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MODELING THE EFFECTS OF INTRODUCING A NEW ANTIBIOTIC IN A HOSPITAL SETTING: A CASE STUDY

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Abstract. The increase in antibiotic resistance continues to pose a public health risk as very few new antibiotics are being produced, and bacteria resistant to currently prescribed antibiotics is growing. Within a typical hospital setting, one may find patients colonized with bacteria resistant to a single antibiotic, or, of a more emergent threat, patients may be colonized with bacteria resistant to multiple antibiotics. Precautions have been implemented to try to prevent the growth and spread of antimicrobial resistance such as a reduction in the distribution of antibiotics and increased hand washing and barrier preventions; however, the rise of this resistance is still evident. As a result, there is a new movement to try to re-examine the need for the development of new antibiotics. In this paper, we use mathematical models to study the possible benefits of implementing a new antibiotic in this setting; through these models, we examine the use of a new antibiotic that is distributed in various ways and how this could reduce total resistance in the hospital. We compare several different models in which patients colonized with both single and dual-resistant bacteria are present, including a model with no additional treatment protocols for the population colonized with dual-resistant bacteria as well as models including isolation and/or treatment with a new antibiotic. We examine the benefits and limitations of each scenario in the simulations presented.

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1. **Introduction.** Antibiotic resistance is a growing threat to public health as very few new antibiotics are being produced leading to the growth of bacteria resistant to the commonly prescribed antibiotics. Some of the risk factors which have been found to contribute to the development of antibiotic resistance include, but are not limited to, excessive use of antibiotics, antibiotic use in agricultural industries, lack of use of effective preventative infection control measures (such as hand washing), usage restriction of antibiotics, proper isolation of patients with resistant infections, and longer survival of severely ill patients as well as longer life expectancy in the elderly with increased use of antibiotics in both of these situations ([2] and the references therein). Much work has already been done to try to better understand the mechanisms which lead bacteria to form defenses against antibiotics [3, 4, 7, 10, 15, 21, 22, 23, 31] and how these resistant bacteria are transmitted from one individual to another [5, 12, 13, 14, 16, 18, 20, 25, 26, 27, 28, 33, 35]. Some of the latter references rely on mathematical models to try to quantify the effects of various protocols on the transmission of resistant bacteria. In the paper by Bergstrom et al., [5], the authors developed a mathematical model to explore the efficacy of the cycling program within a hospital setting in which they incorporated single resistance to two different antibiotics. Within the scope of the model, it was determined that the cycling of antibiotics, i.e., when one antibiotic is used for a specified period of time and then switched to another antibiotic or class of antibiotics for a specified period of time, was not effective in reducing the overall resistance. In fact, they determined that heterogeneous mixing of antibiotics was more useful in reducing the overall antibiotic resistance in a hospital than any cycling protocol. In case studies related to the cycling of antibiotics [1, 9, 19, 24, 32, 34], the results have been mixed. In some cases, the conclusion was the same as in [5]; cycling did not reduce the overall resistance, and, in some cases, cycling of antibiotics may actually increase the total antibiotic resistance within the hospital [19]. In other cases, there was a limited decrease in the average antibiotic resistance when using a cycling protocol [24, 34]. In most all cases, once the antibiotic was eliminated, there was a decline in resistance to that antibiotic followed by a rapid increase in resistance once the antibiotic was reintroduced [9]. In many of these studies, resistance to a single antibiotic was tracked. However, in the case study by van Loon et al., [19], they noted that multi-drug resistance was also prevalent.

As a response to the existence of multi-drug resistant bacteria, Chow et al., [25], developed a mathematical model to try to quantify the relationship between both single and dual resistant bacteria and the spread of this resistance in a hospital setting. Their findings indicated that although a mixing protocol was best to reduce single resistance (as discussed in [5]), a cycling protocol actually resulted in a lower percentage of patients colonized with dual resistant bacteria. In either case, the total proportion of patients colonized with resistant bacteria in the hospital remained at a relatively high level of over 60% using either protocol. In addition, they noted that there was an inverse relationship between single resistant bacteria and dual resistant bacteria. As the proportion of patients colonized with single resistance decreased, the proportion of patients with dual resistance increased and vice versa. Therefore, a treatment protocol which proved to be beneficial for one group of colonized patients was unfavorable for the other group of colonized patients. In general, Chow demonstrated that isolating a portion of the patients carrying the dual resistant bacteria proved to be most effective in reducing not only the proportion of patients with dual resistance but the overall resistance in the hospital as well.

However, if one includes those patients who are isolated (and still colonized with the dual resistant strain) when calculating the total proportion of patients within the hospital colonized with some kind of resistant bacteria, the overall proportion of patients with resistant bacteria is still quite large. Hence, there is a need to examine other alternatives to reducing the number of patients carrying a resistant bacteria. One such alternative is a renewed push for the development of new antibiotics.

In this article, we seek to quantify the effects of introducing a new antibiotic on the overall resistance in a hospital. The paper will be organized as follows. In Section 2, we will introduce four mathematical models which we will use to evaluate the effectiveness of the introduction of a new antibiotic and the best implementation of the new antibiotic. In Section 3, we will discuss the sensitivity analysis for each of these four models, examining the sensitivity of the model results on the chosen parameter values. In Section 4, we will compare the results from each of the models and discuss the findings. We will conclude with some final remarks in Section 5.

2. **Model formulation.**

In this paper, we discuss four different mathematical models. Two of these models, the Base Model and the Isolation Model, are examined as comparison models. To formulate these models, we modified the mathematical models developed by Chow et al. [25]. The remaining two models, the Random Drug Model and the Targeted Drug Model, are similar models which focus on two different approaches to introducing a new drug into the hospital. We focus on the introduction of an entirely new antibiotic as opposed to simply an upgrade of an antibiotic within the same class as the drugs already employed in the hospital. Due to the chromosomal mutations or acquisition of new genetic material leading to the development of resistant bacteria, if a new antibiotic is introduced which is an upgrade of a current antibiotic, the use of the new antibiotic on patients already colonized with bacteria resistant to the older antibiotic could lead to a new high-level resistant strain [11, 35]. For this reason, we will only consider the case in which the new antibiotic is not an upgrade of an older, more commonly prescribed antibiotic. In considering a new antibiotic with a different mechanism of action than the two drugs in our system, we can assume resistance to the new antibiotic is initially negligible as the rate of mutation is on the order of 10^{-6} [22]. As a result, resistance to a new antibiotic will require a longer period of time to develop.

2.1. **The base model.**

The first model we will introduce is a slightly modified version of the model found in the paper by Chow et al., [25]. We will call this model the Base Model. In this model, we assume there are two antibiotics, which, without loss of generality, we will call drugs 1 and 2 respectively. We consider a compartmental model whose schematic is given in Figure 1 in which patients within a hospital are classified based upon their colonization with respect to these two drugs. Patients may either be colonized with bacteria sensitive to both drugs, S; colonized with bacteria resistant to a single drug, R_1 or R_2; colonized with bacteria resistant to both drugs, R_{12}; or uncolonized, X. Patients colonized with bacteria sensitive to both drugs 1 and 2, S, can be effectively treated with either antibiotic and be cleared. Patients colonized with bacteria resistant to drug 1, R_1, may be successfully treated with drug 2. Similarly, patients colonized with bacteria resistant to drug 2, R_2, can be effectively treated with drug 1. In the Base Model, we assume there is no effective antibiotic which can be utilized to treat the patients colonized with the dual resistant bacteria nor is there a procedure in place, such as isolation, to limit the spread of the dual resistant strain. A description of the

variables and parameters used in our model are given in Tables 1 and 2, where each of the variables are dimensionless as they are proportions of patients in the hospital.

We make various assumptions with this model. First of all, the population size within the hospital is assumed to be sufficiently large to be able to use differential equations to describe our system, and it is assumed that the population within the hospital remains constant, i.e., the total rate of admission is equal to the total rate of discharge. Furthermore, patients can enter the hospital in any of the states. A proportion m_S enter colonized with bacteria sensitive to both drugs, a proportion m_i enter the hospital colonized with bacteria resistant to one of the two drugs, a proportion m_{12} enter colonized with bacteria resistant to both drugs, and the remainder of patients admitted are uncolonized, $m_X = 1 - (m_S + m_1 + m_2 + m_{12})$. Patients stay an average of $\frac{1}{\mu}$ days in the hospital, where μ is the turnover rate in the hospital. While in the hospital, a proportion of the total population will be treated with antibiotics. We assume τ_i is the per capita treatment rate of drug i, and therefore, the total proportion of the hospital being treated with antibiotics per day is $T = \tau_1 + \tau_2$. Furthermore, it is assumed that drugs are prescribed without prior knowledge of the type of bacteria present at the time of the initial prescription as it is not yet common practice to test for resistant bacteria upon entering the hospital. Patients are more likely to be tested for resistant bacteria after one or possibly two drugs have failed to clear the infection. Therefore, it is possible for patients resistant to drug 1, for instance, to be prescribed drug 1; however, these patients will not be cleared until drug 2 is utilized or the patient's immune response causes clearance of the bacteria. It is assumed that without treatment, a patient's immune response will require $\frac{1}{\gamma}$ days to clear the bacteria.

Bacteria are always assumed to be in competition with one another, and, therefore, patients can only be colonized by one bacterial strain at a time. We further assume each patient is equally likely to come in contact with a healthcare worker and, only offset by the ability of the bacterial strain to spread, equally likely to become colonized with one of the strains of bacteria or transmit the bacteria if already colonized upon contact. Patients make β of these effective contacts per unit time. This effective contact rate or transmission rate is offset by fitness costs c_i for the single resistant strains and c_{12} for the dual resistant bacteria. Fitness cost is a parameter which describes the rate at which resistant bacteria revert back to being susceptible in the absence of antibiotic treatment. Resistant bacteria thrive in the presence of antibiotics; however, in an antibiotic-free environment, the resistant bacteria are at a disadvantage and less able to reproduce, thus providing an advantage to the susceptible bacteria. When the fitness cost is high, the ability to reproduce is much lower and thus more difficult to spread. On the other hand, the lower the fitness cost of the resistant bacteria, the easier it is for the bacteria to spread. In this paper, we assume, as Chow did, [25], that the dual resistant strain is harder to spread and, therefore, has a higher fitness cost than the single resistant bacteria. Therefore, in the competition between the dual resistant strain and either the single resistant strain or the sensitive bacteria, the dual resistant strain always loses. This competition between resistant strains is taken into account by the difference in fitness costs. In addition, the ability of one strain to take over another strain is referred to as secondary colonization and is accounted for in the term σ.

