = 0.00006;
beta_lt = 0.00006;
f = 0.5;
f_lt = 0.14;
e = linspace(0,1,50);
h = 0.041;
```

```
h_lt = 0.01;
m = 0.011;
r = 0.01;


S = N-1;
for i = 1: 50
    R_01(i) = ((f*beta_c*S)/(e(i)+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
                + ((f*e(i)*beta_s*S)/((e(i)+mu+m)*(h+mu)));
    R_02(i) = ((f*beta_c*S)/(e(i)+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
                + ((f*e(i)*beta_s*S)/((e(i)+mu+m)*(h+mu)))
                + ((1-f)*f_lt*h*beta_lt*S)/((h+mu)*(h_lt+mu))
                + (f*e(i)*f_lt*h*beta_lt*S)/((e(i)+mu+m)*(h+mu)*(h_lt+mu));
end
plot(e,R_01,'b-',e,R_02,'r-');
LEGEND('Model 1', 'Model 2');
AXIS([0 1 0 5]);
XLABEL('e');
YLABEL('R_0');


%%%Vary h%%%
h = linspace(0,1,50);
e = 0.25;
for i = 1:50
    R_01(i) = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h(i)+mu))
                + ((f*e*beta_s*S)/((e+mu+m)*(h(i)+mu)));
    R_02(i) = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h(i)+mu))
                + ((f*e*beta_s*S)/((e+mu+m)*(h(i)+mu)))
                + ((1-f)*f_lt*h(i)*beta_lt*S)/((h(i)+mu)*(h_lt+mu))
                + (f*e*f_lt*h(i)*beta_lt*S)/((e+mu+m)*(h(i)+mu)*(h_lt+mu));
end
figure;
plot(h,R_01,'b-',h,R_02,'r-');
LEGEND('Model 1', 'Model 2');
AXIS([0 1 0 5]);
XLABEL('h');
YLABEL('R_0');


%%%Vary h_lt%%%
h = 0.041;
h_lt = linspace(0,1,50);
for i = 1:50
    R_01(i) = ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
```

```
                        + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)));
    R_02(i)= ((f*beta_c*S)/(e+mu+m)) + (((1-f)*beta_s*S)/(h+mu))
                        + ((f*e*beta_s*S)/((e+mu+m)*(h+mu)))
                        + ((1-f)*f_lt*h*beta_lt*S)/((h+mu)*(h_lt(i)+mu))
                        + (f*e*f_lt*h*beta_lt*S)/((e+mu+m)*(h+mu)*(h_lt(i)+mu));
end
figure;
plot(h_lt,R_01,'b-',h_lt,R_02,'r-');
LEGEND('Model 1', 'Model 2');
AXIS([0 1 0 5]);
XLABEL('h_lt');
YLABEL('R_0');
```

References

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