A mathematical model of nosocomial infection and antibiotic resistance: evaluating the efficacy of antimicrobial cycling programs and patient isolation on dual resistance

Karen C. Chow, Xiaohong Wang, Carlos Castillo-Chávez
Arizona State University, Tempe, AZ

Abstract

Hospital-acquired infections caused by antibiotic-resistant bacteria pose a significant threat to public health. Antimicrobial cycling, in which antibiotic classes are alternated over time, has previously been suggested as a strategy for curbing the development of resistance in hospitals. A mathematical model of antimicrobial cycling in a hospital setting is developed in order to analyze the efficacy of such a program, with an emphasis on the emergence and significance of dual resistance. Simulation results compare the effects over time of antimicrobial cycling programs with mixing programs and their ability to reduce antimicrobial resistance. Our model also considers the effects of isolating patients harboring dual-resistant bacteria in the hospital.

1 Introduction

Hospital-acquired (nosocomial) infections are costly and dangerous, often resulting in an increase in health care expenses due to lengthened hospital stay and morbidity. The spread of infection is of particular concern in hospitals, where many diseased people with weakened immune systems are situated in close proximity [1].

The problem of infections acquired in the hospital is exacerbated by a rise in resistance to antibiotics, a justifiable concern considering the growing risks and costs associated with nosocomial infections. Antibiotic-resistant bacteria are transmitted between patients in hospitals primarily through contamination of hospital equipment and surfaces as well as human vectors [2]. Previously antibiotic-susceptible bacteria are being replaced by resistant organisms. Coupled with the lack of new antimicrobial development, the increasing frequency in resistance threatens a return to a pre-antibiotic era where current antibiotics are rendered useless [3, 4].

The spread of antibiotic-resistant bacteria has called attention to the need for a method to successfully control it. Antibiotics themselves are the driving force for the rise and persistence of resistance within hospital settings. Resistance could theoretically be reduced by cutting down the overall use of antibiotics, controlling the spread of bacteria, using specific types of antibiotics to which bacteria are not resistant, reducing how long patients stay in the hospital, and monitoring health care workers that may be carrying antibiotic-resistant nosocomial pathogens [5]. But these tactics are more challenging to carry out than they seem. Interventions like these have been proposed for limiting nosocomial infection, particularly to stem the spread of antibiotic-resistant bacteria, by focusing on reducing overall bacterial transmission within a hospital. Some have

proposed to stop the use of all antibiotics in an effort to control the rise of resistance. However, in this day and age of medicine, this is not considered a practical solution [6].

The implementation of any intervention requires an adequate level of compliance, particularly that of physicians who have the authority to decide how a patient is treated in the hospital. A classic intervention technique is to isolate individuals who are symptomatic and confirmed carriers to effectively contain a contagious disease. A successful isolation program requires the implementation of strict hygiene precautions to prevent transmission of infection to health-care workers, who in turn can infect other patients [7]. As a result, physician compliance to any intervention technique as well as the potential effectiveness of an isolation program should be discussed when dealing with the problem of nosocomial infection and resistance to antibiotics.

Mathematical models can be beneficial in evaluating solutions to problems involving infectious disease [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. In epidemiology, mathematical models provide insight into the underlying mechanisms that influence the spread of disease at the population level. This makes even a simple model an incredibly powerful tool for suggesting control strategies and identifying behavior difficult to glean from experimental data [20].

A proposed strategy has been the cycling of formularies of first-line drugs prescribed to hospital patients. This describes a policy where empiric, or first-line, antibiotic drugs are alternated over a span of time in months to years in an attempt to slow the evolution and spread of resistant strains of pathogenic bacteria. Primary treatment of infections by one class of antibiotics is used for some period of time until resistance to it increases; then, the policy calls for switching to a second class of antibiotics for which resistance is rare or absent. This is particularly of importance in the intensive care unit (ICU) where patients are in close contact with one another for a prolonged period of time and more inclined to be administered broad-spectrum antibiotics. The cycling strategy is dependent upon the relationship between a particular antibiotic and the level of resistance to the drug. However, it can be difficult to determine whether or not an intervention was successful or to compare interventions without any quantitative expression. Such quantitative predictions and criteria for their evaluation can be offered through the investigation of mathematical models [6, 21].

Bergstrom, *et al.* [21] developed a model determining whether antimicrobial cycling can be effective at controlling resistance in a hospital setting. The purpose of their study was to isolate and illustrate fundamental ecological processes responsible for the success or failure of antimicrobial cycling programs. Two antimicrobial drugs were considered in this case, and it was assumed that dual resistance had not yet emerged. Their model tracked populations of patients within the hospital according to their colonization status. By running several simulations of their model to compare mixing and cycling drug programs, they were able to show that cycling is unlikely to reduce the carriage of resistant organisms compared to other alternative drug policies [21].

Levin and Bonten published a commentary on Bergstrom, *et al.*'s results discussing how resistance to single antibiotics would be higher with cycling than with mixing. The efficacy of cycling two antibiotics relative to mixing was evaluated using a simple mathematical model of the epidemiology of antibiotic treatment. It is evident that mathematical models can be used to predict the effectiveness of control efforts and how they relate to reduction in frequency of antibiotic resistance. Efforts for controlling resistance should be targeted at the usage and availability of antibiotics, though policies that wish to reduce the level of antibiotic use in hospitals are difficult to implement due to unrelenting medical, social, and economic forces [5, 21].

Mathematical models are useful in that they simplify some aspects of transmission dynamics in order to enhance understanding of other aspects. Although the strategy of antibiotic cycling

appears promising, there is little evidence that repeated cycling is an effective long-term strategy to reduce the emergence and spread of antibiotic resistance. Models have been previously developed for antimicrobial cycling in a hospital setting, and some have shown that cycling is unlikely to reduce rates of resistance [21]. However, no work has been done on incorporating dual-resistant bacterial strains in a mathematical model of antimicrobial cycling. The rise of strains of pathogenic bacteria resistant to multiple antibiotics are of great concern in hospitals, as they result in higher costs of drugs that may or may not be effective against the infection. Investigating the effects of resistance to multiple antibiotics in hospitals and comparing them to single resistance may offer further insight into the dynamics of nosocomial infection transmission. Bergstrom, *et al.*'s model assumes that dual resistance has not yet emerged. With multiple resistance rapidly on the rise across the globe, a model that accounts only for single resistance is insufficient.