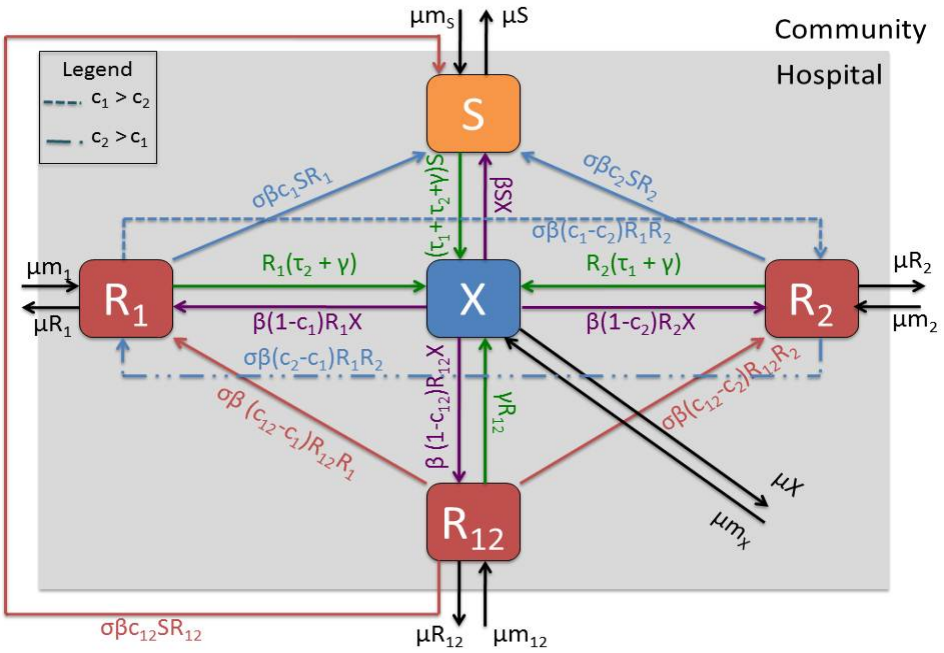

FIGURE 1. Schematic of the Base Model

The equations describing the system are given as

$$\begin{aligned}
\frac{dS}{dt} &= (m_S - S)\mu - (\tau_1+\tau_2+\gamma)S + \beta XS + \beta\sigma(c_1R_1 + c_2R_2 + c_{12}R_{12})S \\
\frac{dR_1}{dt} &= (m_1 - R_1)\mu - (\tau_2+\gamma)R_1 + \beta(1-c_1)XR_1 \\
&\quad +\beta\sigma[(c_{12}-c_1)R_{12} + (c_2-c_1)R_2 - c_1S]R_1 \\
\frac{dR_2}{dt} &= (m_2 - R_2)\mu - (\tau_1+\gamma)R_2 + \beta(1-c_2)XR_2 \\
&\quad +\beta\sigma[(c_{12}-c_2)R_{12} + (c_1-c_2)R_1 - c_2S]R_2 \\
\frac{dR_{12}}{dt} &= (m_{12} - R_{12})\mu - \gamma R_{12} + \beta(1-c_{12})XR_{12} \\
&\quad -\beta\sigma[c_{12}S + (c_{12}-c_1)R_1 + (c_{12}-c_2)R_2]R_{12} \\
\frac{dX}{dt} &= (m_X - X)\mu + (\tau_1+\tau_2+\gamma)S + (\tau_2+\gamma)R_1 + (\tau_1+\gamma)R_2 + \gamma R_{12} \\
&\quad -\beta[S + (1-c_1)R_1 + (1-c_2)R_2 + (1-c_{12})R_{12}]X
\end{aligned}$$

2.2. **The isolation model.** The Isolation Model is very similar to the Base Model with the addition of a new class of patients, Q, who are colonized with the dual resistant bacteria but now in isolation; see Figure 2. It is estimated that dual resistant patients are identified and isolated at a rate η. The effectiveness of the isolation is accounted for in the parameter ϵ where $\epsilon = 1$ signifies completely effective isolation with no contact between isolated patients and the remainder of hospital

TABLE 1. The Definition of Model Variables

Variables	Description
S	Proportion of patients colonized with bacteria sensitive to both drugs
R_i	Proportion of patients colonized with bacteria resistant to drug i, $i = 1, 2$
R_{12}	Proportion of patients colonized with bacteria resistant to both drugs
X	Proportion of patients uncolonized

TABLE 2. The Definition of Parameters

Parameters	Description	Units
β	Per capita primary transmission rate (colonization rate)	1/day
σ	Relative rate of secondary colonization to that of primary colonization	Dimensionless
c_i	Fitness cost of bacteria resistant to drug i, $i = 1, 2$	Dimensionless
c_{12}	Fitness cost of bacteria resistant to both drugs	Dimensionless
τ_i	Per capita treatment rate of drug i, $i = 1, 2$	1/day
γ	Per capita clearance rate of bacteria due to immune response	1/day
μ	Per capita patient turnover rate in hospital	1/day
m_S	Proportion of admitted patients colonized with sensitive bacteria	Dimensionless
m_i	Proportion of admitted patients colonized with bacteria resistant to drug i, $i = 1, 2$	Dimensionless
m_{12}	Proportion of admitted patients colonized with bacteria resistant to both drugs	Dimensionless

population and $\epsilon = 0$ signifies completely ineffective isolation. In actuality, ϵ most likely lies somewhere between these extreme values.

In the Base Model, the entire hospital is what we will refer to as the active proportion of the population, A, or the proportion of the population subject to colonization or transmission, as we assumed in that model that each patient was equally likely to become colonized with one of the strains of bacteria or transmit the bacteria if already colonized upon contact. In the Isolation Model, the active population is the entire hospital except those which are effectively isolated. If isolation is totally effective, the active proportion of the population is given by $1 - Q$; however, ineffective isolation leads to effective contact between isolated individuals and the rest of the hospital population. Thus, the active proportion of the population is given as $A = 1 - \epsilon Q$ which is equivalent to $A = 1 - Q$ when isolation is totally effective and $A = 1$ (the entire hospital) when isolation is totally ineffective. Depending on the parameter ϵ, the proportion of isolated patients who interact (typically through means of healthcare workers) with the rest of the hospital is given by $(1 - \epsilon)Q$. Modifying the base model, the system of differential equations

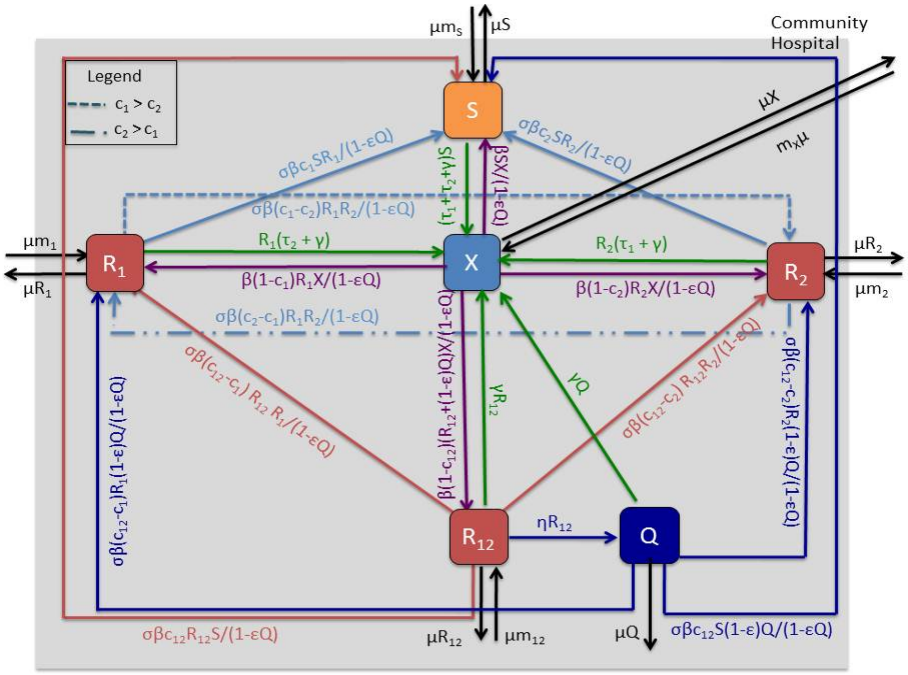

FIGURE 2. Schematic of the Isolation Model

describing the Isolation Model is given by

$$
\begin{aligned}
\frac{dS}{dt} &= (m_S - S)\mu - (\tau_1+\tau_2+\gamma)S + \frac{\beta}{A}XS \\
&\quad + \frac{\beta\sigma}{A}\left[c_1R_1 + c_2R_2 + c_{12}(R_{12} + (1-\epsilon)Q)\right]S \\
\frac{dR_1}{dt} &= (m_1 - R_1)\mu - (\tau_2+\gamma)R_1 + \frac{\beta}{A}(1-c_1)XR_1 \\
&\quad + \frac{\beta\sigma}{A}\left[(c_2-c_1)R_2 + (c_{12}-c_1)(R_{12}+(1-\epsilon)Q) - c_1S\right]R_1 \\
\frac{dR_2}{dt} &= (m_2 - R_2)\mu - (\tau_1+\gamma)R_2 + \frac{\beta}{A}(1-c_2)XR_2 \\
&\quad + \frac{\beta\sigma}{A}\left[(c_1-c_2)R_1 + (c_{12}-c_2)(R_{12}+(1-\epsilon)Q) - c_2S\right]R_2 \\
\frac{dR_{12}}{dt} &= (m_{12} - R_{12})\mu - \gamma R_{12} - \eta R_{12} + \frac{\beta}{A}(1-\epsilon)QX + \frac{\beta}{A}(1-c_{12})XR_{12} \\
&\quad - \frac{\beta\sigma}{A}\left[c_{12}S + (c_{12}-c_1)R_1 + (c_{12}-c_2)R_2\right]R_{12} \\
\frac{dQ}{dt} &= \eta R_{12} - \mu Q - \gamma Q - \frac{\sigma\beta}{A}\left[c_{12}S + (c_{12}-c_1)R_1 + (c_{12}-c_2)R_2\right](1-\epsilon)Q \\
\frac{dX}{dt} &= (m_X - X)\mu + (\tau_1+\tau_2+\gamma)S + (\tau_2+\gamma)R_1 + (\tau_1+\gamma)R_2 + \gamma(R_{12}+Q) \\
&\quad - \frac{\beta}{A}\left[S + (1-c_1)R_1 + (1-c_2)R_2 + (1-c_{12})(R_{12}+(1-\epsilon)Q)\right]X
\end{aligned}
$$

