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A Mathematical Model for Antibiotic Resistance in a Hospital Setting with a Varying Population

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A Mathematical Model for Antibiotic Resistance in a Hospital Setting with a Varying Population

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by

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ABSTRACT

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Antibiotic-resistant bacteria (ARB) is causing increased health risk and cost to society. Mathematical models have been developed to study the transmission of resistant bacteria and the efficacy of preventive measures to slow its spread within a hospital setting. The majority of these models have assumed a constant total hospital population with the admission and discharge rates being equal throughout the duration. But a typical hospital population varies from day to day and season to season. In this thesis, we apply variable admission and discharge daily rates to existing deterministic and stochastic models which examine the transmission of single and dual resistant bacteria. We perform stability and equilibrium analyses as well as a sensitivity analysis on the resulting model.

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1 INTRODUCTION

The threat of Antibiotic-Resistant Bacteria (ARB) continues to grow. ARB is a principal cause of nosocomial infection, that is, a hospital-acquired infection (HAI) [1]. These hospital-acquired infections are a primary factor in increased medical costs, increased lengths of stay(LOS), and higher mortality rates and suffering [7]. Some of the risk factors associated with the spread of ARB are antibiotic usage in agriculture, poor hygiene both within and outside of the hospital, indiscriminate antibiotic dosage regimens, and improperly managed isolation of patients with known ARB-linked infections [1]. Also included in this list are the longer survival periods of elderly patients and our increased life expectancy [1]. Compounding the problem is that there have been lengthy lapses in the search for and development of new classes of antibiotics [1, 21].

Mathematical models have been developed to simulate the spread of epidemics of diseases such as dengue fever and hoof-and-mouth disease throughout different regions of the world [2, 23]. Included among these are epidemics caused by ARB such as methicillin-resistant staphylococcus aureus (MRSA). Due to it being extremely resistant to the present classes of antibiotics, MRSA is extremely difficult to treat and clear. Elevated ARB levels, mostly originating in hospital or nursing home settings, have given rise to new models that at first investigated single resistance [3, 15, 18, 20, 24]. These models examined the effects of different types of dosage regimens and the isolation of known ARB-infected patients in hospital settings. Bacteria resistant to a single antibiotic may come into contact with another type of bacteria resistant to a second antibiotic subsequently evolving into bacteria resistant to multiple antibiotics.

This has led to a new generation of models such as Chow et al. [6], who studied the efficacy of dosage protocols such as cycling versus mixing for multiple ARB isolation procedures. Joyner et al. ([16] and those therein) followed suit with a study on the effect of a new class of antibiotics to treat dual-resistant bacteria. Some of the previous models were deterministic in nature which is an effective tool when simulating large population dynamics. Other models incorporated stochastic processes which are well-suited for small population dynamics [5]. The majority of papers published that studied ARB in hospital settings assumed a constant population with admission and discharge rates being the same [6, 16]. But in truth, hospital populations fluctuate both daily and seasonally along with spikes that occur due to special holidays or disasters [4, 9, 10]. We feel it is important to incorporate this phenomenon into the model.

In this thesis, we seek to determine the effect that varying hospital admission and discharge rates have on both single- and multiple- ARB levels. In chapter 2 we discuss the variable admission and discharge rates that we used to replace the constant rate of admission and discharge. These rates are based on empirical data and will replace the constant rate of admission and discharge in the previous deterministic and stochastic models developed by Joyner et al.,[5, 16]. In chapter 3 we develop a deterministic model compartmentalized into five subpopulations based on bacteria type. In chapter 4, we develop a corresponding stochastic model. In chapter 5 we perform a sensitivity analysis of the model results on selected parameter values. We then determine the resistance-free equilibrium and stability of the model system in chapter 6. Finally, we summarize the results in chapter 7.

2 THE VARIABLE ADMISSION AND DISCHARGE RATES

As stated previously, the hospital population does not stay constant. Studies have shown that fluctuation occurs naturally [4, 9, 12, 19, 22]. On average, the highest admission rates occur on Monday and Tuesday followed by a gradual decline during the remainder of the week. The discharge rates follow a similar pattern with maximum discharge rates occurring toward the end of the work week. This phenomenon results in longer length of stay (LOS) for patients admitted over the weekend. Data from recent studies describe the phenomena. A Greek study [4] demonstrated a daily and seasonal flucuation that coincided with weather and holiday patterns. A Singapore study [10] showed a periodic daily fluctuation.

For the simulations in this thesis, we focused on the admission and discharge rates taken from a Toronto hospital study [22]. This 3-year study examined whether the balance between daily hospital admissions and discharges affected the next-day emergency department (ED) length of stay. The means of the daily admissions and discharges are listed in table 1. We use the Poisson distribution with these daily admission and discharge means to generate a potential yearlong pattern in daily admissions and discharges. The Poisson distribution is a discrete probability distribution and can be applied when the events can be counted in whole numbers over a specified time interval. In our case, we are interested in the number of admissions and discharges during a single day. Figures 1 and 2 contain compact boxplots of 500 trials of yearlong daily admissions, discharges and total changes, respectively. These figures illustrate the variation in admissions, discharges and total hospital population for the Toronto hospital. Assuming the movement of patients into and out of other

hospitals is similar to the Toronto study, there could be a rather significant increase or decrease in the patient population on a given day as seen in Figure 2. In the next section, we explore how this variation might affect the antibiotic resistance found in a hospital.

Table 1: Daily Admissions and Discharges

Description	M	T	W	Th	F	S	S
Admissions	57.3	61.7	60.8	58.8	53.8	35.0	34.1
Discharges	49.3	53.6	56.4	58.4	67.0	43.2	33.8

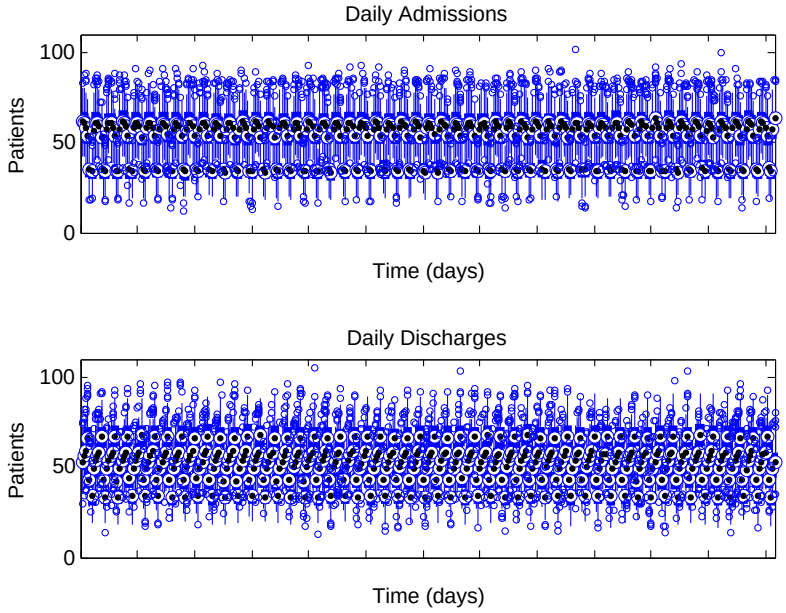

Figure 1: A yearlong series of boxplots of daily admission and discharge rates for 500 trials using the Poisson distribution with the means in Table 1

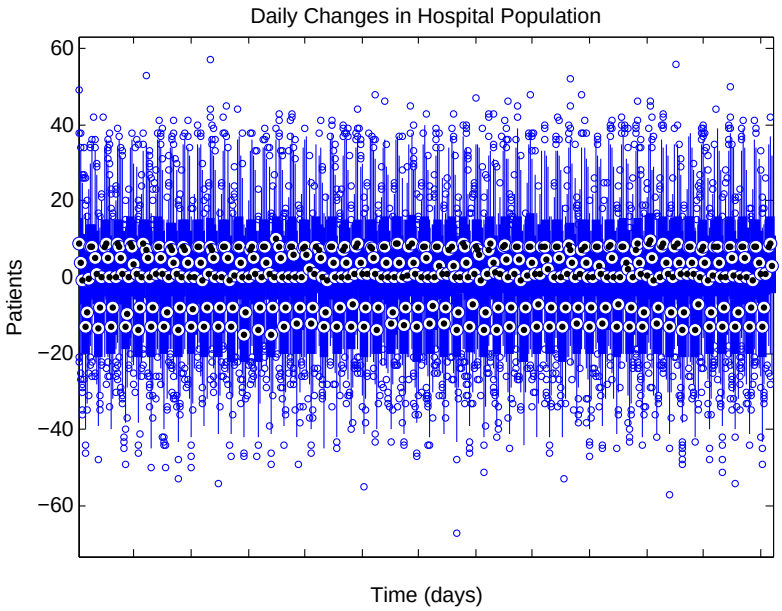

Figure 2: A yearlong series of boxplots of daily changes for 500 trials using the Poisson distribution with the means in Table 1

3 THE DETERMINISTIC MODEL

The deterministic model in this paper is adapted from a model created by Joyner et al., [16] that was concerned with not only resistance to either a particular drug 1 or drug 2, but also resistance to both drugs. We classify the members of the community and the hospital patients with regard to type of bacterial colonization. We assume the five bacterial classifications to be people colonized with bacteria that is *sensitive* to both drugs 1 and 2, *resistant* to either of the two drugs, *resistant* to both drugs 1 and 2, and those *uncolonized* by any form of bacteria. A person classified as sensistive is infected with bacteria that can be treated with either drug. A person infected with bacteria resistant to either drug 1 or drug 2 can be treated and cleared with the other drug. A person infected with dual-resistant bacteria cannot be cleared with either drug. Within the hospital, we let the state variables, S, R_1, R_2, R_{12}, and X represent the number of hospital patients in each bacterial classification, respectively. N will represent the total patient population. For example, R_1 represents the number of patients infected with bacteria resistant to drug 1 and X represents the number of patients uncolonized.

We let the parameter, m_S, represent the proportion of admissions that are colonized with bacteria sensitive to both drugs, m_1 and m_2 represent the proportion of admissions that are colonized with bacteria resistant to either drug 1 or drug 2, respectively, m_{12} represent that proportion of admissions that are colonized with bacteria resistant to both drugs and m_X represent the proportion of admissions that are uncolonized. We let $\lambda = \lambda(t)$ represent the daily number of admissions and $\mu = \mu(t)$ represent the daily number of discharges as discussed in the preceding section. As

mentioned in the previous section (and depicted in figure 2), there could be a significant variation in the hospital population. However, hospitals have a limited capacity which must be considered when simulating admissions and discharges. Note that in the event that the total hospital population increases to 105% of the capacity due to a patient overflow, since this often happens in a hospital, we arbitrarily assign λ=0 for that day, in effect having patients leave without being admitted. Therefore, λm_S represents the total number of admissions colonized with bacteria sensitive to both drugs and $\mu\frac{S}{N}$ will represent the total number of patients with sensitive bacteria discharged from the hospital.