In this paper, we incorporate dual resistance to antibiotics in such a way that the spreading effects of these dual-resistant bacterial strains can be studied within the hospital setting. Analysis and numerical simulations of the model are used to evaluate the efficacy of a cycling protocol versus a mixing protocol as well as the effects of varying physician compliance and isolation interventions. This paper is organized as follows: Chapter 2 presents the formulation of the mathematical model comprising a system of ordinary differential equations as well as stability analysis on a susceptible-only equilibrium; simulations of the model including the parameters used are shown, discussed, and compared to previous results in Chapter 3; a model incorporating isolation of patients with dual resistance is in Chapter 4; a summary of our findings and their implications are discussed in Chapter 5; and major conclusions are briefly summarized in Chapter 6.

2 Mathematical Model

2.1 Formulation of the Model

Taking into account the fact that infection with strains resistant to multiple antibiotics is common in hospital settings, especially in ICUs, a mathematical model is developed. The transmission

dynamics are governed by the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= (m-S)\mu - (\tau_1+\tau_2+\gamma)S + \sigma\beta(c_1R_1+c_2R_2+c_{12}R_{12})S + \beta SX, \\
\frac{dR_1}{dt} &= (m_1-R_1)\mu - (\tau_2+\gamma)R_1 + \beta(1-c_1)R_1X + \sigma\beta c_{12}R_{12}R_1 \\
&\quad -\sigma\beta(c_1S+(c_1-c_2)R_2)R_1, \\
\frac{dR_2}{dt} &= (m_2-R_2)\mu - (\tau_1+\gamma)R_2 + \beta(1-c_2)R_2X + \sigma\beta c_{12}R_{12}R_2 \\
&\quad -\sigma\beta(c_2S+(c_2-c_1)R_1)R_2, \\
\frac{dR_{12}}{dt} &= (m_{12}-R_{12})\mu - \gamma R_{12} + \beta(1-c_{12})R_{12}X - \sigma\beta c_{12}(S+(1-c_1)R_1+(1-c_2)R_2)R_{12}, \\
\frac{dX}{dt} &= (1-m-m_1-m_2-m_{12}-X)\mu + (\tau_1+\tau_2+\gamma)S + (\tau_2+\gamma)R_1 + (\tau_1+\gamma)R_2 \\
&\quad +\gamma R_{12} - \beta X(S+(1-c_1)R_1+(1-c_2)R_2+(1-c_{12})R_{12}).
\end{aligned} \tag{1}$$

This mathematical model tracks several patient populations throughout a hospital according to their colonization status, depicted in Figure 1. Is it important to note that the model excludes the actual development of resistance through mutation since we are interested primarily in the transmission dynamics between patients rather than the dynamics due to conjugation and mutation at the bacterial level. The state variables and parameters in the model are listed in Table 1. The X group represents the proportion of patients who are uncolonized by the bacterial species of interest. The term "uncolonized" is considered in an epidemiological context, including patients who harbor only a bacterial population too small to transmit to other patients, rendering patients more likely to be infected by new strains. The S group represents the proportion of patients colonized by the bacterial species of interest susceptible to both drugs.

There are three R groups, R_1, R_2, and R_{12}, representing patients colonized by strains resistant to drug 1, drug 2, and both drugs 1 and 2, respectively. To simplify the model, we assume that the total patient population size in the hospital remains constant such that the sum of the state variables X, S, R_1, R_2, and R_{12} is one. Patients enter the hospital in any of the states X, S, R_1, R_2, and R_{12} at rates μ(1 - m - m_1 - m_2 - m_{12}), μm, μm_1, μm_2, and μm_{12} per day. The parameter μ represents the patient turnover rate in the hospital. On average, patients leave the hospital after staying $1/\mu$ days. Patients colonized with susceptible bacteria and left untreated will remain colonized an average of $1/\gamma$ days. Drug 1 and drug 2 are used at rates τ_1 and τ_2. It is assumed that any bacterial strains without resistance to any of the drugs are cleared with drug use.

The colonization rate or primary transmission rate, proportional to the frequencies of each strain, is described using the rate constant β. The fitness costs to bacteria are described by c_1, c_2, and c_{12}, where a lower fitness cost corresponds to a strain that is easier to spread. Fitness cost is a biological parameter that describes the selective pressure exerted by antibiotics on a bacterial population. In the presence of antibiotics, the resistant bacteria are at an advantage, but the development of their resistance comes at a cost to fitness. In the absence of antibiotics,

the resistant bacteria are less fit, rendering them less able to reproduce, and thus the susceptible bacteria are at an advantage [22]. The fitness costs c_1 and c_2 are assumed to be equal for single resistant strains, and c_{12} is assumed to be greater as that the strain resistant to both drugs is more difficult to spread with a smaller initial population of patients infected with the dual-resistant strain.

The relative rate of secondary colonization to that of primary colonization is described by σ. In order to simplify the model, we assume that individuals can only be effectively colonized by one type of bacterium at a time. We also assume that the bacterial strains are in constant competition with one another and that secondary colonization can only occur by colonization with more fit strains. The parameter σ is multiplied by the fitness cost according to [21] since the fitness cost of the bacteria also affects secondary colonization. The parameter α represents physician compliance to an antibiotic therapy program and is equal to the fraction of patients receiving the currently indicated drug; this parameter will be used only in numerical simulations.