2.3. **The random drug model.** Both the Random Drug Model and the Targeted Drug Model involve the introduction of an entirely new antibiotic into the hospital, which we will refer to as drug 3. The two models differ in the targeted recipients of the new drug. In the Random Drug Model, it is assumed that physicians have no limitations on their ability to prescribe the new antibiotic and are as equally likely to choose drug 3 as they are to choose drug 1 or 2. Hence, in this model, we are assuming heterogeneous mixing of antibiotics 1, 2, and 3 at equal rates, $\tau_1 = \tau_2 = \tau_3$ where τ_3 is the per capita treatment rate of drug 3 per day. In comparing this model to the previous models, we assume the total proportion of the hospital being treated per day, T, remains the same as in the Base Model and Isolation Model. In both the Base Model and the Isolation Model, drugs 1 and 2 were assumed to be equally likely to be prescribed resulting in $T = \tau_1 + \tau_2$ with $\tau_1 = \tau_2 = \frac{T}{2}$. In the Random Drug Model, T remains fixed where now $T = \tau_1 + \tau_2 + \tau_3$ with $\tau_i = \frac{T}{3}$, for $i = 1, 2, 3$. Thus, the introduction of drug 3 inherently reduces the per capita treatment rate of both drugs 1 and 2 while keeping the total proportion of treated patients per day within the hospital the same. In this model, it is again assumed that there is no a priori knowledge of the type of bacteria, if any, within the patient. However, patients colonized with single resistance can now be cleared when prescribed two of the three possible drugs. For instance, patients colonized with bacteria resistant to drug 1, R_1, can be cleared using either drugs 2 or 3. Similarly, patients colonized with bacteria resistant to drug 2, R_2, can be cleared when prescribed drugs 1 or 3. Patients sensitive to all the drugs, S, will be cleared regardless of which drug they are prescribed. Nonetheless, there is still the possibility, as with the previous two models, that patients resistant to, for example, drug 1, will still be prescribed drug 1 and thus will not be cleared until prescribed either drug 2 or 3. However, in the Random Drug Model, a mechanism, beyond the patient's own immune system, exists to clear patients colonized with bacteria resistant to both drugs 1 and 2, namely the prescription of drug 3. The set of differential equations describing the Random Drug Model is given by the following equations.

$$\begin{aligned}
\frac{dS}{dt} &= (m_S - S)\mu - (\tau_1 + \tau_2 + \tau_3 + \gamma)S + \beta XS \\
&\quad + \beta\sigma(c_1R_1 + c_2R_2 + c_{12}R_{12})S \\
\frac{dR_1}{dt} &= (m_1 - R_1)\mu - (\tau_2 + \tau_3 + \gamma)R_1 + \beta(1 - c_1)XR_1 \\
&\quad + \beta\sigma[(c_{12} - c_1)R_{12} + (c_2 - c_1)R_2 - c_1S]R_1 \\
\frac{dR_2}{dt} &= (m_2 - R_2)\mu - (\tau_1 + \tau_3 + \gamma)R_2 + \beta(1 - c_2)XR_2 \\
&\quad + \beta\sigma[(c_{12} - c_2)R_{12} + (c_1 - c_2)R_1 - c_2S]R_2 \\
\frac{dR_{12}}{dt} &= (m_{12} - R_{12})\mu - (\tau_3 + \gamma)R_{12} + \beta(1 - c_{12})XR_{12} \\
&\quad - \beta\sigma[c_{12}S + (c_{12} - c_1)R_1 + (c_{12} - c_2)R_2]R_{12} \\
\frac{dX}{dt} &= (m_X - X)\mu + (\tau_1 + \tau_2 + \tau_3 + \gamma)S \\
&\quad + (\tau_2 + \tau_3 + \gamma)R_1 + (\tau_1 + \tau_3 + \gamma)R_2 + (\tau_3 + \gamma)R_{12} \\
&\quad - \beta[S + (1 - c_1)R_1 + (1 - c_2)R_2 + (1 - c_{12})R_{12}]X
\end{aligned}$$

2.4. **The targeted drug model.** In the Random Drug Model, it is assumed that the new drug is readily available to be prescribed to all patients. Conversely, the

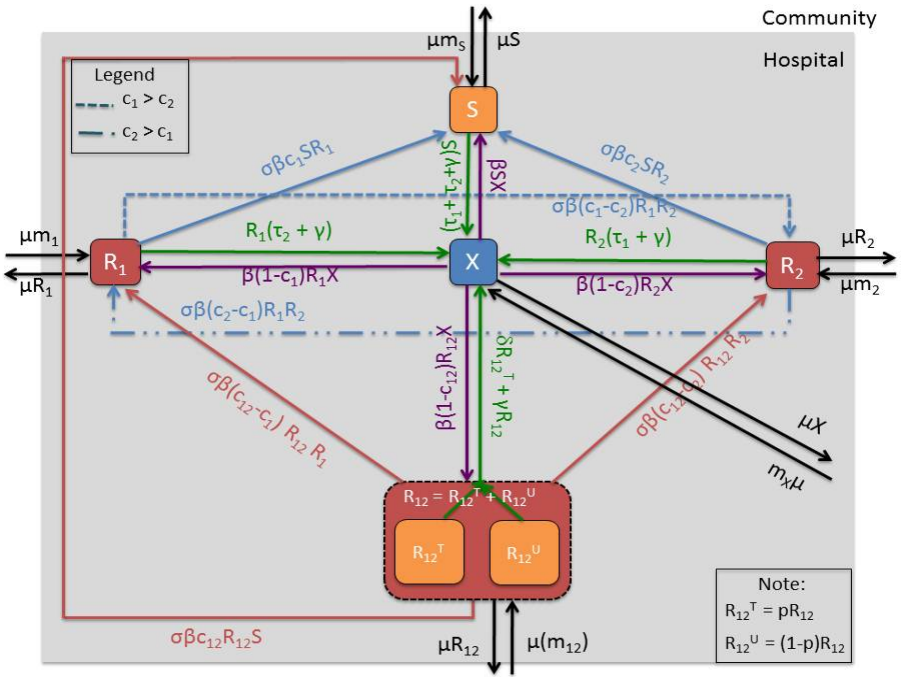

FIGURE 3. Schematic of the Targeted Drug Model

Targeted Drug Model only allows drug 3 to be prescribed to those patients known to be resistant to both drugs 1 and 2. As in the development of the Random Drug Model, the Targeted Drug Model still keeps the total proportion of patients treated per day, $T = \tau_1 + \tau_2 + \tau_3$, fixed in order to compare this model with the preceding three models. However, we no longer assume all three drugs are used at the same treatment rate $\tau_1 = \tau_2 = \tau_3$. As physicians still have drugs 1 and 2 readily available for treatment of the entire hospital population, it is assumed, as before, that physicians are no more likely to choose drug 1 over drug 2, so τ_1 is set equal to τ_2. However, τ_3 is now a function of time. It is assumed that some percentage p of patients colonized with dual resistance are identifiable, either by testing or failure of clearance by both drugs 1 and 2, and chosen for treatment (some of the identified population may not be treated for various reasons such as terminal illness, etc.). The only antibiotic available which can be used to successfully clear these patients is drug 3. As τ_3 is defined to be the per capita treatment rate of drug 3 or the portion of patients within the hospital treated with drug 3 per day, τ_3 is given by $\tau_3 = pR_{12}$ per day. For example, if 24% of the patients in the hospital are colonized with dual resistance bacteria on a given day and physicians in the hospital can identify and choose to treat 75% of these patients with drug 3, then $p = 0.75$ and the per capita treatment rate of drug 3 is given by $\tau_3 = pR_{12} = 0.75(0.24) = 0.18$ per day. On the other hand, if only 10% of these patients are identified and treated, then $\tau_3 = 0.10(0.24) = 0.024$ per day. Therefore, the chosen rate for τ_3 depends on the proportion of patients which can readily be identified and treated with the appropriate drug. However, since R_{12} is a function of time, τ_3 also changes across time. In the same scenario as above, if only 12% of the hospital is colonized with

dual resistant bacteria, and again 75% of these patients can be identified and treated with the appropriate drug, then the per capita treatment rate with drug 3 is now given by $\tau_3 = 0.75(0.12) = 0.09$ per day instead of 0.18 per day when 24% of the hospital was colonized with dual resistant bacteria. Therefore, the treatment rate is dependent on the total proportion of patients colonized with dual resistance in the hospital and the ability to identify a portion of those patients. As the proportion of patients in the hospital colonized with dual resistant bacteria increases, it is intuitive that the treatment rate with drug 3 (the drug of choice for patients colonized with dual resistance) should also increase; however, when only a small number of patients are colonized with dual resistance, it is natural for the treatment rate with drug 3 to be lower as only those colonized with dual resistance are treated with drug 3. As it is assumed that the total per capita treatment rate with all antibiotics, T, is fixed and the treatment rate with drug 3, τ_3, changes with time, then both τ_1 and τ_2 are functions of time given by $\tau_1 = \tau_2 = \frac{1}{2}(T - \tau_3)$. The schematic for this model is given in Figure 3 where the parameter $\delta = 1/\text{day}$ is introduced only to help distinguish between the proportion of patients colonized with dual resistance who are identified and treated, $R^T = pR_{12}$ (dimensionless quantity), and the actual treatment rate with drug 3, $\tau_3 = \delta p R_{12}$ (units 1/day). The corresponding equations are given by

$$\begin{aligned}
\frac{dS}{dt} &= (m_S - S)\mu - (\tau_1 + \tau_2 + \gamma)S + \beta XS + \beta\sigma(c_1R_1 + c_2R_2 + c_{12}R_{12})S \\
\frac{dR_1}{dt} &= (m_1 - R_1)\mu - (\tau_2 + \gamma)R_1 + \beta(1 - c_1)XR_1 \\
&\quad + \beta\sigma[(c_{12} - c_1)R_{12} + (c_2 - c_1)R_2 - c_1S]R_1 \\
\frac{dR_2}{dt} &= (m_2 - R_2)\mu - (\tau_1 + \gamma)R_2 + \beta(1 - c_2)XR_2 \\
&\quad + \beta\sigma[(c_{12} - c_2)R_{12} + (c_1 - c_2)R_1 - c_2S]R_2 \\
\frac{dR_{12}}{dt} &= (m_{12} - R_{12})\mu - (\delta p + \gamma)R_{12} + \beta(1 - c_{12})XR_{12} \\
&\quad - \beta\sigma[c_{12}S + (c_{12} - c_1)R_1 + (c_{12} - c_2)R_2]R_{12} \\
\frac{dX}{dt} &= (m_X - X)\mu + (\tau_1 + \tau_2 + \gamma)S + (\tau_2 + \gamma)R_1 + (\tau_1 + \gamma)R_2 + (\delta p + \gamma)R_{12} \\
&\quad - \beta[S + (1 - c_1)R_1 + (1 - c_2)R_2 + (1 - c_{12})R_{12}]X
\end{aligned}$$