We let γ represent the rate of bacterial clearance due to the body's immune system response which we assume to be a constant for all patients. We assume that there is no discrimination concerning the dosage administration. All patients are equally likely to be given drug 1 or drug 2. The rates of clearance are represented by parameters τ_1 and τ_2. Patients colonized with a sensitive strain can be cleared using either drug 1 or drug 2. A patient colonized with bacteria resistant to drug 1 can be cleared with drug 2 and vice versa. A patient colonized with a dual-resistant strain is unaffected by either drug and thus can be cleared only by an immune system response. We assume that a patient can be colonized by only one strain at any given time and that there is no secondary colonization. We also assume that patient-hospital staff contacts are equally likely and therefore a patient is equally likely to become colonized with a particular bacterial strain-sensitive, singly-resistant or dual-resistant. We assign β to be the number of effective contacts by a patient per day. One more factor for consideration is that the evolution of antibiotic resistance comes with a cost

[17]. A cell mutation that successfully counters a specific antibiotic attack mechanism also weakens certain cell defense mechanisms against the human immune system and other non-mutated bacteria. Microbiologists call this phenomenon *fitness cost* [17]. Mutated resistant bacteria have less ability to reproduce and defend themselves and thus a higher fitness cost. So, in the absence of an antibiotic, sensitive bacteria will dominate. We also assume that a greater degree of mutation must occur for dual resistant bacteria to develop and so the fitness cost for dual ARB is higher than that of single ARB. We assign the parameters c_1, c_2, and c_{12} to the R_1, R_2, and R_{12} populations, respectively. Figure 3 shows the possible transistions into and out of hospital subpopulations. Table 2 summarizes the different compartments or subpopulations. We describe the parameters in table 3. The values assigned to the parameters for the simulations are also listed in table 3. The ODE system that describes the compartmental model depicted by figure 3 is given in equation (1).

Figure 4 contains solution plots of system 1 where $\lambda(t)$ and $\mu(t)$ are calculated two different ways. The bold plot is the result of using $\lambda(t)$ and $\mu(t)$ that are calculated by first taking random draws from a Poisson distribution with daily means given in table 1 for a year long variation in hospital population. This is performed for 500 different trials to find an average yearly variation. This mean is essentially a slight variation about the means from table 1. Given that there could be significant variation about the means, we include three other solution plots which are generated where $\lambda(t)$ and $\mu(t)$ are Poisson-distributed values of the original admission and discharge averages taken from the Toronto study. These figures give a more accurate depiction of what might happen in a single hospital during the course of a year.

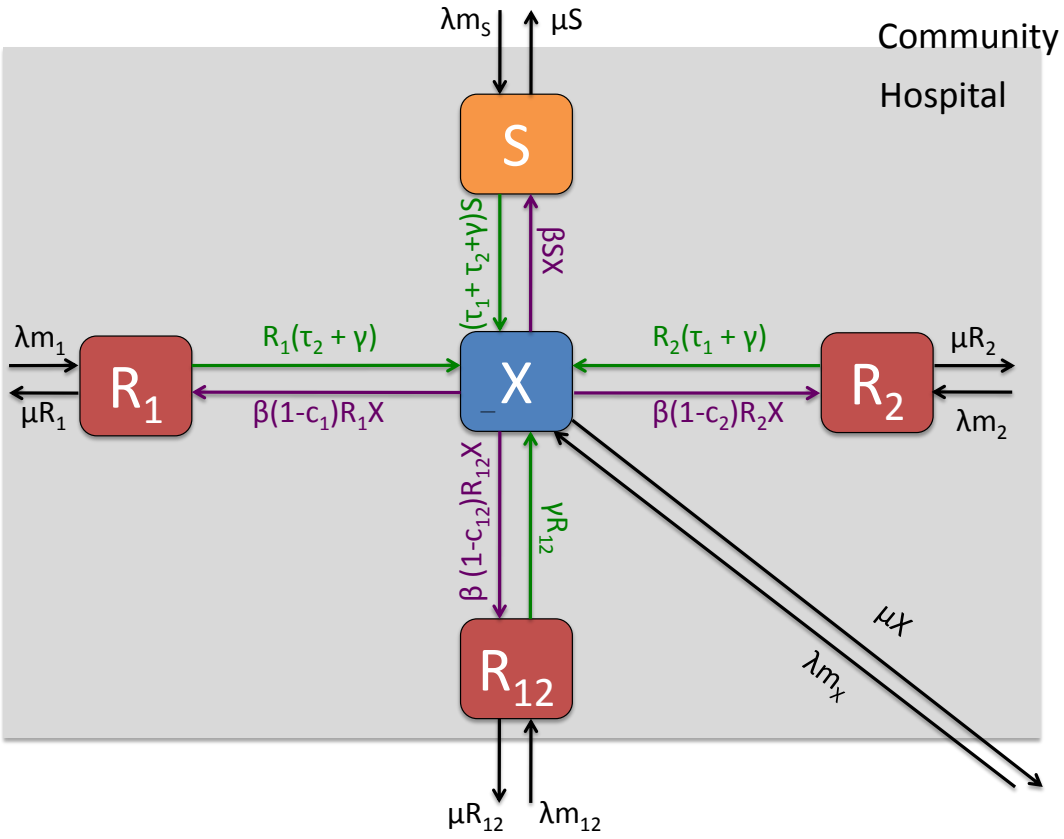

Figure 3: Schematic showing the compartment to compartment transitions and rates

Table 2: List of State Variables

Variable	Description
S	number of patients colonized with sensitive bacteria
R_1	number of patients colonized with bacteria resistant to drug 1
R_2	number of patients colonized with bacteria resistant to drug 2
R_{12}	number of patients colonized with bacteria resistant to drugs 1 and 2
X	number of patients uncolonized

Table 3: List of Parameters

Parameter	Description	Units	Assigned Values
β	Number of effective contacts per day	1/day	1
γ	Clearance rate due to immune system response	1/day	0.03
m_S	Proportion of community colonized with sensitive bacteria	dimensionless	0.7
m_1	Proportion of community colonized with bacteria resistant to drug 1	dimensionless	.05
m_2	Proportion of community colonized with bacteria resistant to drug 2	dimensionless	.05
m_{12}	Proportion of community colonized with bacteria resistant to drugs 1 & 2	dimensionless	.04
m_X	Proportion of community uncolonized	dimensionless	.16
τ_1	Per capita treatment rate of drug 1	1/day	.39
τ_2	Per capita treatment rate of drug 2	1/day	.39
c_1	Fitness cost of bacteria resistant to drug 1	dimensionless	.05
c_2	Fitness cost of bacteria resistant to drug 2	dimensionless	.05
c_{12}	Fitness cost of bacteria resistant to drugs 1 and 2	dimensionless	.15
λ	Daily Admission	Patients/day	Varies
μ	Daily Admission	Patients/day	Varies

$$\frac{dS}{dt} = \lambda(t)m_s - \mu(t)S(t)/N(t) - (\tau_1+\tau_2+\gamma)S(t) + \beta S(t)X(t)/N(t) \tag{1}$$

$$\frac{dR_1}{dt} = \lambda(t)m_1 - \mu(t)R_1(t)/N(t) - (\tau_2+\gamma)R_1(t) + \beta(1-c_1)R_1(t)X(t)/N(t)$$

$$\frac{dR_2}{dt} = \lambda(t)m_2 - \mu(t)R_2(t)/N(t) - (\tau_1+\gamma)R_2(t) + \beta(1-c_2)R_2(t)X(t)/N(t)$$

$$\frac{dR_{12}}{dt} = \lambda(t)m_{12} - \mu(t)R_{12}(t)/N(t) - \gamma R_{12}(t) + \beta(1-c_{12})R_{12}(t)X(t)/N(t)$$

$$\frac{dX}{dt} = \lambda(t)m_x - \mu(t)X(t)/N(t) + (\tau_1+\tau_2+\gamma)S(t) + (\tau_2+\gamma)R_1(t) + (\tau_1+\gamma)R_2(t)$$
$$+ \gamma R_{12}(t) - \frac{\beta}{N(t)}X(t)(S(t) + R_1(t)(1-c_1) + R_2(t)(1-c_2) + R_{12}(t)(1-c_{12}))$$

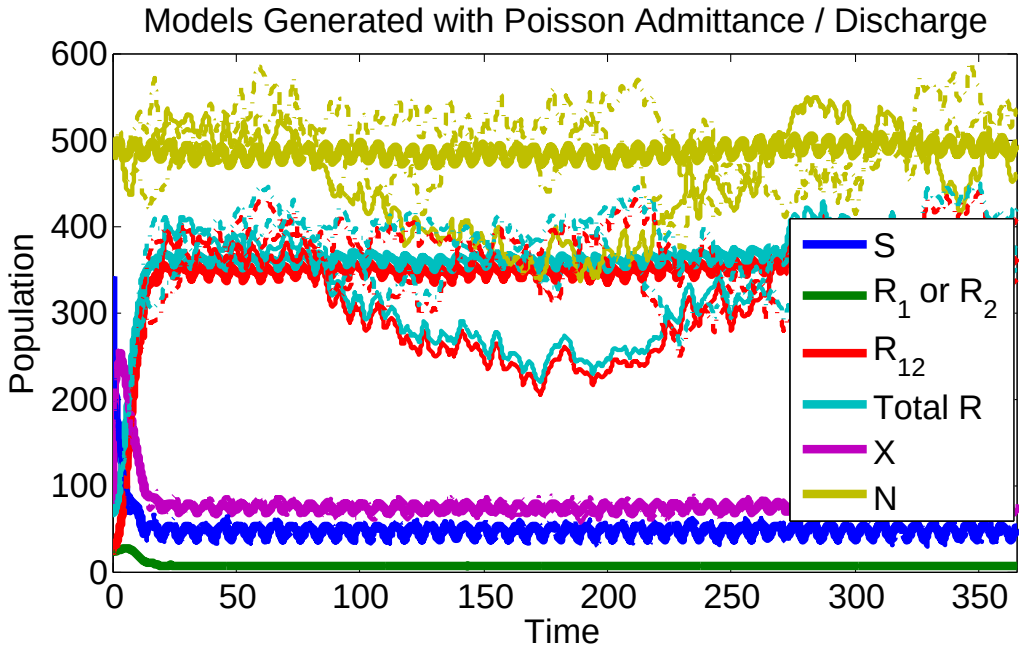

Figure 4: Deterministic simulations of system 1 using parameter values in Table 3: The bold plot is a realization where λ and μ were generated using Poisson-distributed means of 500 trials generated using the Toronto data and the other 3 plots are 3 realizations for yearly variations generated using the Poisson distribution applied directly to the empirical means from the Toronto study.

We see from figure 4 that the different bacterial populations rise and fall as the patient population changes. But we note for two of the simulations that in a matter of weeks the dual-resistant strain, and so the total resistance, increases dramatically then lessens during midyear only to increase again. We also compare the variation in the *proportion* of the hospital colonized with dual resistance in Figure 5. The average

yearly total proportions colonized with some type of resistance are 71.5%, 73.3% and 73.5% for the three individual year realizations.