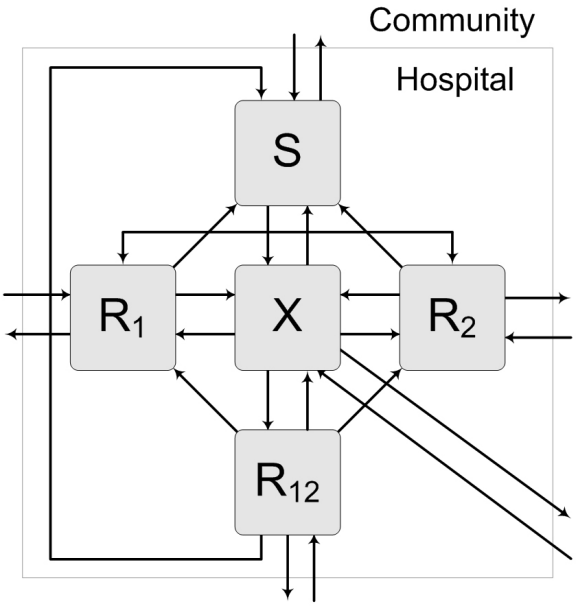

Figure 1: Schematic of the model incorporating dual resistance.

2.2 Equilibrium and Stability Analysis

The basic reproductive rate of susceptible bacteria in a hypothetical institution where all hosts entered uncolonized (X), or when $m = m_1 = m_2 = m_{12} = 0$, can be computed as

$$\Re_S = \frac{\beta}{\tau_1 + \tau_2 + \mu + \gamma}. \tag{2}$$

Similarly, let $\Re_{R_1}$, $\Re_{R_2}$, and $\Re_{R_{12}}$ denote the basic reproductive rates of bacteria resistant to drug 1, drug 2, and both drugs 1 and 2 in a hypothetical institution, respectively. We have

$$\Re_{R_1} = \frac{\beta(1 - c_1)}{\tau_2 + \mu + \gamma}, \tag{3}$$

Table 1: State variables and defined parameters of the mathematical model.

State Variable	Description
$S(t)$	Proportion of patients colonized by susceptible bacteria at time t
$R_1(t)$	Proportion of patients colonized by bacterial strain resistant to drug 1 at time t
$R_2(t)$	Proportion of patients colonized by bacterial strain resistant to drug 2 at time t
$R_{12}(t)$	Proportion of patients colonized by bacterial strain resistant to both drugs 1 and 2 at time t
$Q(t)$	Proportion of patients colonized with bacterial strain resistant to both drugs 1 and 2 in isolation at time t
$X(t)$	Proportion of patients uncolonized by the bacterial species of interest at time t

Parameter	Description	Value	Source
β	Per capita primary transmission rate (colonization rate)	1 day^{-1}	[21]
σ	Relative rate of secondary colonization to that of the primary colonization $\in (0, 1)$	0.25	[21]
τ_i	Per capita treatment rate of drug i, $i = 1, 2$	0.38 day^{-1}	
γ	Per capita clearance rate of bacteria due to immune response	0.03 day^{-1}	[6, 21]
μ	Per capita patient turnover rate in the hospital	0.10 day^{-1}	[6, 21]
m	Proportion of admitted patients already colonized with sensitive bacteria	0.70	[6, 21]
μm_i	Rate at which patients colonized by bacterial strains resistant to drug i enter the hospital	0-0.07 day^{-1}	[21]
c_i	Fitness cost of a bacterial strain resistant to drug i, $i = 1, 2$	0.05	
c_{12}	Fitness cost of a bacterial strain resistant to both drugs 1 and 2	0.15	
α	Physician compliance, fraction of patients receiving the currently indicated drug in a cycling program	0.80	[21]
η	Per capita isolation rate of patients colonized by bacterial strains resistant to both drugs 1 and 2	0.01-0.025 day^{-1}	
ϵ	Effectiveness of isolation, fraction of patients perfectly isolated	0.5-1	[23]

$$\Re_{R_2} = \frac{\beta(1-c_2)}{\tau_1+\mu+\gamma}, \tag{4}$$

$$\Re_{R_{12}} = \frac{\beta(1-c_{12})}{\mu+\gamma}. \tag{5}$$

If $m_i \neq 0$ for $i = 1, 2$, then patients colonized with bacteria resistant to drug i are always present because they are constantly entering the hospital. Similarly, patients colonized with bacteria resistant to both drugs 1 and 2 are always present if $m_{12} \neq 0$. However, since drug-resistant bacteria are less common in developed countries such as the U.S., m_1, m_2 and m_{12} are very small, and we can assume that $m_1 = m_2 = m_{12} = 0$. The total population size in the hospital is constant, where $S + R_1 + R_2 + R_{12} + X = 1$. Since the population is constant, System 1 can be reduced to four-dimensions. Hence, we only need to study the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= (m-S)\mu - (\tau_1+\tau_2+\gamma)S + \sigma\beta(c_1R_1 + c_2R_2 + c_{12}R_{12})S \\
&\quad +\beta S(1-S-R_1-R_2-R_{12}), \\
\frac{dR_1}{dt} &= -R_1\mu - (\tau_2+\gamma)R_1 + \beta(1-c_1)R_1(1-S-R_1-R_2-R_{12}) + \sigma\beta c_{12}R_{12}R_1 \\
&\quad -\sigma\beta(c_1S + (c_1-c_2)R_2)R_1, \\
\frac{dR_2}{dt} &= -R_2\mu - (\tau_1+\gamma)R_2 + \beta(1-c_2)R_2(1-S-R_1-R_2-R_{12}) + \sigma\beta c_{12}R_{12}R_2 \\
&\quad -\sigma\beta(c_2S + (c_2-c_1)R_1)R_2, \\
\frac{dR_{12}}{dt} &= -R_{12}\mu - \gamma R_{12} + \beta(1-c_{12})R_{12}(1-S-R_1-R_2-R_{12}) \\
&\quad -\sigma\beta c_{12}(S + (1-c_1)R_1 + (1-c_2)R_2)R_{12}
\end{aligned} \tag{6}$$

There is no disease-free equilibrium because $m > 0$. One of the boundary equilibria is $E_0 = (S^*, 0, 0, 0)$, with

$$S^* = \frac{\beta - (\mu+\tau_1+\tau_2+\gamma) + \sqrt{(\mu+\tau_1+\tau_2+\gamma-\beta)^2 + 4m\beta\mu}}{2\beta}. \tag{7}$$