2.5. **Equilibrium and stability analysis.** We only perform the complete equilibrium analysis on the Random Drug Model. The stability analysis for the Base Model, Isolation Model and Targeted Drug Model can be obtained following the same steps as performed for the Random Drug Model and are stated at the end of this section.

In all of the models, we assume that patients can enter the hospital in any of the given states. Although it is unrealistic to assume that all the patients entering the hospital will be uncolonized, it is possible for the proportion of patients entering the hospital colonized with resistant bacteria to be small. As a result, we assume it is impossible for a disease-free equilibrium. Instead, we are interested in a boundary equilibrium in which all the patients are either uncolonized or colonized with only sensitive bacteria; thus we focus on a resistant-free equilibrium (RFE), $E_R = (S, R_1, R_2, R_{12}, X) = (S^*, 0, 0, 0, X^*)$. To perform the stability analysis on the Random Drug Model, we use the assumption that there is a fixed

population to first reduce the system by letting $X = 1 - (S + R_1 + R_2 + R_{12})$ and thus in the reduced system (equation 2), we need to only consider the equilibrium $E_R = (S^*, 0, 0, 0)$ where X^* can be calculated by $X^* = 1 - S^*$. S^* can be found by solving $\frac{dS}{dt}|_{E_R} = 0$ resulting in

$$S^* = \frac{\beta - (\tau_1 + \tau_2 + \tau_3 + \gamma + \mu) \pm \sqrt{(\tau_1 + \tau_2 + \tau_3 + \gamma + \mu - \beta)^2 + 4\beta\mu m_S}}{2\beta}. \quad (1)$$

The reduced system is given by

$$\begin{aligned}
\frac{dS}{dt} &= (m_S - S)\mu - (\tau_1 + \tau_2 + \tau_3 + \gamma)S + \beta S(1 - S - R_1 - R_2 - R_{12}) \\
&\quad + \beta\sigma(c_1R_1 + c_2R_2 + c_{12}R_{12})S \\
\frac{dR_1}{dt} &= (m_1 - R_1)\mu - (\tau_2 + \tau_3 + \gamma)R_1 + \beta(1 - c_1)R_1(1 - S - R_1 - R_2 - R_{12}) \\
&\quad + \beta\sigma[(c_{12} - c_1)R_{12} + (c_2 - c_1)R_2 - c_1S]R_1 \\
\frac{dR_2}{dt} &= (m_2 - R_2)\mu - (\tau_1 + \tau_3 + \gamma)R_2 + \beta(1 - c_2)R_2(1 - S - R_1 - R_2 - R_{12}) \\
&\quad + \beta\sigma[(c_{12} - c_2)R_{12} + (c_1 - c_2)R_1 - c_2S]R_2 \\
\frac{dR_{12}}{dt} &= (m_{12} - R_{12})\mu - (\tau_3 + \gamma)R_{12} + \beta(1 - c_{12})R_{12}(1 - S - R_1 - R_2 - R_{12}) \\
&\quad - \beta\sigma[c_{12}S + (c_{12} - c_1)R_1 + (c_{12} - c_2)R_2]R_{12} \quad (2)
\end{aligned}$$

Using the next generation approach, [30], we analyze the stability of the RFE. We first reorder the system of differential equations so all the resistant states are coupled together first followed by the sensitive state, R_1, R_2, R_{12}, S. We then linearize the reordered system about the RFE. The Jacobian matrix evaluated at the RFE is given by

$$J = \left[\begin{array}{ccc|c}
J_{11} & 0 & 0 & 0 \\
0 & J_{22} & 0 & 0 \\
0 & 0 & J_{33} & 0 \\
\hline
\beta S^*(\sigma c_1 - 1) & \beta S^*(\sigma c_2 - 1) & \beta S^*(\sigma c_{12} - 1) & J_{44}
\end{array}\right]$$

where

$$\begin{aligned}
J_{11} &= -(\mu + \tau_2 + \tau_3 + \gamma) + \beta(1 - c_1)(1 - S^*) - \sigma\beta c_1 S^* \\
J_{22} &= -(\mu + \tau_1 + \tau_3 + \gamma) + \beta(1 - c_2)(1 - S^*) - \sigma\beta c_2 S^* \\
J_{33} &= -(\mu + \tau_3 + \gamma) + \beta(1 - c_{12})(1 - S^*) - \sigma\beta c_{12} S^* \\
J_{44} &= -(\mu + \tau_1 + \tau_2 + \tau_3 + \gamma) + \beta(1 - 2S^*)
\end{aligned}$$

The terms are split into the rates of new colonizations with resistant bacteria,

$$F = \left[\begin{array}{ccc}
F_{11} & 0 & 0 \\
0 & F_{22} & 0 \\
0 & 0 & F_{33}
\end{array}\right]$$

where

$$\begin{aligned}
F_{11} &= \beta(1 - c_1)(1 - S^*) - \sigma\beta c_1 S^* \\
F_{22} &= \beta(1 - c_2)(1 - S^*) - \sigma\beta c_2 S^* \\
F_{33} &= \beta(1 - c_{12})(1 - S^*) - \sigma\beta c_{12} S^*
\end{aligned}$$

and all other transitions

$$V = \begin{bmatrix} \mu+\tau_2+\tau_3+\gamma & 0 & 0 \\ 0 & \mu+\tau_1+\tau_3+\gamma & 0 \\ 0 & 0 & \mu+\tau_3+\gamma \end{bmatrix}.$$

V is a nonsingular matrix and the matrix product FV^{-1} is called the next generation matrix for the model. The entries F_{ij} signify the rate at which infected individuals in compartment j produce new infections in compartment i near the RFE while the entries V_{jk}^{-1} of the matrix

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu+\tau_2+\tau_3+\gamma} & 0 & 0 \\ 0 & \frac{1}{\mu+\tau_1+\tau_3+\gamma} & 0 \\ 0 & 0 & \frac{1}{\mu+\tau_3+\gamma} \end{bmatrix}$$

represent the average length of time an individual spends in compartment j during its lifetime, again assuming that the population remains near the RFE. Using ideas similar to [30], we can define

$$\begin{aligned} R_S &= \rho(FV^{-1}) \\ &= \max\left\{ \frac{\beta(1-c_1)(1-S^*)-\sigma\beta c_1 S^*}{\mu+\tau_2+\tau_3+\gamma}, \frac{\beta(1-c_2)(1-S^*)-\sigma\beta c_2 S^*}{\mu+\tau_1+\tau_3+\gamma}, \right. \\ &\qquad \left. \frac{\beta(1-c_{12})(1-S^*)-\sigma\beta c_{12} S^*}{\mu+\tau_3+\gamma} \right\} \end{aligned} \tag{3}$$

where $\rho(A)$ is the spectral radius of the matrix A. Using results in [30], we have the following theorem.

Theorem 2.1. *The resistant-free equilibrium for the Random Drug Model, $E_R = (S^*, 0, 0, 0)$, is locally asymptotically stable if and only if $R_S < 1$ where R_S is defined by (3) and S^* is given by (1).*

For the Base Model, a comparable equilibrium analysis is performed by Chow et. al. ([9]). We simply restate the results in the following theorem to provide a complete stability analysis for all the models included in this paper.

Theorem 2.2. *The resistant-free equilibrium for the Base Drug Model, $E_B = (S^\dagger, 0, 0, 0)$, is locally asymptotically stable if and only if $R_B < 1$ where R_B is defined by*

$$\begin{aligned} R_B &= \max\left\{ \frac{\beta(1-c_1)(1-S^\dagger)-\sigma\beta c_1 S^\dagger}{\mu+\tau_2+\gamma}, \frac{\beta(1-c_2)(1-S^\dagger)-\sigma\beta c_2 S^\dagger}{\mu+\tau_1+\gamma}, \right. \\ &\qquad \left. \frac{\beta(1-c_{12})(1-S^\dagger)-\sigma\beta c_{12} S^\dagger}{\mu+\gamma} \right\} \end{aligned}$$

and $S^\dagger$ is given by

$$S^\dagger = \frac{\beta-(\tau_1+\tau_2+\gamma+\mu)+\sqrt{(\tau_1+\tau_2+\gamma+\mu-\beta)^2+4\beta\mu m_S}}{2\beta}. \tag{4}$$

Using a similar equilibrium analysis on the Isolation and Targeted Drug Models as done with the Random Drug Model, we have similar results.