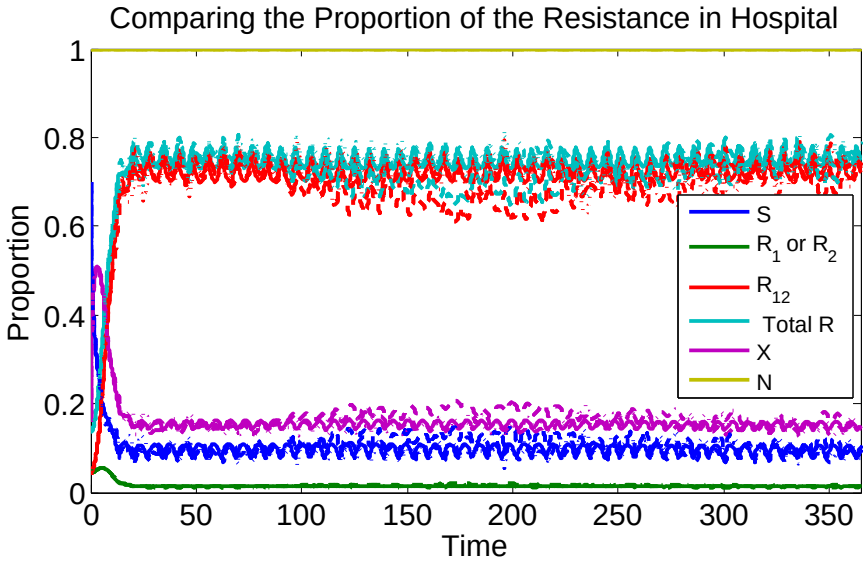

Figure 5: The proportion of the hospital colonized with resistant bacteria.

4 THE STOCHASTIC MODEL

A deterministic model is an effective tool when performing analyses of dynamical systems involving large populations, but over half of all hospitals in the United States have bed capacities under 200 units [11]. The fluctuations that are inherently part of smaller population dynamical systems are more accurately modeled using a stochastic model. To derive the stochastic model, we consider a continuous time Markov chain (CTMC) with state space $\mathbf{Z}^6$. We consider an *event* to be the transition of a single patient from one bacterial category to another or a patient being admitted or discharged. The probability of such an event only depends on the state at the previous time, (the memorylessness property). We define the probability that S increases by one person while X decreases by one person below. The eighteen probabilities of all possible one-person changes are listed in 7. The possible transitions and probabilities are summarized in table 4.

$$\begin{aligned} &Prob\{S(t+dt) = i+1, R_1(t+dt) = j, R_2(t+dt) = k, R_{12}(t+dt) = m, \\ &X(t+dt) = n-1, N(t+dt) = q | S(t) = i, R_1(t) = j, R_2(t) = k, \\ &R_{12} = m, X(t) = n, N(t) = q\} = \beta SX/N dt + o(dt). \end{aligned} \tag{2}$$

We let Δt represent the length of time for a single event to occur. At time t, let $\mathbf{X}(t) = \{S(t), R_1(t), R_2(t), R_{12}(t), X(t)\} = \mathbf{x}$, then state $\mathbf{x}$ jumps to state $\mathbf{x} + \mathbf{v_j}$ in time Δt with probability $\zeta_j(\mathbf{x})\Delta t + o(\Delta t)$, i.e., $Prob\{\mathbf{X}(t+\Delta t) = \mathbf{x} + \mathbf{v}_j | \mathbf{X}(t) = \mathbf{x}\} = \zeta_j(\mathbf{x})\Delta t + o(\Delta t)$, $j = 1, 2, \ldots, l, \mathbf{x} = (S, R_1, R_2, R_{12}, X, N)^T \in \mathbf{Z}^6$. Here $\mathbf{v}_j$

is the transition vector, ζ_j is the transition rate for reaction j and l denotes the number of transitions. Equations (16) through (33) define the transition probabilities. Table 4 summarizes the transition probabilities. Simulations are given using the Gillespie Stochastic Simulation Algorithm outlined in table 5. We note that the simulations given use the "mean" rates for admissions and discharges. Varying the rates of admission and discharge, as we did in Figure 4, there will be even more variation in the resistance.

Table 4: Transition Probabilities

Transition $[\Delta S, \Delta R_1, \Delta R_2, \Delta R_{12}, \Delta X, \Delta N]$	Description	Probability
$[1,0,0,0,-1,0]$	$S\uparrow\ X\downarrow$	$\beta SX/N\Delta t + o\Delta t$
$[-1,0,0,0,1,0]$	$S\downarrow\ X\uparrow$	$S(\gamma+\tau_1+\tau_2)\Delta t + o(\Delta t)$
$[0,1,0,0,-1,0]$	$R_1\uparrow\ X\downarrow$	$\beta(1-c_1)R_1X/N\Delta t + o(\Delta t)$
$[0,-1,0,0,1,0]$	$R_1\downarrow\ X\uparrow$	$R_1(\gamma+\tau_2)\Delta t + o(\Delta t)$
$[0,0,1,0,-1,0]$	$R_2\uparrow\ X\downarrow$	$\beta(1-c_2)R_2X/N\Delta t + o(\Delta t)$
$[0,0,-1,0,1,0]$	$R_2\downarrow\ X\uparrow$	$R_2(\gamma+\tau_1)\Delta t + o(\Delta t)$
$[0,0,0,1,-1,0]$	$R_{12}\uparrow\ X\downarrow$	$\beta(1-c_{12})R_{12}X/N\Delta t + o(\Delta t)$
$[0,0,0,-1,1,0]$	$R_{12}\downarrow\ X\uparrow$	$R_{12}\gamma\Delta t + o(\Delta t)$
$[1,0,0,0,0,1]$	$S\uparrow$	$\lambda m_S\Delta t + o(\Delta t)$
$[-1,0,0,0,0,-1]$	$S\downarrow$	$\mu S/N\Delta t + o(\Delta t)$
$[0,1,0,0,0,1]$	$R_1\uparrow$	$\lambda m_1\Delta t + o(\Delta t)$
$[0,-1,0,0,0,-1]$	$R_1\downarrow$	$\mu R_1/N\Delta t + o(\Delta t)$
$[0,0,1,0,0,1]$	$R_2\uparrow$	$\lambda m_2\Delta t + o(\Delta t)$
$[0,0,-1,0,0,-1]$	$R_2\downarrow$	$\mu R_2/N\Delta t + o(\Delta t)$
$[0,0,0,1,0,1]$	$R_{12}\uparrow$	$\lambda m_{12}\Delta t + o(\Delta t)$
$[0,0,0,-1,0,-1]$	$R_{12}\downarrow$	$\mu R_{12}/N\Delta t + o(\Delta t)$
$[0,0,0,0,1,1]$	$X\uparrow$	$\lambda m_X\Delta t + o(\Delta t)$
$[0,0,0,0,-1,-1]$	$X\downarrow$	$\mu X/N\Delta t + o(\Delta t)$

Table 5: The Gillespie Algorithm

1.	Initialize the system state
2.	Determine the transition rates from one compartment to another
3.	Calculate the sum of all transition rates
4.	Monte Carlo steps to determine the time to and type of transition
5.	Calculate the transition and update the time
6.	Iterate until the time is expired.

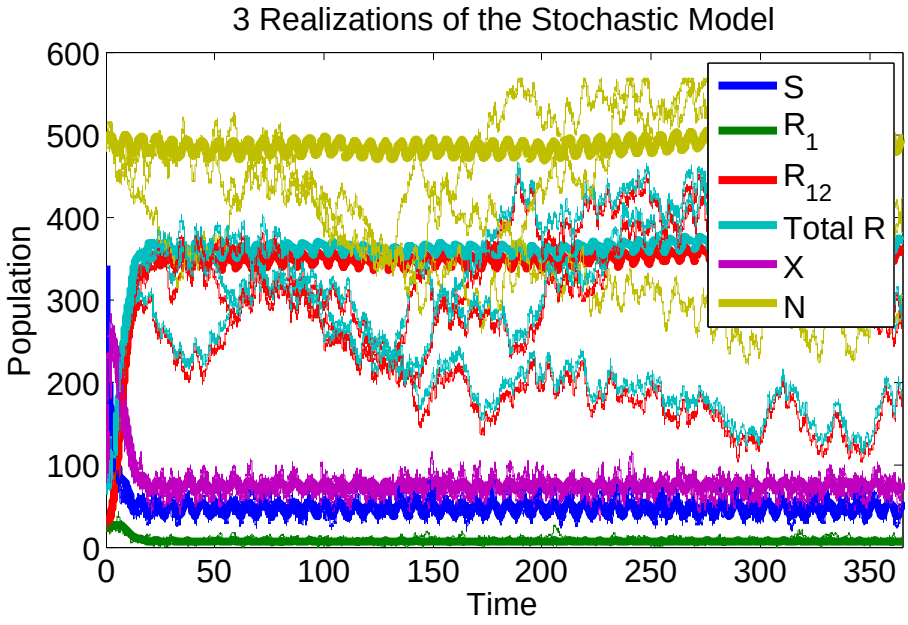

Figure 6: Stochastic Model: 3 realizations of the distribution of patient population categorized by type of antibiotic resistance along with the deterministic model

Since the hospital at which the Toronto study was performed has a bed capacity of over five hundred beds, we scale our empirical data to one-fifth the size and

regenerate realizations following the process previously described. Table 6 contains our new admission and discharge data and figure 7 shows the realizations for a smaller capacity hospital.

Table 6: Scaled Daily Admissions and Discharges

Description	M	T	W	Th	F	S	S
Admissions	11.5	12.3	12.2	11.8	10.8	7.0	6.8
Discharges	9.9	10.7	11.3	11.7	13.4	8.6	6.8

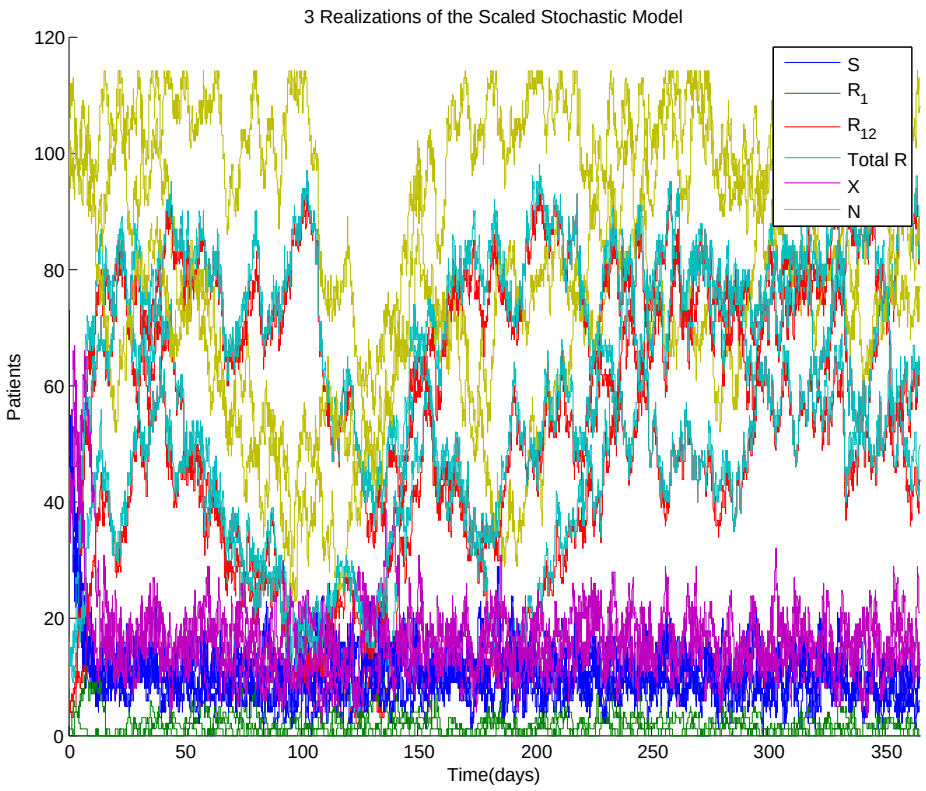

Figure 7: Stochastic Model: 3 realizations of the distribution of patient population categorized by type of resistance in a smaller hospital

We notice that, as with the deterministic model, the dual-resistant strain increases rapidly at the onset and appears to maintain this level although in one of the three small hospital realizations it does drop to a level only slightly above the single resistance strains. There is also a large variation in the behavior of the resistance as opposed to the deterministic model 4. In a small hospital, variation from the expected trend is likely.