The Jacobian at E_0 can be computed as follows

$$J_0 = \begin{pmatrix} \beta-(\mu+\tau_1+\tau_2+\gamma)-2\beta S^* & \sigma\beta c_1S^* - \beta S^* & \sigma\beta c_2S^* - \beta S^* & \sigma\beta c_{12}S^* - \beta S^* \\ 0 & J_0(2,2) & 0 & 0 \\ 0 & 0 & J_0(3,3) & 0 \\ 0 & 0 & 0 & J_0(4,4) \end{pmatrix}, \tag{8}$$

where

$$J_0(2,2) = \beta(1-c_1)(1-S^*) - \sigma c_1 \beta S^* - \mu - \gamma - \tau_2,$$
$$J_0(3,3) = \beta(1-c_2)(1-S^*) - \sigma c_2 \beta S^* - \mu - \gamma - \tau_1,$$
$$J_0(4,4) = \beta(1-c_{12})(1-S^*) - \sigma c_{12} \beta S^* - \mu - \gamma.$$

We know that E_0 is locally asymptotically stable if and only if all eigenvalues of the matrix J_0 have a negative real part [20]. Since J_0 is an upper triangular matrix, it is easy to obtain the eigenvalues of J_0, namely

$$\lambda_{01} = \beta - (\mu + \tau_1 + \tau_2 + \gamma) - 2\beta S^*,$$
$$\lambda_{02} = J_0(2,2) = \beta(1-c_1)(1-S^*) - \sigma c_1 \beta S^* - \mu - \gamma - \tau_2,$$
$$\lambda_{03} = J_0(3,3) = \beta(1-c_2)(1-S^*) - \sigma c_2 \beta S^* - \mu - \gamma - \tau_1,$$
$$\lambda_{04} = J_0(4,4) = \beta(1-c_{12})(1-S^*) - \sigma c_{12} \beta S^* - \mu - \gamma.$$

Since

$$\begin{aligned}\lambda_{01} &= \beta - (\mu + \tau_1 + \tau_2 + \gamma) - [\beta - (\mu + \tau_1 + \tau_2 + \gamma) + \sqrt{(\mu + \tau_1 + \tau_2 + \gamma - \beta)^2 + 4m\beta\mu}] \\ &= -\sqrt{(\mu + \tau_1 + \tau_2 + \gamma - \beta)^2 + 4m\beta\mu} < 0,\end{aligned}$$

we only need to make $\lambda_{02} < 0,\ \lambda_{03} < 0,\ \lambda_{04} < 0$ in order to guarantee the local stability of E_0. Notice that

$$\begin{aligned}\lambda_{02} < 0 &\Leftrightarrow \beta(1-c_1)(1-S^*) < \sigma c_1 \beta S^* + \mu + \gamma + \tau_2 \\ &\Leftrightarrow \frac{\beta(1-c_1)(1-S^*)}{\mu + \gamma + \tau_2} < \frac{\sigma c_1 \beta S^*}{\mu + \gamma + \tau_2} + 1 \\ &\Leftrightarrow \Re_{R_1} < \frac{\sigma c_1 \beta S^*}{(1-S^*)(\mu + \gamma + \tau_2)} + \frac{1}{1-S^*}.\end{aligned} \tag{9}$$

This can also be expressed as

$$\lambda_{02} < 0 \Leftrightarrow [(1-S^*) - \sigma S^* \frac{c_1}{1-c_1}]\Re_{R_1} < 1 \tag{10}$$

where $(1-S^*)$ is the proportion available for primary colonization at E_0 and $\sigma S^* \frac{c_1}{1-c_1}$ is the proportion of R_1 infections recolonized by S^* bacteria at E_0. The difference of these two terms is the reduction factor in the transmission of R_1 at E_0 due to established S-type colonizations.

Similarly, we can derive the following inequalities from $\lambda_{03} < 0$ and $\lambda_{04} < 0$, respectively, such that

$$\lambda_{03} < 0 \Leftrightarrow \Re_{R_2} < \frac{\sigma c_2 \beta S^*}{(1-S^*)(\mu + \gamma + \tau_1)} + \frac{1}{1-S^*} \tag{11}$$

$$\Leftrightarrow [(1-S^*) - \sigma S^* \frac{c_2}{1-c_2}]\Re_{R_2} < 1, \tag{12}$$

$$\lambda_{04} < 0 \Leftrightarrow \Re_{R_{12}} < \frac{\sigma c_{12}\beta S^*}{(1-S^*)(\mu+\gamma)} + \frac{1}{1-S^*} \tag{13}$$

$$\Leftrightarrow [(1-S^*) - \sigma S^* \frac{c_{12}}{1-c_{12}}]\Re_{R_{12}} < 1. \tag{14}$$

Therefore, we have the following:

Theorem $E_0 = (S^*, 0, 0, 0)$ *is locally asymptotically stable if and only if the following holds*

$$R^S = \max([(1-S^*)-\sigma S^* \frac{c_1}{1-c_1}]\Re_{R_1}, [(1-S^*)-\sigma S^* \frac{c_2}{1-c_2}]\Re_{R_2}, [(1-S^*)-\sigma S^* \frac{c_{12}}{1-c_{12}}]\Re_{R_{12}}) \tag{15}$$

where

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

When $R^S < 1$, then $\Re_{R_1}, \Re_{R_2}, \Re_{R_{12}} < 1$. Since we are studying the persistence of resistant strains, this is the equilibrium of interest.

3 Comparison of Antimicrobial Cycling and Mixing Programs Through Simulation of the Model

Further analysis of the model through numerical simulation provides useful predictions on the effects of policies for antibiotic usage in hospitals. In this paper, we focus on the effects of antimicrobial cycling programs relative to mixing regimes, with further assessment of the impact of physician compliance and isolation interventions. In order to assess the impact due to different usage policies, the equations in System 1 were simulated using MATLAB® with appropriate parameter values for each condition.

3.1 Determination of the Parameters

The mathematical model presented in this paper tracks several patient populations throughout a hospital according to their colonization status. The parameter values used in the simulations are shown in Table 1 and are either determined from previous work [6, 21, 23] or selected to demonstrate the effects of dual-resistance by considering their effects on the reproductive numbers for each patient group. If the basic reproductive number $\Re_S < 1$, the disease will die out; if $\Re_S > 1$, the disease will be endemic [20]. For the purposes of modeling a situation where susceptible bacteria remain in an institution, it is assumed that $\Re_S > 1$ in order to ensure their endemicity.