Theorem 2.3. *The resistant-free equilibrium for the Isolation Model,* $E_I = (S^\dagger, 0, 0, 0, 0)$*, is locally asymptotically stable if and only if* $R_I < 1$ *where* R_I *is defined by*

$$\begin{aligned} R_I &= \rho(FV^{-1}) \\ &= \max\left\{ \frac{\beta(1-c_1)(1-S^\dagger) - \sigma\beta c_1 S^\dagger}{\mu+\tau_2+\gamma}, \frac{\beta(1-c_2)(1-S^\dagger) - \sigma\beta c_2 S^\dagger}{\mu+\tau_1+\gamma}, \right. \\ &\qquad \left. \frac{\beta(1-c_{12})(1-S^\dagger) - \sigma\beta c_{12} S^\dagger}{\mu+\gamma+\eta}, \frac{-\sigma\beta(1-\epsilon)c_{12}S^\dagger}{\mu+\gamma} \right\} \end{aligned}$$

and $S^\dagger$ *is given by (4).*

Theorem 2.4. *The resistant-free equilibrium for the Targeted Drug Model,* $E_T = (S^\dagger, 0, 0, 0)$*, is locally asymptotically stable if and only if* $R_T < 1$ *where* R_T *is defined by*

$$\begin{aligned} R_T &= \max\left\{ \frac{\beta(1-c_1)(1-S^\dagger) - \sigma\beta c_1 S^\dagger}{\mu+\tau_2+\gamma}, \frac{\beta(1-c_2)(1-S^\dagger) - \sigma\beta c_2 S^\dagger}{\mu+\tau_1+\gamma}, \right. \\ &\qquad \left. \frac{\beta(1-c_{12})(1-S^\dagger) - \sigma\beta c_{12} S^\dagger}{\mu+\delta p+\gamma} \right\} \end{aligned}$$

and $S^\dagger$ *is given by (4).*

3. **Sensitivity analysis.** The ultimate goal of this paper is to determine the effect of introducing a new drug in combating resistance within a hospital. Analyzing the sensitivity of the model to changes in parameters will provide information about how much the results of our model will be affected by changes in parameter values. If the state variables are very sensitive to the changes of the parameter, then it is necessary to explore the effects of the parameter changes on the resulting state variables within the model. Moreover, it will be necessary to be able to accurately estimate these parameters for more accurate findings. Additionally, the sensitivity analysis will give insight into which variables, and hence processes, may work to either increase or decrease resistance within the hospital.

To calculate the sensitivity of the state variables to the parameters, we perform the traditional sensitivity analysis [8] by calculating $\frac{\partial \mathbf{x}}{\partial \mathbf{q}_j}$ for each state variable $\mathbf{x} = [S, R_1, R_2, R_{12}, X, (Q)]$ and each parameter $\mathbf{q}_j$ in the system where

$$\mathbf{q} = [\beta, \sigma, \gamma, \mu, m_S, m_1, m_2, m_{12}, c_1, c_2, c_{12}, \tau_1, \tau_2, \tau_3, T, \eta, \epsilon, p]$$

represents all the possible parameter values for the four models. To compute the relative ranking of the parameters, i.e., to determine which parameter has the most effect on the state variables, we use the modified l_2 norm

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

which normalizes the sensitivity values by removing the units. To determine the sensitivity of the total resistance $R = R_1 + R_2 + R_{12}(+Q)$ in the hospital we use the formula

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

Figures 4 and 5 show the overall results of the sensitivity analysis. The parameters resulting in the largest relative change in the state values for all the models are the per capita primary transmission rate β, the per capita treatment rates τ_i or, equivalently, the overall antibiotic treatment rate T, the per capita patient turnover rate in the hospital μ, and to a lesser degree the initial population sizes m_1, m_2 and m_S. In addition, changes in the per capita isolation rate η in the Isolation Model and changes in the proportion of patients colonized with dual resistance that are identified and treated p in the Targeted Drug Model also have a large relative effect on the state variables in each of these models. Small changes in the estimates of these parameter values may result in relatively large changes in the resulting state variables. On the other hand, changes in the relative rate of secondary colonization to that of primary colonization σ, fitness costs of the resistant bacteria, c_1, c_2, and c_{12}, as well as the per capita clearance rate of bacteria due to the immune response γ result in very little change in the overall state values. Therefore, small variations in estimates of these parameters will not, in general, effect the overall model results significantly. The one exception is in the Random Drug Model where the fitness cost of the dual resistant strain c_{12} appears to effect the state variables on the same order as changes in either τ_1 or τ_2.

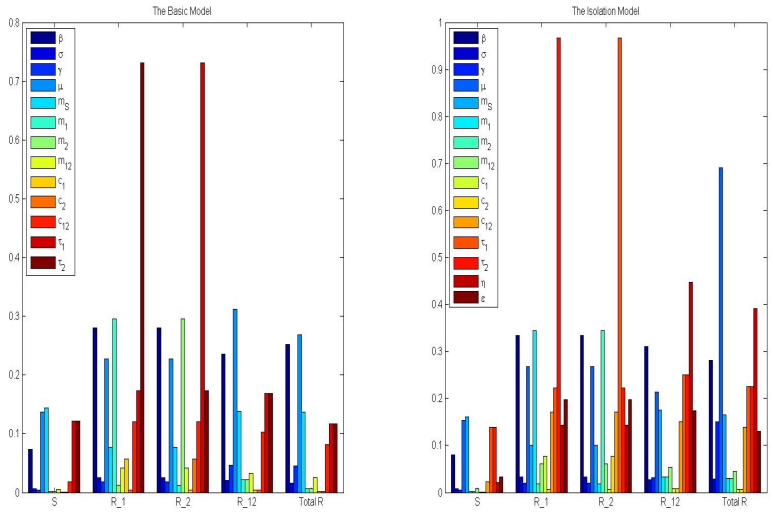

FIGURE 4. Relative Sensitivity of the Basic Model and Isolation Model with respect to the Parameters

In Figure 6, $\frac{d\mathbf{x}}{d\beta}$ is plotted versus time where $\mathbf{x} = [S, R_1, R_2, R_{12}]$. In general, $\frac{d\mathbf{x}}{d\beta} > 0$ across time except in a small window of time in which $\frac{dS}{d\beta}$ is negative. This illustrates what one would expect: on average, increasing the transmission rate increases the proportion of patients colonized with both sensitive and resistant bacteria. In all but the Targeted Drug Model, the change is R_{12} with respect to β is largest signifying that increasing β causes the greatest increase in the proportion of patients colonized with dual resistant bacteria and hence also has a significant effect on the total population colonized with resistant bacteria (also shown in the

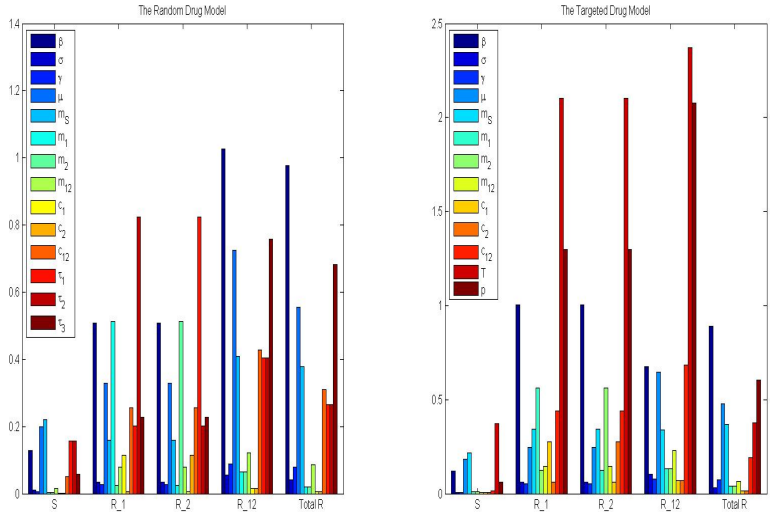

FIGURE 5. Relative Sensitivity of the Random Drug Model and Targeted Drug Model with respect to the Parameters

figure). In the Targeted Drug Model, where drug 3 is used to treat a portion of the patients colonized with dual resistance, and the per capita treatment rate of drug 3 increases as R_{12} increase, the change in β has a more significant effect on the proportion of patients colonized with single resistant bacteria. One possible cause for this switch could be a result of the treatment regime for drug 3 set forth in this model. As patients carrying dual resistant bacteria increase, treatment of these patients with drug 3 also increases. Recall, that the total proportion of patients treated remain constant, thus increasing τ_3 reduces the per capita treatment rates with drugs 1 and 2, the only drugs allowed to treat patients colonized with single resistance. In any of the cases, however, an increase in β results in an increase in total resistance within the hospital.

Variation in the per capita treatment rate also appears to have one of the most significant effect on changes in the state variables. Drug 1 is used to treat patients colonized with both sensitive bacteria as well as bacteria resistant to drug 2; therefore, in the Base Model, Isolation Model and Random Drug Model, where τ_1 is fixed, increasing the value of τ_1 will result in the greatest rate of decrease in R_2, see Figure 7. Similarly, increasing the value of τ_2 results in the greatest rate of decrease in R_1 (Figure 8). In constructing the model, we did not explicitly assume that the use of drug 1 increased resistance to drug 1 or the use of drug 2 increased resistance to drug 2 although this is a popular argument in lobbying for a reduction in the overall antibiotic use [27, 33]. However, the sensitivity analysis does indeed show that at least initially, an increase in τ_1 results in an increase in resistance to drug 1, R_1. Similarly, an increase in τ_2 results initially in an increase in resistance to drug 2, R_2. However, it is interesting to note that after a short period of time, increasing τ_1 actually causes a decrease in R_1 after which increasing τ_1 has minimal, if any, effect in either direction on R_1. The same is true for τ_2. On the other hand, increasing τ_1 or τ_2 increases the proportion of patients colonized with dual resistant