5 EQUILIBRIUM AND STABILITY

In this model, we are concerned with a resistance-free equilibrium which we designate as RFE. The resistance-free state is $\{S, R_1, R_2, R_{12}, X, N\} = \{S(t), 0, 0, 0, X(t), N(t)\}$. We note that with our varying population, a zero resistance level within the hospital implies that the proportions of the general population entering the hospital, m_1, m_2, or m_{12} must equal zero. This can be seen by examining the requirements for a resistance-free state further. In a resistance-free state $N(t) = S(t) + X(t)$. Therefore

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS}{dt} + \frac{dX}{dt} \\ &= \lambda m_s - \mu\frac{S}{N} - (\tau_1 + \tau_2 + \gamma)S + \frac{\beta SX}{N} \\ &\quad + \lambda m_x - \mu\frac{X}{N} + (\tau_1 + \tau_2 + \gamma)S - \frac{\beta SX}{N} \end{aligned} \tag{3}$$

using the system in equation 1 with $R_1 = R_2 = R_{12} = 0$. Therefore

$$\begin{aligned} \frac{dN}{dt} &= \lambda(m_s + m_x) - \mu\left(\frac{S+X}{N}\right) \\ &= \lambda(m_s + m_x) - \mu \end{aligned} \tag{4}$$

However

$$\frac{dN}{dt} = \lambda(m_s + m + x + m_1 + m_2 + m_{12}) - \mu$$

which implies that m_1, m_2, and m_{12} should all equal zero in the resistance free state. The variability in the hospital population causes the equilibrium to be time-dependent. The demographic equation for the dynamics of the total population is given by:

$N' = \lambda - \mu$ where λ and μ are in units of individuals per day. Letting r represent $\frac{\lambda-\mu}{N}$ with units 1/day we have $N' = rN$ which has the general solution $N = N_0 e^{rt}$. Depending on the value of r, we have either exponential growth, decay or stability.

We base our equilibrium and stability analysis on work by Hadeler [13], who determined that the time-dependent solutions of a resistance-free system are stable (unstable) if the corresponding steady-state exponential solutions of the equivalent *normalized* system is stable (unstable). We first normalize the state variables with respect to the total population, N. Then we determine the normalized system of differential equations with respect to time. We set $s = S/N$, $r_1 = R_1/N$, $r_2 = R_2/N$, $r_{12} = R_{12}/N$, $x = X/N$, $\tilde{\lambda} = \lambda/N,$ and $\tilde{\mu} = \mu/N$.

$$\{S, R_1, R_2, R_{12}, X, \lambda, \mu\} \xrightarrow{\text{normalized as}} \{s, r_1, r_2, r_{12}, x, \tilde{\lambda}, \tilde{\mu}\}$$

Therefore, $s + r_1 + r_2 + r_{12} + x = 1$. So our six state variables, $\{S, R_1, R_2, R_{12}, X, N\}$, are now reduced to 5 state variables, $\{s, r_1, r_2, r_{12}, x\}$. Next we derive the equations for the derivatives of the normalized variables. We determine s':

$$\begin{aligned} s &= \frac{S}{N} \\ s' &= \frac{NS' - N'S}{N^2} \\ &= \frac{S'}{N} - \frac{N'}{N} \cdot \frac{S}{N} \\ &= \frac{\lambda m_s - \mu \frac{S}{N} - (\tau_1 + \tau_2 + \gamma)S + \beta \frac{SX}{N}}{N} - \frac{\lambda - \mu}{N} \cdot \frac{S}{N} \\ s' &= \tilde{\lambda}(m_s - s) - (\tau_1 + \tau_2 + \gamma)s + \beta s x \end{aligned} \tag{5}$$

We can derive the other normalized ODE's in similar fashion to obtain the equivalent non-homogeneous system in equation (6):

$$
\begin{aligned}
s' &= \tilde{\lambda}(m_s - s) - (\tau_1 + \tau_2 + \gamma)s + \beta s x \qquad (6)\\
r_1' &= \tilde{\lambda}(m_1 - r_1) - (\tau_2 + \gamma)r_1 + \beta(1 - c_1)r_1 x\\
r_2' &= \tilde{\lambda}(m_2 - r_2) - (\tau_1 + \gamma)r_2 + \beta(1 - c_2)r_2 x\\
r_{12}' &= \tilde{\lambda}(m_{12} - r_{12}) - \gamma r_{12} + \beta(1 - c_{12})r_{12} x\\
x' &= \tilde{\lambda}(m_x - x) - \beta x(s + (1 - c_1)r_1 + (1 - c_2)r_2 + (1 - c_{12})r_{12})\\
&\quad + (\tau_1 + \tau_2 + \gamma)s + (\tau_2 + \gamma)r_1 + (\tau_1 + \gamma)r_2 + \gamma r_{12}.
\end{aligned}
$$

We now can determine the equilibrium and stability of this normalized system. To do this we first note that the resistance-free equilibrium is $\{s^*, 0, 0, 0, x^*\}$ where $x^* = 1 - s^*$. We evaluate s' at the RFE and set the expression equal to zero to determine the value at the equilibrium of s^* in terms of the parameters. We obtain

$$
s^* = \frac{\beta - \tau_1 - \tau_2 - \gamma - \tilde{\lambda} + \sqrt{(\beta - \tau_1 - \tau_2 - \gamma - \tilde{\lambda})^2 + 4\beta\tilde{\lambda}m_s}}{2\beta}. \qquad (7)
$$

To analyze the stability of this equilibrium we follow the next generation approach outlined by P. van den Driessche and J. Watmough [8]. We reorganize the reduced ODE system, listing the ODEs pertaining to the resistant proportion variables first. The reorganized, normalized system is given by equation (8).

$$
\begin{aligned}
r_1' &= \tilde{\lambda}(m_1 - r_1) - (\tau_2 + \gamma)r_1 + \beta(1 - c_1)r_1 x \\
r_2' &= \tilde{\lambda}(m_2 - r_2) - (\tau_1 + \gamma)r_2 + \beta(1 - c_2)r_2 x \\
r_{12}' &= \tilde{\lambda}(m_{12} - r_{12}) - \gamma r_{12} + \beta(1 - c_{12})r_{12} x \\
s' &= \tilde{\lambda}(m_s - s) - (\tau_1 + \tau_2 + \gamma)s + \beta s x \\
x' &= \tilde{\lambda}(m_x - x) + \beta x(s + (1 - c_1)r_1 + (1 - c_2)r_2 + (1 - c_{12})r_{12}) \\
&\quad + (\tau_1 + \tau_2 + \gamma)s + (\tau_2 + \gamma)r_1 + (\tau_1 + \gamma)r_2 + \gamma r_{12}.
\end{aligned} \tag{8}
$$

Since $s + r_1 + r_2 + r_{12} + x = 1$ in the normalized system, we may eliminate x' from consideration and thus the reduced system is

$$
\begin{aligned}
r_1' &= \tilde{\lambda}(m_1 - r_1) - (\tau_2 + \gamma)r_1 + \beta(1 - c_1)r_1 x \\
r_2' &= \tilde{\lambda}(m_2 - r_2) - (\tau_1 + \gamma)r_2 + \beta(1 - c_2)r_2 x \\
r_{12}' &= \tilde{\lambda}(m_{12} - r_{12}) - \gamma r_{12} + \beta(1 - c_{12})r_{12} x \\
s' &= \tilde{\lambda}(m_s - s) - (\tau_1 + \tau_2 + \gamma)s + \beta s x
\end{aligned} \tag{9}
$$

where $x = 1 - (s + r_1 + r_2 + r_{12})$. We linearize about the RFE by determining the Jacobian of our reduced system and evaluating this matrix at s^*. The Jacobian matrix is

$$
\text{Jac} = \begin{bmatrix}
J_{11} & 0 & 0 & -\beta(1 - c_1)r_1 \\
0 & J_{22} & 0 & -\beta(1 - c_2)r_2 \\
0 & 0 & J_{33} & -\beta(1 - c_{12}r_{12} \\
-\beta s & -\beta s & -\beta s & J_{44}
\end{bmatrix}
$$

where

$$J_{11} = -(\tilde{\lambda} + \tau_2 + \gamma) + \beta(1 - c_1)(1 - s^*) \tag{10}$$

$$J_{22} = -(\tilde{\lambda} + \tau_1 + \gamma) + \beta(1 - c_2)(1 - s^*)$$

$$J_{33} = -(\tilde{\lambda} + \gamma) + \beta(1 - c_{12})(1 - s^*)$$

$$J_{44} = -\tilde{\lambda} - (\tau_1 + \tau_2 + \gamma) + \beta(x - s).$$

Using the next generation approach, we need to only focus on the portion of the Jacobian which pertains to the resistant population, i.e., the upper 3x3 matrix of Jac. We then separate the J_{ii}'s, the diagonal elements of the Jacobian, into rates of new colonizations (given in blue) and other transitions (given in red) represented by F_{ii} and V_{ii}, respectively, forming two new matrices given by equations (11) and (12). We let

$$F = \begin{bmatrix} F_{11} & 0 & 0 \\ 0 & F_{22} & 0 \\ 0 & 0 & F_{33} \end{bmatrix} \tag{11}$$

where

$$F_{11} = \beta(1 - c_1)(1 - s^*)$$

$$F_{22} = \beta(1 - c_2)(1 - s^*)$$

$$F_{33} = \beta(1 - c_{12})(1 - s^*).$$

and

$$V = \begin{bmatrix} V_{11} & 0 & 0 \\ 0 & V_{22} & 0 \\ 0 & 0 & V_{33} \end{bmatrix} \tag{12}$$

where

$$V_{11} = \tilde{\lambda} + \tau_2 + \gamma$$

$$V_{22} = \tilde{\lambda} + \tau_1 + \gamma$$

$$V_{33} = \tilde{\lambda} + \gamma.$$

The next generation matrix is the square matrix, $G = FV^{-1}$, in which the ijth element of G, g_{ij}, is the expected number of secondary transistions of type i caused by a single infected individual of type j.

$$FV^{-1} = \begin{bmatrix} \frac{\beta(1-c_1)(1-s^*)}{\tilde{\lambda}+\tau_2+\gamma} & 0 & 0 \\ 0 & \frac{\beta(1-c_2)(1-s^*)}{\tilde{\lambda}+\tau_1+\gamma} & 0 \\ 0 & 0 & \frac{\beta(1-c_{12})(1-s^*)}{\tilde{\lambda}+\gamma} \end{bmatrix}.$$

We let R_s denote the spectral radius of FV^{-1} (the maximum of the eigenvalues of the matrix). In other words

$$R_s = \max\left\{ \frac{\beta(1-c_1)(1-s^*)}{\tilde{\lambda}+\tau_2+\gamma}, \frac{\beta(1-c_2)(1-s^*)}{\tilde{\lambda}+\tau_1+\gamma}, \frac{\beta(1-c_{12})(1-s^*)}{\tilde{\lambda}+\gamma} \right\}. \tag{13}$$

Using results from Van den Driessche et al.[8], we have the following theorem concerning our normalized system:

Theorem 5.1 *The resistant-free equilibrium for the normalized model, $RFE = (s^*, 0, 0, 0, x^*)$, is locally asymptotically stable if and only if $R_s < 1$ where R_s is defined by equation* (13) *and s^* is given by* (7).