3.2 Antimicrobial Cycling Programs

An antimicrobial cycling program alternates empiric classes of antibiotics over a given span of time in an attempt to control the spread of resistant bacteria in a hospital. The mathematical model is simulated in an antimicrobial cycling program to show the consequences of the spreading of dual-resistant bacteria in a hospital setting. By incorporating the presence and spread of dual-resistant pathogens, as our model does, we show that dual resistance has a significant effect and should be considered when developing a strategy to curtail resistance in hospitals.

We compare our simulation results with a mathematical model previously developed by Bergstrom *et al.* [21] to explore the efficacy of cycling programs. Although the previous model accounts for many features of hospital-acquired infections by considering two antimicrobial drugs, the authors focused solely on single resistance, assuming in the model that dual resistance had not yet emerged or appeared. The model addresses the *emergence* of dual resistance, but it does not incorporate spreading or dynamics of dual-resistant bacteria in the hospital [21].

The model presented in this paper builds upon the previous model but is still focused on examining the efficacy of cycling programs. However, our model assumes that dual resistance is already present in the hospital, thus considering the effect of spreading dual-resistant bacteria among patients. In fact, Bergstrom *et al.* [21] stated that multiple resistance is common in hospital wards, especially in ICUs. They argued, however, that the dual-resistant strain is impervious to the use of antibiotics regardless of the cycling and mixing policies. We show that dual resistance does indeed produce bacteria with greater defenses against antimicrobials, but instituting a particular usage policy or taking into account different levels of physician compliance can result in controlled levels of dual resistance.

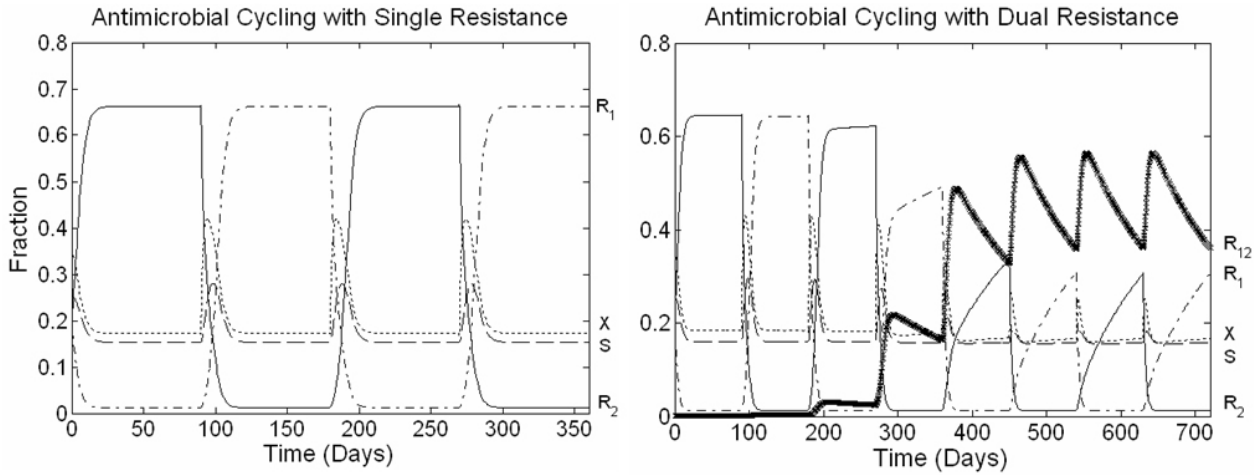

Figure 2: LEFT: Antibiotic cycling program with single resistance, as developed by Bergstrom *et al.* Strain frequencies over time for a cycling program with a drug switch every 90 days and 80% physician compliance ($\alpha = 0.8$). Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0$; $c_1 = 0$; $c_2 = 0$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; $\gamma = 0.03$; and $\alpha = 0.8$ [21]. RIGHT: Antibiotic cycling program incorporating dual resistance. Strain frequencies over time for a cycling program with a drug switch every 90 days and 80% physician compliance ($\alpha = 0.8$). Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0$; $c_1 = 0.05$; $c_2 = 0.05$; $c_{12} = 0.15$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; $\gamma = 0.03$; and $\alpha = 0.8$.

The plot on the left of Figure 2 shows the strain frequencies over time for a cycling program with a drug switch every 90 days and 80% physician compliance as developed by Bergstrom *et al.* Instituting a new drug results in the climbing frequency of the strain resistant to that drug and declining frequency of the strain resistance to the unused drug. After switching, strains resistant to the newly instituted drug are rare, resulting in the new antibiotic being temporarily more effective than usual. This is apparent in the brief upward surge in the fraction of uncolonized patients

immediately after each switch [21].

Incorporation of dual resistance in the model in System 1 also demonstrates that the cyclic use of antibiotics results in a cyclic incidence of strain frequencies upon numerical simulation, as shown in the plot on the right of Figure 2. A low R_{12} population is maintained for nearly one year before rapidly increasing and then stabilizing at a fraction of approximately 0.45. As the population of R_{12} rapidly increases, R_1 and R_2 decrease and level out at an average fraction significantly lower than that of the strain resistant to both drugs. Additionally, after each drug switch, the curve representing the fraction of uncolonized patients X exhibits a brief upward surge.

Figure 3 shows various combinations of resistant cases when cycling occurs with periods of 365, 90, and 14 days. As the cycling period decreases, the levels of total patients carrying resistant bacteria remains relatively consistent. Regardless of cycling period length, the fraction of patients colonized by R_{12} remains higher than the sum total of R_1 and R_2, with total resistance levels reaching upwards of 0.7. At each drug switch, R_{12} surges upward while R_1+R_2 drops downward, indicating that the drug switch causes the R_1+R_2 to dip temporarily in population size since either R_1 or R_2 is treated with the drug. The clearance of one of the drug-resistant strains gives a brief competitive advantage to R_{12}, allowing it to thrive in the presence of a drug switch.