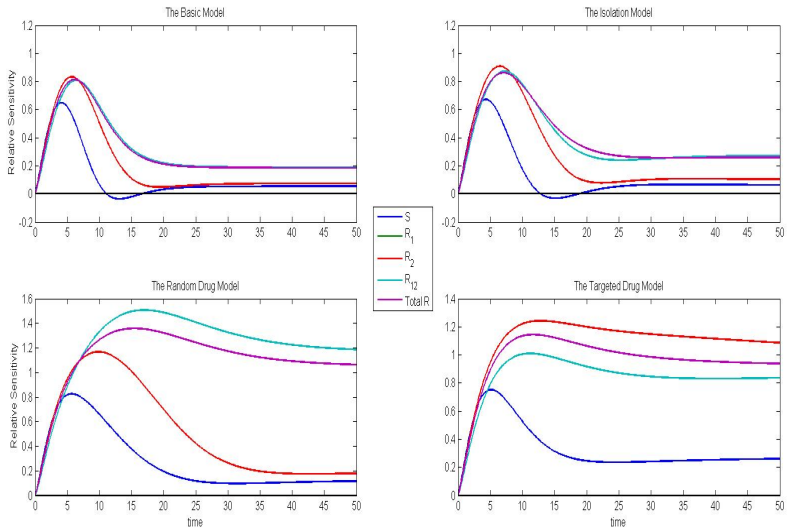

FIGURE 6. Relative Sensitivity of the State Variables with respect to the Transmission Rate β for All Models

bacteria, R_{12}. Although the rate of increase is smaller after the first window of time, the variation in R_{12} due to changes in τ_1 or τ_2 does not reduce to 0 as in the case with R_2 or R_1 respectively. Instead, the rate of increase in R_{12} with respect to either τ_1 or τ_2 levels off to a near constant rate. Similar results were found in the Random Drug Model where τ_3 is the fixed per capita treatment rate with drug 3 which is used to treat all patients in the hospital. Since drug 3 was used to treat all patients, an increase in τ_3 results initially in a decrease in the proportion of patients colonized with either sensitive or resistant bacteria. However, after a certain period of time, an increase in τ_3 starts to increase both colonizations with sensitive bacteria as well as colonizations with bacteria resistant to a single antibiotic while still resulting in a decrease in both R_{12} and the total resistant population in the hospital.

In addition to the rate of colonization and treatment rate, the change in the rate of patient turnover, μ, results in an increase in the proportion of patients colonized with sensitive bacteria and an eventual increase in the patients colonized with single resistance. The time at which an increase in μ results in an increase in patients colonized with single resistance R_1 or R_2 varies depending on the model, see Figure 9. In all models, increasing μ reduces both the proportion of patients colonized with dual resistant bacteria as well as the total resistance in the hospital. Therefore, increasing the turnover rate in the hospital may aid in the overall reduction in resistant bacteria.

In addition to giving insight into which parameter values need to be estimated precisely to produce accurate results, sensitivity analysis can also give intuition into which processes effect total resistance in the hospital the most, and hence give direction into where effort should be focused in order to reduce the total level of overall resistance. For example, depending on which scenario or model best fits

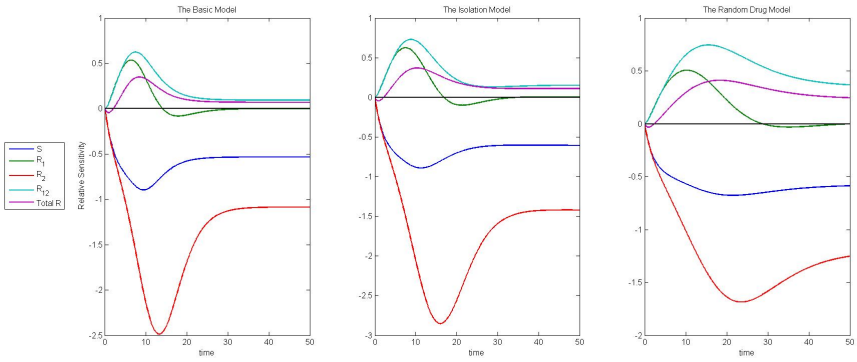

FIGURE 7. Relative Sensitivity of the State Variables with respect to τ_1 for the Basic Model, Isolation Model and Random Drug Model

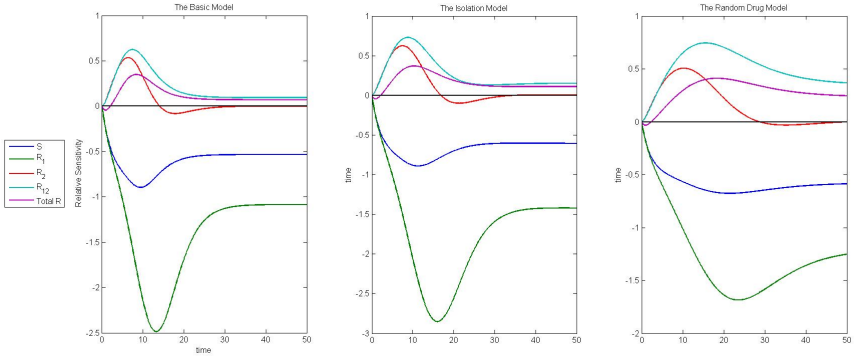

FIGURE 8. Relative Sensitivity of the State Variables with respect to τ_2 for the Basic Model, Isolation Model and Random Drug Model

the hospital of interest and the time elapse within the system, it might be possible to determine how one might go about trying to control overall resistance. For instance, Figure 10 shows the variation in total resistance across time with respect to the parameters for both the Base Model and Isolation Model. In both models, the sensitivity analysis suggests that decreasing β, the rate of transmission, as well as τ_1 and τ_2, the per capita treatment rates of drugs 1 and 2, and increasing μ, the turnover rate in the hospital, the total resistance should decrease at the fastest rate. In the Random Drug Model (Figure 11), the largest rate of decrease should be found by again reducing β and increasing τ_3 and μ. In the Targeted Drug Model (Figure 11), again decreasing β and the overall per capita treatment rate T while increasing μ and p, the portion of patients identified with dual resistant bacteria and treated, should result in the greatest decrease in overall resistance. We will examine these parameter changes in Section 4.

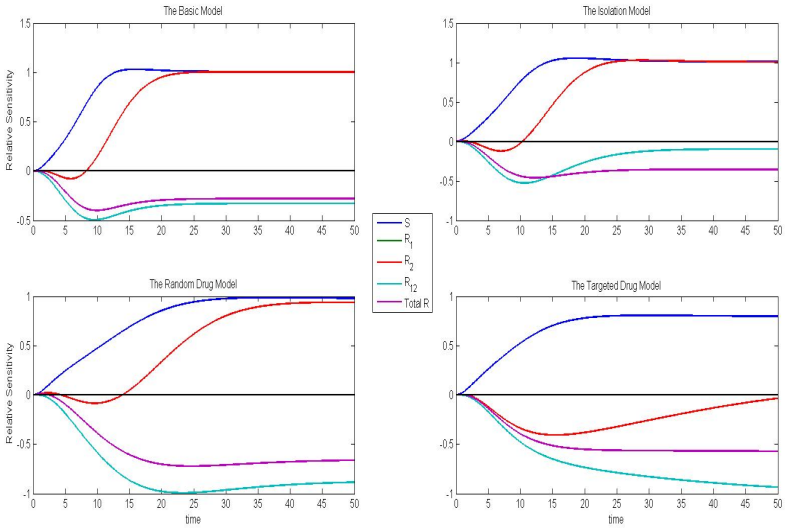

FIGURE 9. Relative Sensitivity of the State Variables with Respect to μ for All Models

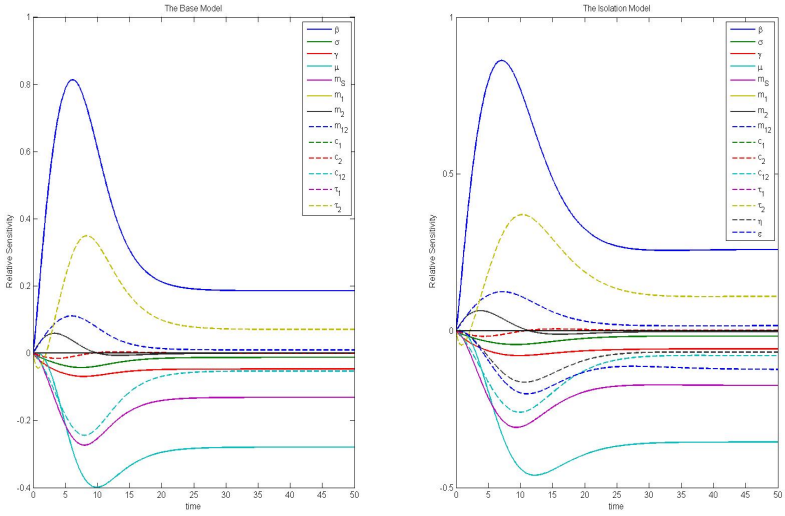

FIGURE 10. Sensitivity of Total Resistance for the Basic Model and the Isolation Model

4. **Results.** Using the parameter values in Table 3, the simulations for all the models can be found in Figure 12. In all the models, except the Targeted Drug Model, the proportion of patients colonized with dual resistant bacteria, R_{12}, reaches an

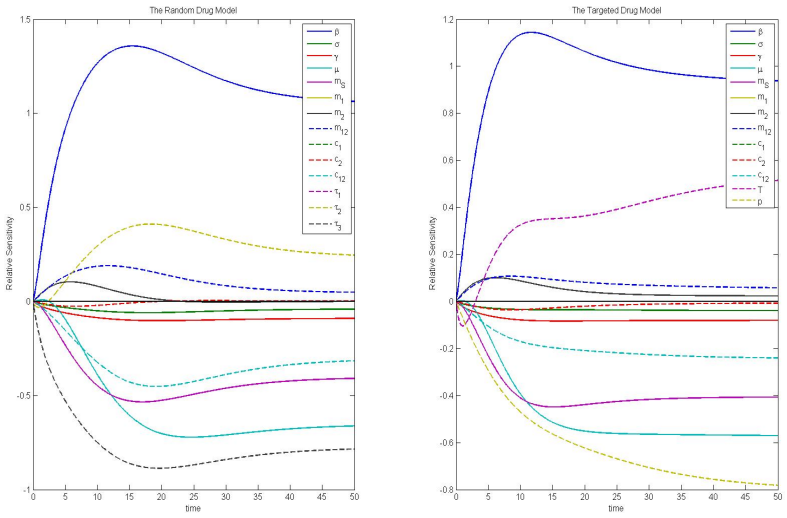

FIGURE 11. Sensitivity of Total Resistance for the Random Drug Model and the Targeted Drug Model

equilibrium at a much higher level than that for any of the single resistant states. However, in the Targeted Drug Model, the change in both the single and dual resistant strains follow a similar path and level off at nearly equal values. Examining the total resistance level within each of the models, the introduction of a new drug greatly reduces the overall resistance within the hospital as one would expect. However, the Targeted Drug Model depends on the portion of patients p one can identify as carrying the dual resistant strain of bacteria. Figure 13 shows the effect of varying p on the average total resistance compared to the average total resistance of the other three models. Assuming the hospital can identify and successfully treat approximately 25-26% of the dual resistant patients, with all other parameter values fixed, model results suggest it would be more beneficial to treat only those patients who have no other drugs available to clear the resistant bacteria. Hence, findings suggest using a new antibiotic on only the portion of patients who carry a bacterial strain resistant to all other antibiotics is beneficial in reducing the average total resistance within the hospital, and this method of implementation limits the use of the antibiotic which will most likely result in a longer time until the initial mutation of a resistant strain forms [22].