Based on theory developed by Hadeler [13], we have the following theorem concerning our original system.

Theorem 5.2 *The resistant-free state for the model given by equation (1),* $RFE = (S(t), 0, 0, 0, X(t), N(t))$, *is locally asymptotically stable if and only if* $R_s < 1$ *where* R_s *is defined by equation* (13) *and* s^* *is given by* (7).

6 SENSITIVITY ANALYSIS

The objective of this paper is to determine the effect that a fluctuating hospital population has on the resistance within a hospital. Performing a sensitivity analysis of the model with regard to changes in the parameters will provide information about the degree to which the results of this model will be affected by increases or decreases in the parameter values. State variables' high sensitivity to parameter changes, necessitates the exploration of the effects of the parameter changes on the resultant variables within the model. We also need accurate estimations of these parameters to achieve a higher degree of precision in our findings. Through the process of sensitivity analysis we gain an understanding of which variables and processes may work to change the level of resistance within the hospital.

We utilize the traditional sensitivity analysis [14] by deriving $\frac{\partial \mathbf{x}}{\partial \mathbf{q}_j}$ for each state variable $\mathbf{x} = [S, R_1, R_2, R_{12}, X, N]$ and each parameter q_j in the system (except the fitness cost parameters) where

$$\mathbf{q} = [\beta, \gamma, m_s, m_1, m_2, m_{12}, m_x, \tau_1, \tau_2, \lambda, \mu]$$

represents the possible parameter values for our model. We first determine the partials of the system ODE's with respect to our selected parameters. The full ODE system consisting of 60 equations is listed in 7. We then calculate a relative ranking of the parameters to ascertain which parameter impacts the state variables most by using

the modified L_2 norm

$$\left\| \frac{\partial \mathbf{x}}{\partial \mathbf{q}_j} \right\|_2 = \frac{1}{\max \mathbf{x}} \left[\frac{1}{t_f - t_0} \int_{t_0}^{t_f} \left(\frac{\partial \mathbf{x}}{\partial \mathbf{q}_j} \mathbf{q}_j \right)^2 dt \right]^{1/2} \tag{14}$$

that normalizes the sensitivity values by eliminating the units. We determine the sensitivity of the hospital's total resistance $R = R_1 + R_2 + R_{12}$ using the formula

$$\begin{aligned} \left\| \frac{\partial \mathbf{R}}{\partial \mathbf{q}_j} \right\|_2 &= \frac{1}{\max R} \left[\frac{1}{t_f - t_0} \int_{t_0}^{t_f} \left(\frac{\partial R}{\partial \mathbf{q}_j} \mathbf{q}_j \right)^2 dt \right]^{1/2} \\ &= \frac{1}{\max R} \left[\frac{1}{t_f - t_0} \int_{t_0}^{t_f} \left(\left(\frac{\partial R_1}{\partial \mathbf{q}_j} + \frac{\partial R_2}{\partial \mathbf{q}_j} + \frac{\partial R_{12}}{\partial \mathbf{q}_j} \right) \mathbf{q}_j \right)^2 dt \right]^{1/2}. \end{aligned} \tag{15}$$

Since our intent in this paper is to refine previous compartmental models which assumed a fixed population, we examine side by side results of the analyses of two similar models that differ only in the assumption that the hospital has a fixed or varying population. To obtain parameters for a fixed population, we determine the means of the seven admission rates and of the seven discharge rates in the Toronto data. We then assign this average to λ and μ for our model. Figure 8 shows the overall results and the more pronounced impact that β, the per capital primary transmission rate, has on the levels of the dual-resistance and total overall resistance within a hospital. The two models are very similar with regard to the degree in which the remainder of the investigated parameters affect the levels of the sensitive and singly-resistant strains of bacteria. In the case of dual and total resistance, we see that in the constant population model, the daily change, $\lambda = \mu$, has a rather large effect, outweighing all other parameters on these two levels, but if the population varies, the

primary transmission rate of bacteria, β, has an even greater effect than the admission or discharge rates.

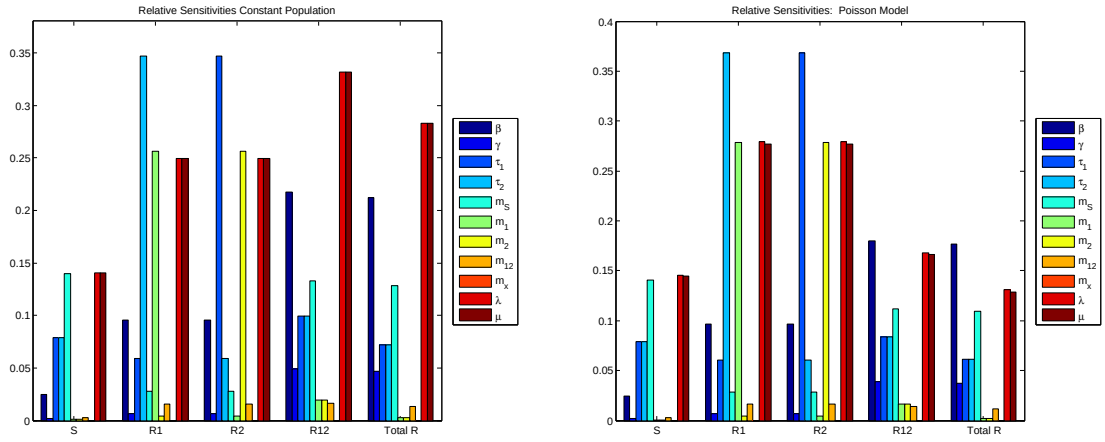

Figure 8: The figure on the left shows the relative sensitivity to the parameters if the hospital has a fixed population and the figure on the right shows the relative sensitivity to the parameters if the hospital population varies.

7 CONCLUSION

By accounting for varying patient levels, we have created a more accurate mathematical model of the transmission of antibiotic-resistant bacteria within a hospital setting. We created both deterministic and stochastic models for a large hospital and also a stochastic model for a smaller hospital. Our stability analysis indicated that in order to obtain a resistance-free environment, one must restrict (or effectively isolate) those patients admitted with resistant bacteria. Only then can one implement appropriate hygeine practices and dosage practices to reach a resistance-free environment. Through a sensitivity analysis we determined that the effective transmission rate, β, has an even greater effect than previous constant population models detected. Since the effective transmission rate can be more easily regulated by hygiene practices and hospital protocols more than the other parameters, this fact should be noted. We also note that the effect of β increased when considering a constant population versus a varying population. This seems to indicate that the varying population actually aids in reducing resistance in a hospital and the primary mechanism for reducing resistance is indeed hygiene practices as indicate by the term β. Nonetheless, admittance and discharge practices still play an important role in the increase/decrease of bacterial resistance in a hospital. These varying population models can also be implemented in researching how best to structure other means of resistance reduction such as dosage regimen and isolation.

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APPENDICES

Appendix A:

TRANSITION PROBABILITIES

$$Prob\{S(t+dt)=i+1, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m, \quad (16)$$

$$X(t+dt)=n-1, N(t+dt)=q|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\beta SX/Ndt+o(dt).$$

$$Prob\{S(t+dt)=i-1, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m, \quad (17)$$

$$X(t+dt)=n+1, N(t+dt)=q|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=S(\gamma+\tau_1+\tau_2)dt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j+1, R_2(t+dt)=k, R_{12}(t+dt)=m, \quad (18)$$

$$X(t+dt)=n-1, N(t+dt)=q|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\beta(1-c_1)R_1X/Ndt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j-1, R_2(t+dt)=k, R_{12}(t+dt)=m, \quad (19)$$

$$X(t+dt)=n+1, N(t+dt)=q|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=R_1(\gamma+\tau_2)dt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k+1, R_{12}(t+dt)=m, \quad (20)$$

$$X(t+dt)=n-1, N(t+dt)=q|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\beta(1-c_2)R_2X/Ndt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k-1, R_{12}(t+dt)=m, \tag{21}$$

$$X(t+dt)=n+1, N(t+dt)=q|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=R_2(\gamma+\tau_1)dt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m+1, \tag{22}$$

$$X(t+dt)=n-1, N(t+dt)=q|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\beta(1-c_{12})R_{12}X/Ndt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m-1, \tag{23}$$

$$X(t+dt)=n+1, N(t+dt)=q|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\gamma R_{12}dt+o(dt).$$

$$Prob\{S(t+dt)=i+1, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m, \tag{24}$$

$$X(t+dt)=n, N(t+dt)=q+1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\lambda m_S dt+o(dt).$$

$$Prob\{S(t+dt)=i-1, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m, \tag{25}$$

$$X(t+dt)=n, N(t+dt)=q-1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\mu S/Ndt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j+1, R_2(t+dt)=k, R_{12}(t+dt)=m, \tag{26}$$

$$X(t+dt)=n, N(t+dt)=q+1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\lambda m_1 dt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j-1, R_2(t+dt)=k, R_{12}(t+dt)=m, \quad (27)$$

$$X(t+dt)=n, N(t+dt)=q-1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\mu R_1/Ndt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k+1, R_{12}(t+dt)=m, \quad (28)$$

$$X(t+dt)=n, N(t+dt)=q+1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\lambda m_2 dt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k-1, R_{12}(t+dt)=m, \quad (29)$$

$$X(t+dt)=n, N(t+dt)=q-1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\mu R_2/Ndt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m+1, \quad (30)$$

$$X(t+dt)=n, N(t+dt)=q+1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\lambda m_{12} dt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m-1, \quad (31)$$

$$X(t+dt)=n, N(t+dt)=q-1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\mu R_{12}/Ndt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m, \quad (32)$$

$$X(t+dt)=n+1, N(t+dt)=q+1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\lambda m_X dt+o(dt).$$

$$Prob\{S(t+dt)=i, R_1(t+dt)=j, R_2(t+dt)=k, R_{12}(t+dt)=m, \tag{33}$$

$$X(t+dt)=n-1, N(t+dt)=q-1|S(t)=i, R_1(t)=j, R_2(t)=k,$$

$$R_{12}=m, X(t)=n, N(t)=q\}=\mu X/Ndt+o(dt).$$

Appendix B:

ODE SYSTEM FOR SENSITIVITIES

We let $Q = S + (1-c_1)R_1 + (1-c_2)R_2 + (1-c_{12})R_{12}$ and the partials of Q are:

$$\frac{\partial Q}{\partial \beta} = \frac{\partial S}{\partial \beta} + (1-c_1)\frac{\partial R_1}{\partial \beta} + (1-c_2)\frac{\partial R_2}{\partial \beta} + (1-c_{12})\frac{\partial R_{12}}{\partial \beta} \tag{34}$$

$$\frac{\partial Q}{\partial \tau_1} = \frac{\partial S}{\partial \tau_1} + (1-c_1)\frac{\partial R_1}{\partial \tau_1} + (1-c_2)\frac{\partial R_2}{\partial \tau_1} + (1-c_{12})\frac{\partial R_{12}}{\partial \tau_1} \tag{35}$$

$$\frac{\partial Q}{\partial \tau_2} = \frac{\partial S}{\partial \tau_2} + (1-c_1)\frac{\partial R_1}{\partial \tau_2} + (1-c_2)\frac{\partial R_2}{\partial \tau_2} + (1-c_{12})\frac{\partial R_{12}}{\partial \tau_2} \tag{36}$$

$$\frac{\partial Q}{\partial \gamma} = \frac{\partial S}{\partial \gamma} + (1-c_1)\frac{\partial R_1}{\partial \gamma} + (1-c_2)\frac{\partial R_2}{\partial \gamma} + (1-c_{12})\frac{\partial R_{12}}{\partial \gamma} \tag{37}$$

$$\frac{\partial Q}{\partial m_s} = \frac{\partial S}{\partial m_s} + (1-c_1)\frac{\partial R_1}{\partial m_s} + (1-c_2)\frac{\partial R_2}{\partial m_s} + (1-c_{12})\frac{\partial R_{12}}{\partial m_s} \tag{38}$$

$$\frac{\partial Q}{\partial m_1} = \frac{\partial S}{\partial m_1} + (1-c_1)\frac{\partial R_1}{\partial m_1} + (1-c_2)\frac{\partial R_2}{\partial m_1} + (1-c_{12})\frac{\partial R_{12}}{\partial m_1} \tag{39}$$

$$\frac{\partial Q}{\partial m_2} = \frac{\partial S}{\partial m_2} + (1-c_1)\frac{\partial R_1}{\partial m_2} + (1-c_2)\frac{\partial R_2}{\partial m_2} + (1-c_{12})\frac{\partial R_{12}}{\partial m_2} \tag{40}$$

$$\frac{\partial Q}{\partial m_{12}} = \frac{\partial S}{\partial m_{12}} + (1-c_1)\frac{\partial R_1}{\partial m_{12}} + (1-c_2)\frac{\partial R_2}{\partial m_{12}} + (1-c_{12})\frac{\partial R_{12}}{\partial m_{12}} \tag{41}$$

$$\frac{\partial Q}{\partial m_x} = \frac{\partial S}{\partial m_x} + (1-c_1)\frac{\partial R_1}{\partial m_x} + (1-c_2)\frac{\partial R_2}{\partial m_x} + (1-c_{12})\frac{\partial R_{12}}{\partial m_x} \tag{42}$$

$$\frac{\partial Q}{\partial \lambda} = \frac{\partial S}{\partial \lambda} + (1-c_1)\frac{\partial R_1}{\partial \lambda} + (1-c_2)\frac{\partial R_2}{\partial \lambda} + (1-c_{12})\frac{\partial R_{12}}{\partial \lambda} \tag{43}$$

$$\frac{\partial Q}{\partial \mu} = \frac{\partial S}{\partial \mu} + (1-c_1)\frac{\partial R_1}{\partial \mu} + (1-c_2)\frac{\partial R_2}{\partial \mu} + (1-c_{12})\frac{\partial R_{12}}{\partial \mu} \tag{44}$$

The partials of the state variables are:

$$\frac{d}{dt}\frac{\partial S}{\partial \beta} = \frac{-\mu\left(\frac{dS}{d\beta}N - S\frac{dN}{d\beta}\right)}{N^2} - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \beta} + \frac{XSN + \beta\left(X\frac{\partial S}{\partial \beta} + S\frac{\partial X}{\partial \beta}\right)N - \beta SX\frac{\partial N}{\partial \beta}}{N^2} \tag{45}$$

$$\frac{d}{dt}\frac{\partial R_1}{\partial \beta} = \frac{-\mu\left(\frac{\partial R_1}{\partial \beta}N - \frac{\partial N}{\partial \beta}R_1\right)}{N^2} - (\tau_2+\gamma)\frac{\partial R_1}{\partial \beta} + (1-c_1)\frac{XR_1N + \beta\left(X\frac{\partial R_1}{\partial \beta} + R_1\frac{\partial X}{\partial \beta}\right)N - \beta R_1X\frac{\partial N}{\partial \beta}}{N^2} \tag{46}$$

$$\frac{d}{dt}\frac{\partial R_2}{\partial \beta} = \frac{-\mu\left(\frac{\partial R_2}{\partial \beta}N - \frac{\partial N}{\partial \beta}R_2\right)}{N^2} - (\tau_1+\gamma)\frac{dR_2}{d\beta} + (1-c_2)\frac{XR_2N + \beta\left(X\frac{\partial R_2}{\partial \beta} + R_2\frac{\partial X}{\partial \beta}\right)N - \beta R_2X\frac{\partial N}{\partial \beta}}{N^2} \tag{47}$$

$$\frac{d}{dt}\frac{\partial R_{12}}{\partial \beta} = \frac{-\mu\left(\frac{\partial R_{12}}{\partial \beta}N - \frac{\partial N}{\partial \beta}R_{12}\right)}{N^2} - \gamma\frac{\partial R_{12}}{\partial \beta} + (1-c_{12})\frac{XR_{12}N + \beta\left(X\frac{\partial R_{12}}{\partial \beta} + R_{12}\frac{\partial X}{\partial \beta}\right)N - \beta R_{12}X\frac{\partial N}{\partial \beta}}{N^2} \tag{48}$$

$$\frac{d}{dt}\frac{\partial X}{\partial \beta} = \frac{-\mu\left(\frac{\partial X}{\partial \beta}N - \frac{\partial N}{\partial \beta}X\right)}{N^2} - \frac{XQ + \beta\left(\frac{\partial X}{\partial \beta}Q + \frac{\partial Q}{\partial \beta}\right)N - \frac{\partial N}{\partial \beta}\beta XQ}{N^2} + (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \beta} + (\tau_2+\gamma)\frac{\partial R_1}{\partial \beta} + (\tau_1+\gamma)\frac{\partial R_2}{\partial \beta} + \gamma\frac{\partial R_{12}}{\partial \beta} \tag{49}$$

$$\frac{d}{dt}\frac{\partial S}{\partial \tau_1} = \frac{-\mu\left(\frac{\partial S}{\partial \tau_1}N - S\frac{\partial N}{\partial \tau_1}\right)}{N^2} - S - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \tau_1} + \beta\frac{\left(S\frac{\partial X}{\partial \tau_1} + \frac{\partial S}{\partial \tau_1}X\right)N - SX\frac{\partial N}{\partial \tau_1}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_1}{\partial \tau_1} = \frac{-\mu\left(\frac{\partial R_1}{\partial \tau_1}N - R_1\frac{\partial N}{\partial \tau_1}\right)}{N^2} - (\tau_2+\gamma)\frac{\partial R_1}{\partial \tau_1} + \beta(1-c_1)\frac{\left(\frac{\partial X}{\partial \tau_1}R_1 + \frac{\partial R_1}{\partial \tau_1}X\right)N - R_1X\frac{\partial N}{\partial \tau_1}}{N^2} \tag{50}$$

$$\tag{51}$$

$$\frac{d}{dt}\frac{\partial R_2}{\partial \tau_1} = \frac{-\mu\left(\frac{\partial R_2}{\partial \tau_1}N - R_2\frac{\partial N}{\partial \tau_1}\right)}{N^2} - (\tau_1+\gamma)\frac{\partial R_2}{\partial \tau_1} - R_2 \tag{52}$$
$$+ \beta(1-c_2)\frac{\left(\frac{\partial X}{\partial \tau_1}R_2 + \frac{\partial R_2}{\partial \tau_1}X\right)N - R_2X\frac{\partial N}{\partial \tau_1}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_{12}}{\partial \tau_1} = \frac{-\mu\left(\frac{\partial R_{12}}{\partial \tau_1}N - R_{12}\frac{\partial N}{\partial \tau_1}\right)}{N^2} - \gamma\frac{\partial R_{12}}{\partial \tau_1} \tag{53}$$
$$+ \beta(1-c_{12})\frac{\left(\frac{\partial X}{\partial \tau_1}R_{12} + \frac{\partial R_{12}}{\partial \tau_1}X\right)N - R_{12}X\frac{\partial N}{\partial \tau_1}}{N^2}$$

$$\frac{d}{dt}\frac{\partial X}{\partial \tau_1} = \frac{-\mu\left(\frac{\partial X}{\partial \tau_1}N - X\frac{\partial N}{\partial \tau_1}\right)}{N^2} - \beta\frac{\left(Q\frac{\partial X}{\partial \tau_1} + X\frac{\partial Q}{\partial \tau_1}\right)N - QX\frac{\partial N}{\partial \tau_1}}{N^2}$$
$$+ S + (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \tau_1} + (\tau_2+\gamma)\frac{\partial R_1}{\partial \tau_1} + R_2 + (\tau_1+\gamma)\frac{\partial R_2}{\partial \tau_1} + \gamma\frac{\partial R_{12}}{\partial \tau_1}$$

$$\frac{d}{dt}\frac{\partial S}{\partial \tau_2} = \frac{-\mu\left(\frac{\partial S}{\partial \tau_2}N - S\frac{\partial N}{\partial \tau_2}\right)}{N^2} - S - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \tau_2}$$
$$+ \beta\frac{\left(S\frac{\partial X}{\partial \tau_2} + \frac{\partial S}{\partial \tau_2}X\right)N - SX\frac{\partial N}{\partial \tau_2}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_1}{\partial \tau_2} = \frac{-\mu\left(\frac{\partial R_1}{\partial \tau_2}N - R_1\frac{\partial N}{\partial \tau_2}\right)}{N^2} - R_1 - (\tau_2+\gamma)\frac{\partial R_1}{\partial \tau_2} \tag{54}$$
$$+ \beta(1-c_1)\frac{\left(R_1\frac{\partial X}{\partial \tau_2} + \frac{\partial R_1}{\partial \tau_2}X\right)N - R_1X\frac{\partial N}{\partial \tau_2}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_2}{\partial \tau_2} = \frac{-\mu\left(\frac{\partial R_2}{\partial \tau_2}N - R_2\frac{\partial N}{\partial \tau_2}\right)}{N^2} - (\tau_1+\gamma)\frac{\partial R_2}{\partial \tau_2} \tag{55}$$
$$+ \beta(1-c_2)\frac{\left(R_2\frac{\partial X}{\partial \tau_2} + \frac{\partial R_2}{\partial \tau_2}X\right)N - R_2X\frac{\partial N}{\partial \tau_2}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_{12}}{\partial \tau_2} = \frac{-\mu\left(\frac{\partial R_{12}}{\partial \tau_2}N - R_{12}\frac{\partial N}{\partial \tau_2}\right)}{N^2} - \gamma\frac{dR_{12}}{d\tau_2} \tag{56}$$
$$+ \beta(1-c_{12})\frac{\left(R_{12}\frac{\partial X}{\partial \tau_2} + \frac{\partial R_{12}}{\partial \tau_2}X\right)N - R_{12}X\frac{\partial N}{\partial \tau_2}}{N^2}$$