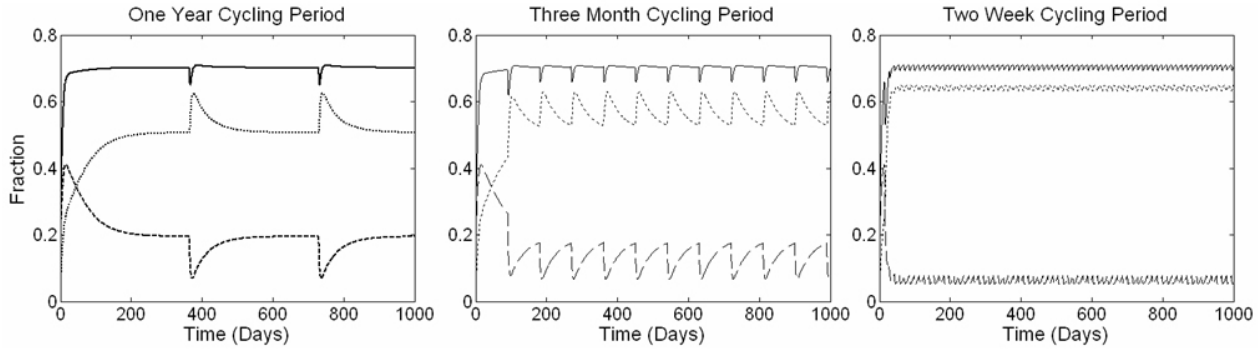

Figure 3: Fraction of patients carrying resistant bacteria for cycle lengths of 1 year (left), 3 months (center), and 2 weeks (right). The solid line indicates $R_1 + R_2 + R_{12}$, the total fraction of patients colonized with resistant bacteria under cycling; the dotted line indicates R_{12}, the fraction of patients colonized with dual-resistant bacteria under cycling; and the dashed line indicates $R_1 + R_2$, the total fraction of patients colonized with single-resistant bacteria under cycling. Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0$; $c_1 = 0.05$; $c_2 = 0.05$; $c_{12} = 0.15$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; $\gamma = 0.03$; and $\alpha = 0.8$.

Figure 4 shows the averaged total fraction of patients uncolonized or colonized by the bacterial strain of interest over a span of one year with cycling. Initially, both the susceptible and uncolonized fractions of patients drop, while the bacteria resistant to drug 2 and both drugs thrive. As time progresses, the bacteria resistant only to drug 2 fall into stable oscillation with those resistant only to drug 1, while the bacteria resistant to both drugs 1 and 2 rise steadily to oscillate around a fraction of 0.57 with a cycling regime.

Priorities must be taken into account when deciding an appropriate antimicrobial usage program. If curbing dual resistance is a greater concern, then a cycling program should be seriously considered. However, if it would benefit more patients to control both single-resistant strains, then

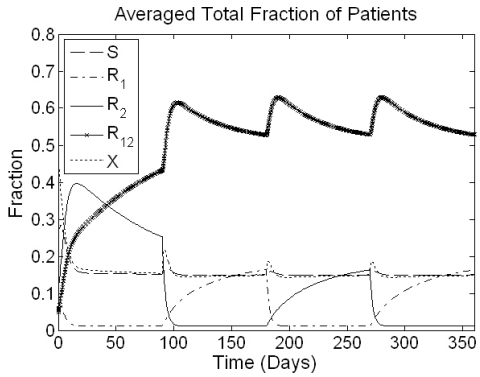

Figure 4: Averaged fractions of patients colonized or uncolonized by bacteria. Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0.02$; $c_1 = 0.05$; $c_2 = 0.05$; $c_{12} = 0.1$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; $\gamma = 0.03$; and $\alpha = 0.8$.

a mixing protocol may be most appropriate.

3.3 Antimicrobial Mixing Programs

In order to determine whether cycling is an effective strategy for reducing the spread of antibiotic-resistant bacteria, a cycling protocol is compared to an alternative program: a random mixing regime. Mixing is the random prescription of drug 1 to half the treated patients and drug 2 to the other patients receiving treatment. This assumes that mixing is a reasonable approximation of current antibiotic usage habits in most hospitals; thus, it can serve as a reference against which cycling can be compared.

Figure 5 shows the long-term mixing program in the total resistant populations. A mixing program would result in high fraction levels of $R_1 + R_2 + R_{12}$ and R_{12} and very low $R_1 + R_2$ levels. Mixing refers to the random prescribing of antimicrobials; if our assumption is that dual resistance is already present in the hospital, dual-resistant bacteria would thrive in an environment where mixing was the primary antimicrobial usage protocol since they would always be resistant to any drug currently being used. The total resistance curve, or patients colonized with resistant bacteria, stabilizes at a fraction of approximately 0.7. Patients colonized with R_{12} are significantly higher fraction than patients colonized with either R_1 or R_2, again reinforcing the impact of dual resistance.

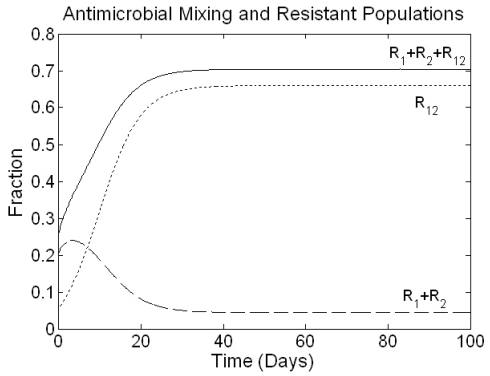

Figure 5: Fraction of patients in a hospital under an antimicrobial mixing regime for the population of patients carrying resistant bacteria. The solid line indicates $R_1 + R_2 + R_{12}$, the dotted line indicates R_{12}, and the dashed line indicates $R_1 + R_2$. Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0.02$; $c_1 = 0.05$; $c_2 = 0.05$; $c_{12} = 0.1$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; $\gamma = 0.03$; $\alpha = 0.8$; $\tau_1 = 0$; and $\tau_2 = 0$.