The precise amount of reduction in total resistance depends on the choice of parameters within the model. Although the best method for determining these parameters and determining uncertainty in the model is to fit the model to actual data from a hospital, we can examine possible benefits in changing the parameters from their original estimates. In Section 3, we presented a sensitivity analysis for each of the models and identified the potential parameters which might be most beneficial in controlling the reduction of the overall resistant bacteria within the hospital. Figures 14 - 16 illustrate a limited study of the effects of varying the most influential parameter values for each of the models. In the sensitivity analysis of the

TABLE 3. The Parameter Values for Simulations

Parameter	Value	Reference
β	1/day	[5, 25]
σ	0.25	[5, 25]
c_i	0.05	[25]
c_{12}	0.15	[25]
T	0.78/day	[17, 29]*
γ	0.03/day	[5, 25, 26]
μ	0.10/day	[5, 25, 26]
m_S	0.7	[5, 25, 26]
m_i	0.05	[25]
m_{12}	0.04	[25]
η	0.1/day	
ϵ	0.9	[6, 25]

* [17] stated 24% of patients received antibiotics in 1979, while in a 2006-2007 study, [29] found 79% of COPD patients used antibiotics at least two consecutive days while hospitalized.

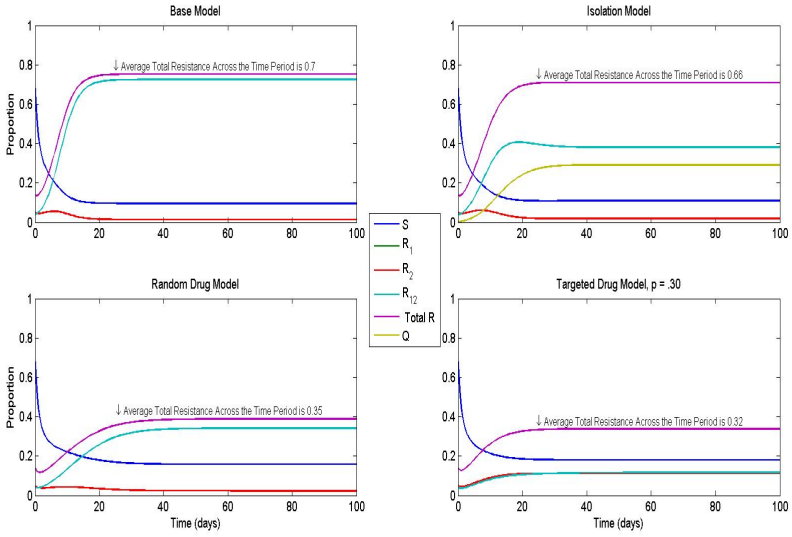

FIGURE 12. Model Simulations showing the Proportion of Each State over Time

Base and Isolation Models, it was discovered that decreasing the transmission rate β and the per capita treatment rates of drugs 1 and 2, τ_1 and τ_2 respectively, while increasing the turnover rate μ of patients within the hospital would be most likely to reduce the average total resistance. To analyze the effects of these changes, we use the initial parameter values in Table 3 and incrementally increase or decrease the parameter values through a percent change in the original values, ranging from the initial value to a 30% increase or reduction in the parameter values. We examine two

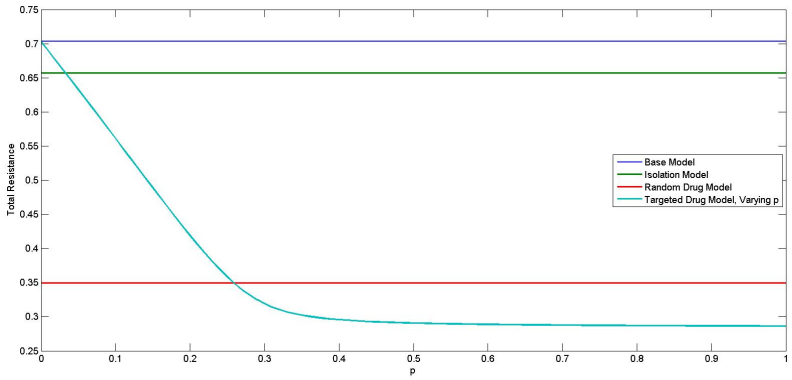

FIGURE 13. Comparison of Total Resistance across All Models Varying the Total Proportion p of Patients Identified and Treated in the Targeted Drug Model

different total time increments since the sensitivity analysis suggests a greater effect of one parameter over another depending on the total time period. In both scenarios, with a maximum 30% change in the variables mentioned, the total resistance within the hospital reduced on average by 15-20% with smaller reductions if only one of the parameter values are changed or if there is a smaller percentage change in the parameter values. We only show the results for the Base Model, but similar results hold for the Isolation Model.

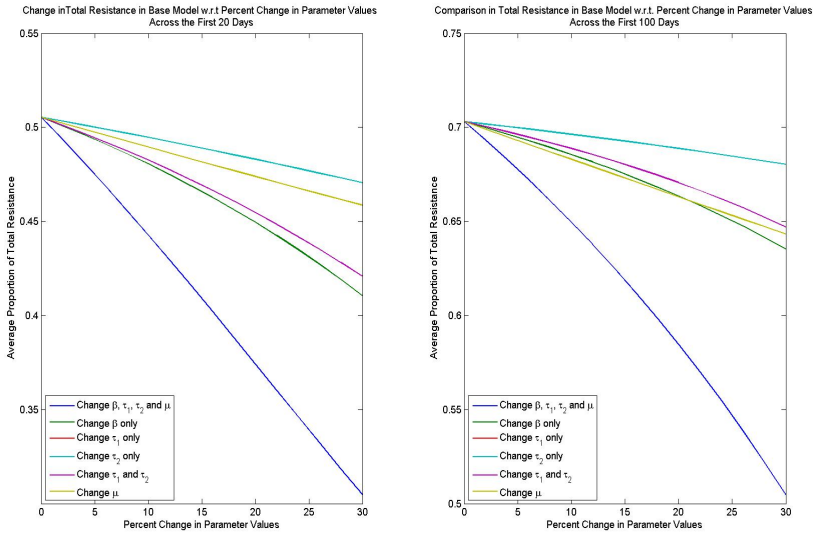

FIGURE 14. Average Total Resistance using the Base Model while Varying Parameter Values

In the Random Drug Model, the sensitivity analysis indicated that decreasing β while increasing τ_3 and μ would likely have the largest effect in reducing average total resistance. Figure 15 examines the change in these variables when varying the percent change in each variable. If reduction of this magnitude is possible, model results indicate the possibility of reducing the average total resistance by an additional 15-20% with the possibility of reducing the total proportion of patients carrying resistant bacteria to less than 15%. However, simply reducing the rate of transmission or colonization still provides significant reduction in the average proportion of patients carrying any type of resistant bacteria. Results are similar with the Targeted Drug Model, as seen in Figure 16, where β and T were reduced while p and μ were increased. Overall, these results indicate that although introduction of a new drug itself provides a substantial improvement towards reducing the average overall resistance in the hospital, it is not the only source of reduction. There is still a need to focus on all aspects of the hospital stay from faster discharges (when possible) to better hygiene practices and barrier preventions as well as the limitation of antibiotic prescriptions to only those instances where it is required.

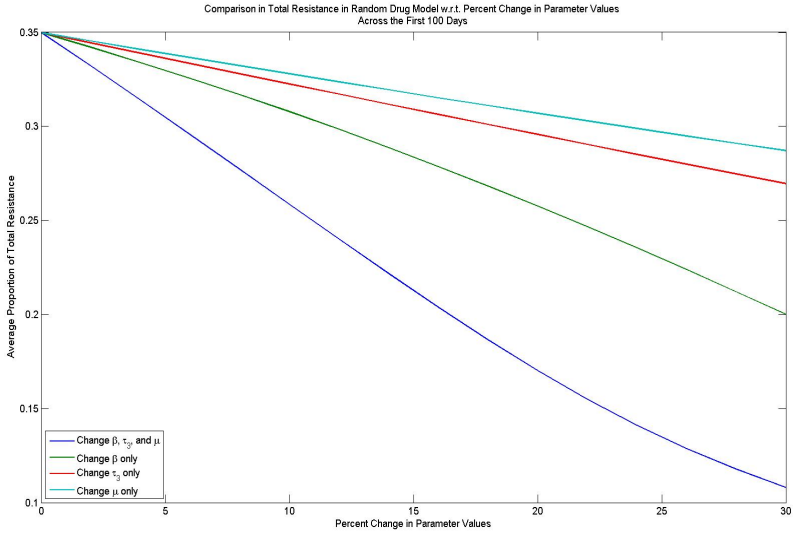

FIGURE 15. Average Total Resistance using the Random Drug Model while Varying Parameter Values

5. **Conclusions.** In this paper, four models were used to examine the benefits of introducing a new antibiotic within a hospital setting to try to combat the increase of patients colonized with resistant bacteria. The first two models, the Base Model and Isolation Models, described the spread of both single and dual resistant bacteria in a hospital setting with no drug available to aid in treating patients colonized with a dual resistant bacterial strain. These models were used as a basis for comparison to both the Random Drug Model and Targeted Drug Model in which a new drug was implemented but with different implementation strategies. The Random Drug Model allowed the new drug to be available to treat all patients while the Targeted