$$\frac{d}{dt}\frac{\partial X}{\partial \tau_2} = -\mu\frac{\frac{\partial X}{\partial \tau_2}N - X\frac{\partial N}{\partial \tau_2}}{N^2} - \beta\frac{\left(\frac{\partial X}{\partial \tau_2}Q + \frac{\partial Q}{\partial \tau_2}X\right)N - QX\frac{\partial N}{\partial \tau_2}}{N^2} \tag{57}$$
$$+ S + R_1 + (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \tau_2} + (\tau_2+\gamma)\frac{\partial R_1}{\partial \tau_2} + (\tau_1+\gamma)\frac{\partial R_2}{\partial \tau_2} + \gamma\frac{\partial R_{12}}{\partial \tau_2}$$

$$\frac{d}{dt}\frac{\partial S}{\partial \gamma} = -\mu\frac{\frac{\partial S}{\partial \gamma}N - \frac{\partial N}{\partial \gamma}S}{N^2} - (\tau_1+\tau_2)\frac{\partial S}{\partial \gamma} - S \tag{58}$$
$$+ \beta\frac{\left(\frac{\partial S}{\partial \gamma}X + \frac{\partial X}{\partial \gamma}S\right)N - SX\frac{\partial N}{\partial \gamma}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_1}{\partial \gamma} = -\mu\frac{\frac{\partial R_1}{\partial \gamma}N - \frac{\partial N}{\partial \gamma}R_1}{N^2} - \tau_2\frac{\partial R_1}{\partial \gamma} - \left(R_1 + \gamma\frac{\partial R_1}{\partial \gamma}\right) \tag{59}$$
$$+ \beta(1-c_1)\frac{\left(\frac{\partial R_1}{\partial \gamma}X + \frac{\partial X}{\partial \gamma}R_1\right)N - R_1X\frac{\partial N}{\partial \gamma}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_2}{\partial \gamma} = -\mu\frac{\frac{\partial R_2}{\partial \gamma}N - \frac{\partial N}{\partial \gamma}R_2}{N^2} - \tau_1\frac{\partial R_2}{\partial \gamma} - \left(R_2 + \gamma\frac{\partial R_2}{\partial \gamma}\right) \tag{60}$$
$$+ \beta(1-c_2)\frac{\left(\frac{\partial R_2}{\partial \gamma}X + \frac{\partial X}{\partial \gamma}R_2\right)N - R_2X\frac{\partial N}{\partial \gamma}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_{12}}{\partial \gamma} = -\mu\frac{\frac{\partial R_{12}}{\partial \gamma}N - \frac{\partial N}{\partial \gamma}R_{12}}{N^2} - \left(R_{12} + \gamma\frac{\partial R_{12}}{\partial \gamma}\right) \tag{61}$$
$$+ \beta(1-c_{12})\frac{\left(\frac{\partial R_{12}}{\partial \gamma}X + \frac{\partial X}{\partial \gamma}R_{12}\right)N - R_{12}X\frac{\partial N}{\partial \gamma}}{N^2}$$

$$\frac{d}{dt}\frac{\partial X}{\partial \gamma} = -\mu\frac{\frac{\partial X}{\partial \gamma}N - \frac{\partial N}{\partial \gamma}X}{N^2} - \beta\frac{\left(\frac{\partial X}{\partial \gamma}Q + \frac{\partial Q}{\partial \gamma}X\right)N - QX\frac{\partial N}{\partial \gamma}}{N^2} \tag{62}$$
$$+ S + R_1 + R_2 + R_{12} + (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \gamma} + (\tau_2+\gamma)\frac{\partial R_1}{\partial \gamma}$$
$$+ (\tau_1+\gamma)\frac{\partial R_2}{\partial \gamma} + \gamma\frac{\partial R_{12}}{\partial \gamma}$$

$$\frac{d}{dt}\frac{\partial S}{\partial m_s} = \lambda - \mu\frac{\frac{\partial S}{\partial m_s}N - \frac{\partial N}{\partial m_s}S}{N^2} - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_s}$$
$$+ \beta\frac{\left(\frac{\partial S}{\partial m_s}X + \frac{\partial X}{\partial m_s}S\right)N - SX\frac{\partial N}{\partial m_s}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_1}{\partial m_s} = -\mu\frac{\frac{\partial R_1}{\partial m_s}N - \frac{\partial N}{\partial m_s}R_1}{N^2} - (\tau_2+\gamma)\frac{\partial R_1}{\partial m_s} \tag{63}$$
$$+ \beta(1-c_1)\frac{\left(\frac{\partial R_1}{\partial m_s}X + \frac{\partial X}{\partial m_s}R_1\right)N - R_1X\frac{\partial N}{\partial m_s}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_2}{\partial m_s} = -\mu\frac{\frac{\partial R_2}{\partial m_s}N - \frac{\partial N}{\partial m_s}R_2}{N^2} - (\tau_1+\gamma)\frac{\partial R_2}{\partial m_s} \tag{64}$$
$$+ \beta(1-c_2)\frac{\left(\frac{\partial R_2}{\partial m_s}X + \frac{\partial X}{\partial m_s}R_2\right)N - R_2X\frac{\partial N}{\partial m_s}}{N^2}$$

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$$\frac{d}{dt}\frac{\partial R_{12}}{\partial m_s} = -\mu\frac{\frac{\partial R_{12}}{\partial m_s}N - \frac{\partial N}{\partial m_s}R_{12}}{N^2} - \gamma\frac{\partial R_{12}}{\partial m_s} \tag{66}$$
$$+ \beta(1-c_{12})\frac{\left(\frac{\partial R_{12}}{\partial m_s}X + \frac{\partial X}{\partial m_s}R_{12}\right)N - R_{12}X\frac{\partial N}{\partial m_s}}{N^2}$$

$$\frac{d}{dt}\frac{\partial X}{\partial m_s} = -\mu\frac{\frac{\partial X}{\partial m_s}N - \frac{\partial N}{\partial m_s}X}{N^2} - \beta\frac{\left(\frac{\partial X}{\partial m_s}Q + \frac{\partial Q}{\partial m_s}X\right)N - QX\frac{\partial N}{\partial m_s}}{N^2} \tag{67}$$
$$+ (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_s} + (\tau_2+\gamma)\frac{\partial R_1}{\partial m_s} + (\tau_1+\gamma)\frac{\partial R_2}{\partial m_s} + \gamma\frac{\partial R_{12}}{\partial m_s}$$

$$\frac{d}{dt}\frac{\partial S}{\partial m_1} = -\mu\frac{\frac{\partial S}{\partial m_1}N - \frac{\partial N}{\partial m_1}S}{N^2} - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_1}$$
$$+ \beta\frac{\left(\frac{\partial S}{\partial m_1}X + \frac{\partial X}{\partial m_1}S\right)N - SX\frac{\partial N}{\partial m_1}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_1}{\partial m_1} = \lambda - \mu\frac{\frac{\partial R_1}{\partial m_1}N - \frac{\partial N}{\partial m_1}R_1}{N^2} - (\tau_2+\gamma)\frac{\partial R_1}{\partial m_1} \tag{68}$$
$$+ \beta(1-c_1)\frac{\left(\frac{\partial R_1}{\partial m_1}X + \frac{\partial X}{\partial m_1}R_1\right)N - R_1X\frac{\partial N}{\partial m_1}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_2}{\partial m_1} = -\mu\frac{\frac{\partial R_2}{\partial m_1}N - \frac{\partial N}{\partial m_1}R_2}{N^2} - (\tau_1+\gamma)\frac{\partial R_2}{\partial m_1} \tag{69}$$
$$+ \beta(1-c_2)\frac{\left(\frac{\partial R_2}{\partial m_1}X + \frac{\partial X}{\partial m_1}R_2\right)N - R_2X\frac{\partial N}{\partial m_1}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_{12}}{\partial m_1} = -\mu\frac{\frac{\partial R_{12}}{\partial m_1}N - \frac{\partial N}{\partial m_1}R_{12}}{N^2} - \gamma\frac{\partial R_{12}}{\partial m_1} \tag{70}$$
$$+ \beta(1-c_{12})\frac{\left(\frac{\partial R_{12}}{\partial m_1}X + \frac{\partial X}{\partial m_1}R_{12}\right)N - R_{12}X\frac{\partial N}{\partial m_1}}{N^2}$$

$$\frac{d}{dt}\frac{\partial X}{\partial m_1} = -\mu\frac{\frac{\partial X}{\partial m_1}N - \frac{\partial N}{\partial m_1}X}{N^2} - \beta\frac{\left(\frac{\partial X}{\partial m_1}Q + \frac{\partial Q}{\partial m_1}X\right)N - QX\frac{\partial N}{\partial m_1}}{N^2} \tag{71}$$
$$+ (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_1} + (\tau_2+\gamma)\frac{\partial R_1}{\partial m_1} + (\tau_1+\gamma)\frac{\partial R_2}{\partial m_1} + \gamma\frac{\partial R_{12}}{\partial m_1}$$

$$\frac{d}{dt}\frac{\partial S}{\partial m_2} = -\mu\frac{\frac{\partial S}{\partial m_2}N - \frac{\partial N}{\partial m_2}S}{N^2} - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_2}$$
$$+ \beta\frac{\left(\frac{\partial S}{\partial m_2}X + \frac{\partial X}{\partial m_2}S\right)N - SX\frac{\partial N}{\partial m_2}}{N^2}$$

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$$\frac{d}{dt}\frac{\partial R_1}{\partial m_2} = -\mu\frac{\frac{\partial R_1}{\partial m_2}N - \frac{\partial N}{\partial m_2}R_1}{N^2} - (\tau_2+\gamma)\frac{\partial R_1}{\partial m_2} + \beta(1-c_1)\frac{\left(\frac{\partial R_1}{\partial m_2}X + \frac{\partial X}{\partial m_2}R_1\right)N - R_1X\frac{\partial N}{\partial m_2}}{N^2} \tag{73}$$

$$\frac{d}{dt}\frac{\partial R_2}{\partial m_2} = \lambda - \mu\frac{\frac{\partial R_2}{\partial m_2}N - \frac{\partial N}{\partial m_2}R_2}{N^2} - (\tau_1+\gamma)\frac{\partial R_2}{\partial m_2} + \beta(1-c_2)\frac{\left(\frac{\partial R_2}{\partial m_2}X + \frac{\partial X}{\partial m_2}R_2\right)N - R_2X\frac{\partial N}{\partial m_2}}{N^2} \tag{74}$$

$$\frac{d}{dt}\frac{\partial R_{12}}{\partial m_2} = -\mu\frac{\frac{\partial R_{12}}{\partial m_2}N - \frac{\partial N}{\partial m_2}R_{12}}{N^2} - \gamma\frac{\partial R_{12}}{\partial m_2} + \beta(1-c_{12})\frac{\left(\frac{\partial R_{12}}{\partial m_2}X + \frac{\partial X}{\partial m_2}R_{12}\right)N - R_{12}X\frac{\partial N}{\partial m_2}}{N^2} \tag{75}$$

$$\frac{d}{dt}\frac{\partial X}{\partial m_2} = -\mu\frac{\frac{\partial X}{\partial m_2}N - \frac{\partial N}{\partial m_2}X}{N^2} - \beta\frac{\left(\frac{\partial X}{\partial m_2}Q + \frac{\partial Q}{\partial m_2}X\right)N - QX\frac{\partial N}{\partial m_2}}{N^2} + (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_2} + (\tau_2+\gamma)\frac{\partial R_1}{\partial m_2} + (\tau_1+\gamma)\frac{\partial R_2}{\partial m_2} + \gamma\frac{\partial R_{12}}{\partial m_2} \tag{76}$$