3.4 Comparison of Cycling and Mixing Programs

Numerical simulations of our model suggest that cycling programs are more effective at reducing dual resistance than mixing programs. Figure 6 compares the cycling and mixing protocols for the fraction of patients colonized with bacteria resistant to both drug 1 and drug 2 for cycling periods of 1 year, 3 months, and 2 weeks. As the cycling period length decreases, the difference between cycling and mixing becomes smaller since a cycling period of zero would basically be a mixing program; thus, the smaller the period, the closer cycling becomes to mixing. Either way, cycling seems to outperform mixing in every case, regardless of cycling period length.

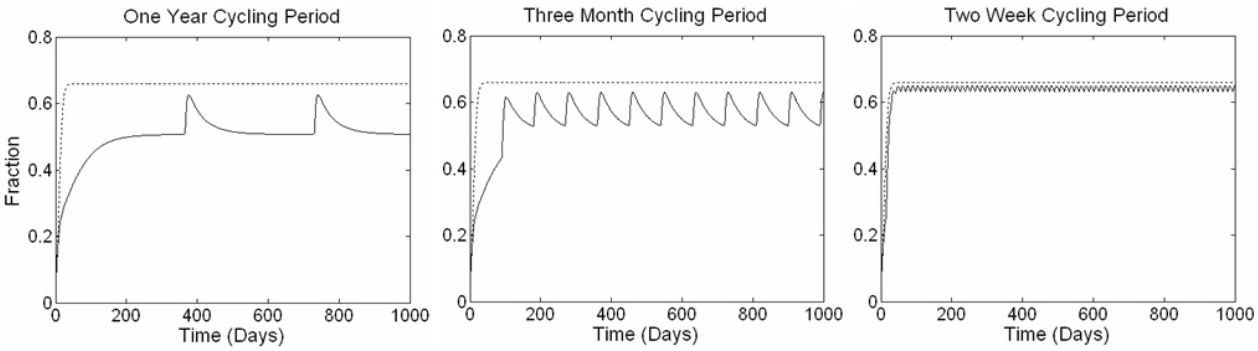

Figure 6: Fraction of patients carrying only dual-resistant bacteria R_{12} for cycle lengths of 1 year (left), 3 months (center), and 2 weeks (right). The solid lines indicate the total fraction of patients colonized with dual-resistant bacteria under cycling, and the dashed lines indicate the total fraction of patients colonized with dual-resistant bacteria under a 50-50 mixing regime. Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0$; $c_1 = 0.05$; $c_2 = 0.05$; $c_{12} = 0.15$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; $\gamma = 0.03$; and $\alpha = 0.8$.

Figure 7 compares cycling and mixing for single resistance versus total resistance (i.e. including R_{12}) for cycling period lengths of 1 year, 3 months, and 2 weeks. The total resistance as a result of both cycling and mixing remain at relatively a similar fraction level of approximately 0.7. This is significantly higher than that of just R_1+R_2 and is the case for each cycling period length. These results further suggest that dual-resistance has a great impact on the fraction of patients colonized by any resistant bacteria.

Figure 8 shows the fraction of patients colonized by resistant bacteria over the span of one year as a function of cycle period averaged over 1000 days. As cycle period length increases, the fraction of infected patients $R_1 + R_2$ under the cycling program increases, resulting in approximately a 15% increase. For the fraction of patients colonized by dual-resistant bacteria, the simulation results are opposite from R_1+R_2, clearly demonstrating an advantage to using a cycling program rather than a mixing program when attempting to reduce dual resistance in hospitals. Finally, as the cycle period length increases, the curve representing the fraction of patients colonized with total resistance under a cycling program is slightly lower than that under a mixing program. Generally, if curbing dual resistance is of greater concern in the hospital, then a cycling program should be used; however, if the priority is to first help patients suffering from single-resistant bacterial infections, then a mixing protocol would be best.

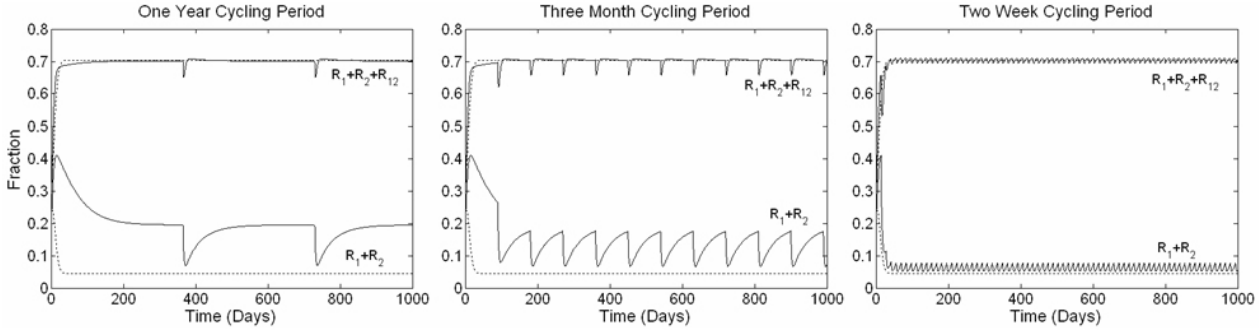

Figure 7: Fraction of patients carrying resistant bacteria for cycle lengths of 1 year (left), 3 months (center), 2 weeks (right). The solid lines indicate the total fraction of patients colonized with resistant bacteria under cycling, and the dashed lines indicate the total fraction of patients colonized with resistant bacteria under a 50-50 mixing regime. Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0$; $c_1 = 0.05$; $c_2 = 0.05$; $c_{12} = 0.15$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; $\gamma = 0.03$; and $\alpha = 0.8$.

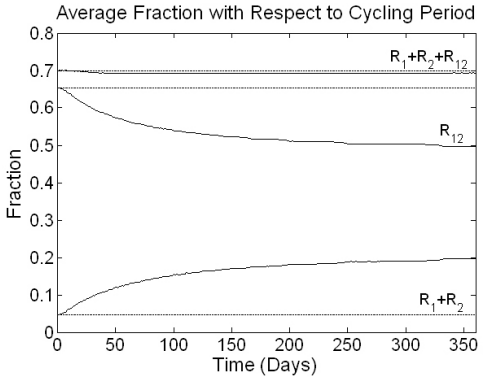

Figure 8: Average fractions of patients colonized by resistant bacteria as a function of cycle period. The dashed line indicates a mixing program, and the solid line indicates a cycling program. Parameter values are as in Table 1.