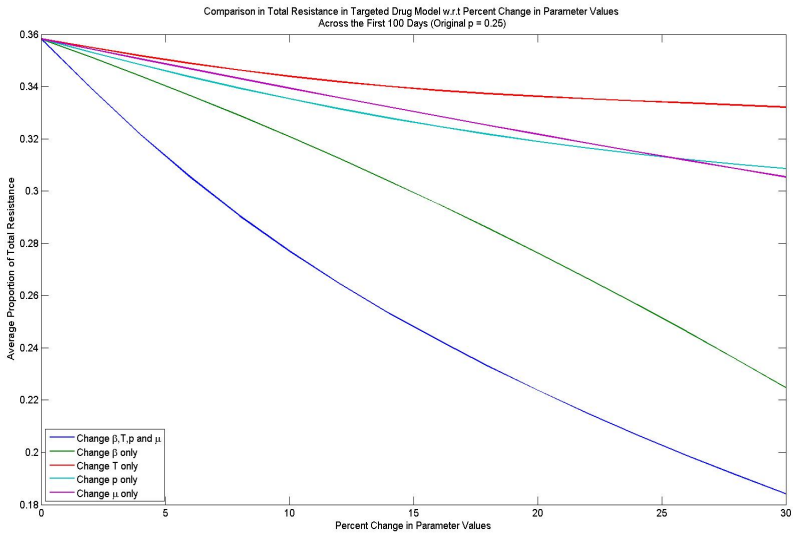

FIGURE 16. Average Total Resistance using the Targeted Drug Model while Varying Parameter Values

Drug Model only allowed the new antibiotic to be prescribed to those patients who were identified as carrying the dual resistant bacteria. We found that introducing a new drug into the hospital resulted in a significant reduction of the average patients carrying dual resistant bacteria, a reduction from approximately 65-72% of the hospital down to between 28-36% of the hospital. Furthermore, the sensitivity of the models were analyzed and parameters most likely to effect the results were identified. A limited analysis was performed by changing those parameters most likely to result in reducing the resistance even further, and if the parameter values were changed by even 10%, there was a potential for another 8-10% reduction in the overall resistance. Hence, introduction of a new antibiotic aids in the fight against the spread of antibiotic resistance in a hospital, but focus on other processes effecting the transmission of the resistance is still important in limiting antibiotic resistance.

REFERENCES

[1] Alberto Sandiumenge, Emili Diaz, Alejandro Rodriguez, Loreto Vidaur, Laura Canadell, Montserrat Olona, Montserrat Rue and Jordi Rello, *Impact of diversity of antibiotic use on the development of antimicrobial resistance*, Journal of Antimicrobial Chemotherapy, **57** (2006), 1197–1204.

[2] Alfonso J. Alanis, *Resistance to antibiotics: Are we in the post-antibiotic era?*, Archives of Medical Research, **36** (2005), 697–705.

[3] Bruce R. Levin and Klas I. Udekwu, *Population dynamics of antibiotic treatment: A mathematical model and hypotheses for time-kill and continuous-culture experiments*, Antimicrobial Agents and Chemotherapy, **54** (2010), 3414–3426.

[4] B. R. Levin, M. Lipsitch, V. Perrot, S. Schrag, R. Antia, L. Simonsen and N. Moore, *The population genetics of antibiotic resistance*, Clinical Infectious Diseases, **24** (1997), S9–S16.

[5] Carl T. Bergstrom, Monique Lo and Marc Lipsitch, *Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals*, PNAS, **101** (2004), 13285–13290.

[6] Christophe Fraser, Steven Riley, Roy M. Anderson and Neil M. Ferguson, *Factors that make an infectious disease outbreak controllable*, PNAS, **101** (2004), 6146–6151.
[7] Csaba Pal, Maria D. Macia, Antonio Oliver, Ira Schachar and Angus Buckling, *Coevolution with viruses drives the evolution of bacterial mutation rates*, Nature, **450** (2007), 1079–1081.
[8] D. M. Hamby, *A review of techniques for parameter sensitivity analysis of environmental models*, Environmental Monitoring and Assessment, **32** (1994), 135–154.
[9] Dale N. Gerding, Tom A. Larson, Rita A. Hughes, Mary Weiler, Carol Shanholtzer and Lance R. Peterson, *Aminoglycoside resistance and aminoglycoside usage: Ten years of experience in one hospital*, Antimicrobial Agents and Chemotherapy, (1991), 1284–1290.
[10] Dan I. Andersson and Bruce R. Levin, *The biological cost of antibiotic resistance*, Current Opinion in Microbiology, **2** (1999), 489–493.
[11] David M. Shlaes, Dale N. Gerding, Joseph F. John Jr., William A. Craig, Donald L. Bornstein, Robert A. Duncan, Mark R. Eckman, William E. Farrer, William H. Greene, Victor Lorian, Stuart Levy, John E. McGowan Jr., Sindy M. Paul, Joel Ruskin, Fred C. Tenover and Chatrchai Watanakunakorn, *Society for healthcare epidemiology of America joint committee on the prevention of antimicrobial resistance: Guidelines for prevention of antimicrobial resistance in hospitals*, Clinical Infectious Diseases, **25** (1997), 584–599.
[12] D. J. Austin and K. G. Kristinsson and R. M. Anderson, *The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance*, PNAS, **96** (1999), 1152–1156.
[13] D. J. Austin, M. Kakehashi and R. M. Anderson, *The transmission dynamics of antibiotic-resistant bacteria: The relationship between resistance in commensal organisms and antibiotic consumption*, Proceedings: Biological Sciences, **264** (1997), 1629–1638.
[14] Eduardo Massad, Marcelo N. Burattini and Francisco A. B. Coutinho, *An optimization model for antibiotic use*, Applied Mathematics and Computation, **201** (2008), 161–167.
[15] Elaine S. Walker and Foster Levy, *Genetic trends in population evolving antibiotic resistance*, Evolution, **55** (2001), 1110–1122.
[16] Erika M. C. D'Agata, Pierre Magal, Damien Olivier, Shigui Ruan and Glenn F. Webb, *Modeling antibiotic resistance in hospitals: The impact of minimizing duration treatment*, Journal of Theoretical Biology, **249** (2007), 487–499.
[17] F. D. Pien and W. K. K. Lau and N. Sur, *Antibiotic use in a small community hospital*, West J. Med., **130** (1979), 498–502.
[18] Glenn F. Webb, Erika M. C. D'Agata, Pierre Magal and Shigui Ruan, *A model of antibiotic-resistant bacterial epidemics*, PNAS, **102** (2005), 13343–13348.
[19] Harald J. van Loon, Menno R. Vriens, Ad C. Fluit, Annet Troelstra, Christiaan van der Werken, Jan Verhoef and Marc J. M. Bonten, *Antibiotic rotation and development of gram-negative antibiotic resistance*, American Journal Respiratory Critical Care Medicine, **171** (2005), 480–487.
[20] Inti Pelupessy, Mac J. M. Bonten and Odo Diekmann, *How to assess the relative importance of different colonization routes of pathogens within hospital settings*, PNAS, **99** (2002), 5601–5605.
[21] Jesus Silva, *Mechanisms of antibiotic resistance*, Current Therapeutic Research, **57** (1996), 30–35.
[22] Jesus Blazquez, Antonio Oliver and Jose-Maria Gomez-Gomez, *Mutation and evolution of antibiotic resistance: Antibiotics as promoters of antibiotic resistance?*, Current Drug Targets, **3** (2002), 345–349.
[23] J. L. Martinez and F. Baquero, *Mutation frequencies and antibiotic resistance*, Antimicrobial Agents and Chemotherapy, **44** (2000), 1771–1777.
[24] Jose-Antonio Martinez, Josep-Maria Nicolas, Francesc Marco, Juan-Pablo Horcajada, Gloria Garcia-Segarra, Antoni Trilla, Carles Codina, Antoni Torres and Josep Mensa, *Comparison of antimicrobial cycling and mixing strategies in two medical intensive care units*, Critical Care Medicine, **34** (2006), 329–335.
[25] Karen Chow, Xiaohong Wang, R. Curtiss III and Carlos Castillo-Chavez, *Evaluating the efficacy of antimicrobial cycling programmes and patient isolation on dual resistance in hospitals*, Journal of Biological Dynamics, **5** (2010), 27–43.
[26] Marc Lipsitch, Carl T. Bergstrom and Bruce R. Levin, *The epidemiology of antibiotic resistance in hospitals: Paradoxes and prescriptions*, PNAS, **97** (2000), 1938–1943.
[27] Marc Lipsitch and Matthew H. Samore, *Antimicrobial use and antimicrobial resistance: A population perspective*, Emerging Infectious Diseases, **8** (2002), 347–354.

[28] Michael Haber, Bruce R. Levin and Piotr Kramarz, *Antibiotic control of antibiotic resistance in hospitals: A simulation study*, BMC Infectious Diseases, **10** (2010).

[29] Michael B. Rothberg, Penelope S. Pekow, Maureen Lahti, Oren Brody, Daniel J. Skiest and Peter K. Lindenauer, *Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease*, JAMA, **303** (2010), 2035–2042.

[30] P. van den Driessche and James Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Mathematical Biosciences, **180** (2002), 29–48.

[31] Richard E. Lenski, *Bacterial evolution and the cost of antibiotic resistance*, International Microbiology, **1** (1998), 265–270.

[32] Robert F. Betts, William M. Valenti, Stanley W. Chapman, Tasnee Chonmaitree, Gail Mowrer, Patricia Pincus, Marjorie Messner and Richard Robertson, *Five-year surveillance of aminoglycoside usage in a university hospital*, Antimicrobial Agents and Chemotherapy, **100** (1984), 219–222.

[33] Sebastian Bonhoeffer, Marc Lipsitch and Bruce R. Levin, *Evaluating treatment protocols to prevent antibiotic resistance*, PNAS, **94** (1997), 12106–12111.

[34] William J. Moss, M. Claire Beers, Elizabeth Johnson, David G. Nichols, Trish M. Perl, James D. Dick, Michael A. Veltri and Rodney E. Willoughby Jr., *Pilot study of antibiotic cycling in a pediatric intensive care unit*, Critical Care Medicine, **30** (2002), 1877–1882.

[35] Y. Claire Wang and Marc Lipsitch, *Upgrading antibiotic use within a class: Tradeoff between resistance and treatment success*, PNAS, **103** (2006), 9655–9660.

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