$$\frac{d}{dt}\frac{\partial S}{\partial m_{12}} = -\mu\frac{\frac{\partial S}{\partial m_{12}}N - \frac{\partial N}{\partial m_{12}}S}{N^2} - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_{12}} + \beta\frac{\left(\frac{\partial S}{\partial m_{12}}X + \frac{\partial X}{\partial m_{12}}S\right)N - SX\frac{\partial N}{\partial m_{12}}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_1}{\partial m_{12}} = -\mu\frac{\frac{\partial R_1}{\partial m_{12}}N - \frac{\partial N}{\partial m_{12}}R_1}{N^2} - (\tau_2+\gamma)\frac{\partial R_1}{\partial m_{12}} + \beta(1-c_1)\frac{\left(\frac{\partial R_1}{\partial m_{12}}X + \frac{\partial X}{\partial m_{12}}R_1\right)N - R_1X\frac{\partial N}{\partial m_{12}}}{N^2} \tag{77}$$

$$\frac{d}{dt}\frac{\partial R_2}{\partial m_{12}} = -\mu\frac{\frac{\partial R_2}{\partial m_{12}}N - \frac{\partial N}{\partial m_{12}}R_2}{N^2} - (\tau_1+\gamma)\frac{\partial R_2}{\partial m_{12}} + \beta(1-c_2)\frac{\left(\frac{\partial R_2}{\partial m_{12}}X + \frac{\partial X}{\partial m_{12}}R_2\right)N - R_2X\frac{\partial N}{\partial m_{12}}}{N^2} \tag{78}$$

$$\frac{d}{dt}\frac{\partial R_{12}}{\partial m_{12}} = \lambda - \mu\frac{\frac{\partial R_{12}}{\partial m_{12}}N - \frac{\partial N}{\partial m_{12}}R_{12}}{N^2} - \gamma\frac{\partial R_{12}}{\partial m_{12}} + \beta(1-c_{12})\frac{\left(\frac{\partial R_{12}}{\partial m_{12}}X + \frac{\partial X}{\partial m_{12}}R_{12}\right)N - R_{12}X\frac{\partial N}{\partial m_{12}}}{N^2} \tag{79}$$

$$\tag{80}$$

$$\frac{d}{dt}\frac{\partial X}{\partial m_{12}} = -\mu\frac{\frac{\partial X}{\partial m_{12}}N - \frac{\partial N}{\partial m_{12}}X}{N^2} - \beta\frac{\left(\frac{\partial X}{\partial m_{12}}Q + \frac{\partial Q}{\partial m_{12}}X\right)N - QX\frac{\partial N}{\partial m_{12}}}{N^2} \tag{81}$$
$$+ (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_{12}} + (\tau_2+\gamma)\frac{\partial R_1}{\partial m_{12}} + (\tau_1+\gamma)\frac{\partial R_2}{\partial m_{12}} + \gamma\frac{\partial R_{12}}{\partial m_{12}}$$
$$\frac{d}{dt}\frac{\partial S}{\partial m_x} = -\mu\frac{\frac{\partial S}{\partial m_x}N - \frac{\partial N}{\partial m_x}S}{N^2} - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_x}$$
$$+ \beta\frac{\left(\frac{\partial S}{\partial m_x}X + \frac{\partial X}{\partial m_x}S\right)N - SX\frac{\partial N}{\partial m_x}}{N^2}$$
$$\frac{d}{dt}\frac{\partial R_1}{\partial m_x} = -\mu\frac{\frac{\partial R_1}{\partial m_x}N - \frac{\partial N}{\partial m_x}R_1}{N^2} - (\tau_2+\gamma)\frac{\partial R_1}{\partial m_x} \tag{82}$$
$$+ \beta(1-c_1)\frac{\left(\frac{\partial R_1}{\partial m_x}X + \frac{\partial X}{\partial m_x}R_1\right)N - R_1X\frac{\partial N}{\partial m_x}}{N^2}$$
$$\frac{d}{dt}\frac{\partial R_2}{\partial m_x} = -\mu\frac{\frac{\partial R_2}{\partial m_x}N - \frac{\partial N}{\partial m_x}R_2}{N^2} - (\tau_1+\gamma)\frac{\partial R_2}{\partial m_x} \tag{83}$$
$$+ \beta(1-c_2)\frac{\left(\frac{\partial R_2}{\partial m_x}X + \frac{\partial X}{\partial m_x}R_2\right)N - R_2X\frac{\partial N}{\partial m_x}}{N^2}$$
$$\frac{d}{dt}\frac{\partial R_{12}}{\partial m_x} = -\mu\frac{\frac{\partial R_{12}}{\partial m_x}N - \frac{\partial N}{\partial m_x}R_{12}}{N^2} - \gamma\frac{\partial R_{12}}{\partial m_x} \tag{84}$$
$$+ \beta(1-c_{12})\frac{\left(\frac{\partial R_{12}}{\partial m_x}X + \frac{\partial X}{\partial m_x}R_{12}\right)N - R_{12}X\frac{\partial N}{\partial m_x}}{N^2}$$
$$\frac{d}{dt}\frac{\partial X}{\partial m_x} = \lambda - \mu\frac{\frac{\partial X}{\partial m_x}N - \frac{\partial N}{\partial m_x}X}{N^2} - \beta\frac{\left(\frac{\partial X}{\partial m_x}Q + \frac{\partial Q}{\partial m_x}X\right)N - QX\frac{\partial N}{\partial m_x}}{N^2} \tag{85}$$
$$+ (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial m_x} + (\tau_2+\gamma)\frac{\partial R_1}{\partial m_x} + (\tau_1+\gamma)\frac{\partial R_2}{\partial m_x} + \gamma\frac{\partial R_{12}}{\partial m_x}$$
$$\frac{d}{dt}\frac{\partial S}{\partial \lambda} = m_s - \mu\frac{\frac{\partial S}{\partial \lambda}N - \frac{\partial N}{\partial \lambda}S}{N^2} - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \lambda}$$
$$+ \beta\frac{\left(\frac{\partial S}{\partial \lambda}X + \frac{\partial X}{\partial \lambda}S\right)N - SX\frac{\partial N}{\partial \lambda}}{N^2}$$
$$\frac{d}{dt}\frac{\partial R_1}{\partial \lambda} = m_1 - \mu\frac{\frac{\partial R_1}{\partial \lambda}N - \frac{\partial N}{\partial \lambda}R_1}{N^2} - (\tau_2+\gamma)\frac{\partial R_1}{\partial \lambda} \tag{86}$$
$$+ \beta(1-c_1)\frac{\left(\frac{\partial R_1}{\partial \lambda}X + \frac{\partial X}{\partial \lambda}R_1\right)N - R_1X\frac{\partial N}{\partial \lambda}}{N^2}$$

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$$\frac{d}{dt}\frac{\partial R_2}{\partial \lambda} = m_2 - \mu\frac{\frac{\partial R_2}{\partial \lambda}N - \frac{\partial N}{\partial \lambda}R_2}{N^2} - (\tau_1+\gamma)\frac{\partial R_2}{\partial \lambda} \tag{88}$$
$$+ \beta(1-c_2)\frac{\left(\frac{\partial R_2}{\partial \lambda}X + \frac{\partial X}{\partial \lambda}R_2\right)N - R_2 X\frac{\partial N}{\partial \lambda}}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_{12}}{\partial \lambda} = m_{12} - \mu\frac{\frac{\partial R_{12}}{\partial \lambda}N - \frac{\partial N}{\partial \lambda}R_{12}}{N^2} - \gamma\frac{\partial R_{12}}{\partial \lambda} \tag{89}$$
$$+ \beta(1-c_{12})\frac{\left(\frac{\partial R_{12}}{\partial \lambda}X + \frac{\partial X}{\partial \lambda}R_{12}\right)N - R_{12} X\frac{\partial N}{\partial \lambda}}{N^2}$$

$$\frac{d}{dt}\frac{\partial X}{\partial \lambda} = m_x - \mu\frac{\frac{\partial X}{\partial \lambda}N - \frac{\partial N}{\partial \lambda}X}{N^2} - \beta\frac{\left(\frac{\partial X}{\partial \lambda}Q + \frac{\partial Q}{\partial \lambda}X\right)N - QX\frac{\partial N}{\partial \lambda}}{N^2} \tag{90}$$
$$+ (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \lambda} + (\tau_2+\gamma)\frac{\partial R_1}{\partial \lambda} + (\tau_1+\gamma)\frac{\partial R_2}{\partial \lambda} + \gamma\frac{\partial R_{12}}{\partial \lambda}$$

$$\frac{d}{dt}\frac{\partial S}{\partial \mu} = -\left(\frac{S}{N} + \mu\frac{\frac{\partial S}{\partial \mu}N - \frac{\partial N}{\partial \mu}S}{N^2}\right) - (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \mu}$$
$$+ \beta\frac{\left(\frac{\partial S}{\partial \mu}X + \frac{\partial X}{\partial \mu}S\right)N - \frac{\partial N}{\partial \mu}SX}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_1}{\partial \mu} = -\frac{R_1}{N} - \mu\frac{\frac{\partial R_1}{\partial \mu}N - \frac{\partial N}{\partial \mu}R_1}{N^2} - (\tau_2+\gamma)\frac{\partial R_1}{\partial \mu} \tag{91}$$
$$+ \beta(1-c_1)\frac{\left(\frac{\partial R_1}{\partial \mu}X + \frac{\partial X}{\partial \mu}R_1\right)N - \frac{\partial N}{\partial \mu}R_1 X}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_2}{\partial \mu} = -\frac{R_2}{N} - \mu\frac{\frac{\partial R_2}{\partial \mu}N - \frac{\partial N}{\partial \mu}R_2}{N^2} - (\tau_1+\gamma)\frac{\partial R_2}{\partial \mu} \tag{92}$$
$$+ \beta(1-c_2)\frac{\left(\frac{\partial R_2}{\partial \mu}X + \frac{\partial X}{\partial \mu}R_2\right)N - \frac{\partial N}{\partial \mu}R_2 X}{N^2}$$

$$\frac{d}{dt}\frac{\partial R_{12}}{\partial \mu} = -\frac{R_{12}}{N} - \mu\frac{\frac{\partial R_{12}}{\partial \mu}N - \frac{\partial N}{\partial \mu}R_{12}}{N^2} - \gamma\frac{\partial R_{12}}{\partial \mu} \tag{93}$$
$$+ \beta(1-c_{12})\frac{\left(\frac{\partial R_{12}}{\partial \mu}X + \frac{\partial X}{\partial \mu}R_{12}\right)N - \frac{\partial N}{\partial \mu}R_{12} X}{N^2}$$

$$\frac{d}{dt}\frac{\partial X}{\partial \mu} = -\frac{X}{N} - \mu\frac{\frac{\partial X}{\partial \mu}N - \frac{\partial N}{\partial \mu}X}{N^2} - \beta\frac{\left(\frac{\partial X}{\partial \mu}Q + \frac{\partial Q}{\partial \mu}X\right)N - \frac{\partial N}{\partial \mu}QX}{N^2} \tag{94}$$
$$+ (\tau_1+\tau_2+\gamma)\frac{\partial S}{\partial \mu} + (\tau_2+\gamma)\frac{\partial R_1}{\partial \mu}(\tau_1+\gamma)\frac{\partial R_2}{\partial \mu} + \gamma\frac{\partial R_{12}}{\partial \mu}$$

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