3.5 Physician Compliance

Physician compliance is an important factor in evaluating antimicrobial cycling programs. Compliance is described as the fraction of patients that receive the currently indicated drug. When $\alpha = 1$, all patients are receiving the currently indicated drug, and when $\alpha = 0$, half of the patients receive drug 1 while the other half receives drug 2.

The plot on the left of Figure 9 shows the effect of varying physician compliance α on patients colonized by bacteria resistant to either drug 1 or drug 2 over two years. The level of physician compliance results in a dramatic shift in resistance. Interestingly, resistance levels increase when physicians are more compliant with the cycling program. As previously stated, when α is zero, half of the patients receive drug 1 while the other half receives drug 2. It then makes sense that a lower compliance level closer to zero in a cycling program essentially becomes a mixing program, which is 50-50 by nature. Thus, by administering each drug to half the population, rather than one drug at any given time, more of the R_1+R_2 population benefits.

The plot in the center of Figure 9 shows the effect of varying physician compliance α on patients colonized by bacteria resistant to both drugs 1 and 2. As expected, lower compliance resulted in relatively stable and low fitness cost. This means that these dual-resistant strains are able to more easily spread at lower physician compliances. Again, this reinforces the idea that a cycling program is more effective in reducing dual resistance. Thus, greater compliance to a cycling program limits the spread of dual resistance.

The plot on the right of Figure 9 shows the effect of varying physician compliance α on total resistance in the hospital. Increasing compliance results in slightly increased resistance levels. The curves seem to converge, where 90% compliance results in the highest fraction approaching 0.7. With regards to total resistance, physician compliance with a cycling program does not result in a dramatic shift in the number of patients colonized with resistance in the hospital.

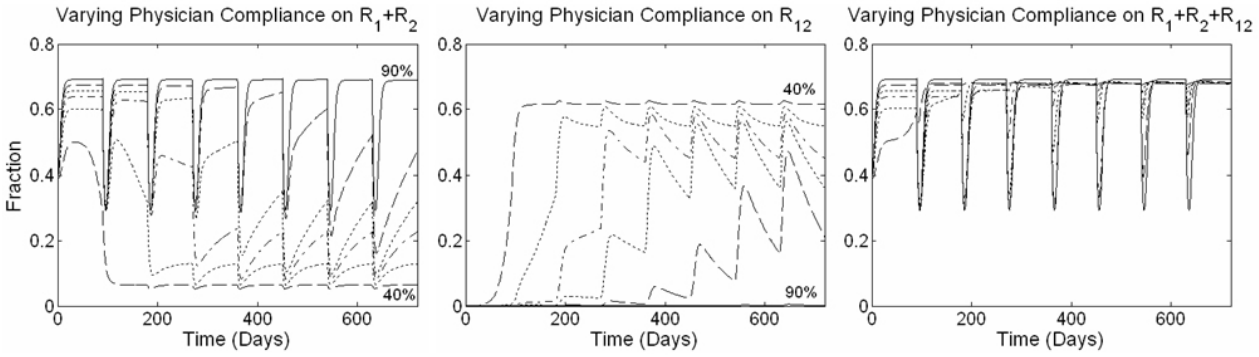

Figure 9: The effect of varying physician compliance α on $R_1 + R_2$ (left), R_{12} (center), and $R_1 + R_2 + R_{12}$ (right). Physician compliance was varied from 40-90% to compare the long-term effects of low compliance versus high compliance over two years. Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0$; $c_1 = 0.05$; $c_2 = 0.05$; $c_{12} = 0.15$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; and $\gamma = 0.03$.

4 Isolation of Patients with Dual-Resistant Strains

Since nosocomial transmission of antibiotic-resistant bacterial strains is driven by contact with patients in the hospital, an intervention of interest is the isolation of infected patients. Essentially, identified carriers of resistant bacteria can be treated in single rooms with barrier precautions [24] to restrict contact with the rest of the patient population in the hospital. With the addition of a new class of isolated individuals Q and the assumption that infected patients are not entering the hospital from the outside community, the mathematical model is updated to include the following system of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= (m-S)\mu - (\tau_1+\tau_2+\gamma)S + \sigma\beta(c_1\tfrac{R_1}{1-\epsilon Q} + c_2\tfrac{R_2}{1-\epsilon Q} + c_{12}\tfrac{R_{12}+(1-\epsilon)Q}{1-\epsilon Q})S + \beta S\tfrac{X}{1-\epsilon Q},\\
\frac{dR_1}{dt} &= (m_1-R_1)\mu - (\tau_2+\gamma)R_1 + \beta(1-c_1)R_1\tfrac{X}{1-\epsilon Q} + \sigma\beta c_{12}\tfrac{R_{12}+(1-\epsilon)Q}{1-\epsilon Q}R_1\\
&\quad -\sigma\beta(c_1\tfrac{S}{1-\epsilon Q} + (c_1-c_2)\tfrac{R_2}{1-\epsilon Q})R_1,\\
\frac{dR_2}{dt} &= (m_2-R_2)\mu - (\tau_1+\gamma)R_2 + \beta(1-c_2)R_2\tfrac{X}{1-\epsilon Q} + \sigma\beta c_{12}\tfrac{R_{12}+(1-\epsilon)Q}{1-\epsilon Q}R_2\\
&\quad -\sigma\beta(c_2\tfrac{S}{1-\epsilon Q} + (c_2-c_1)\tfrac{R_1}{1-\epsilon Q})R_2,\\
\frac{dR_{12}}{dt} &= (m_{12}-R_{12})\mu - \eta R_{12} - \gamma R_{12} + \beta(1-c_{12})(R_{12}+(1-\epsilon)Q)\tfrac{X}{1-\epsilon Q}\\
&\quad -\sigma\beta c_{12}(\tfrac{S+(1-c_1)R_1+(1-c_2)R_2}{1-\epsilon Q})R_{12},\\
\frac{dQ}{dt} &= -\mu Q + \eta R_{12} - \sigma\beta c_{12}(\tfrac{S+(1-c_1)R_1+(1-c_2)R_2}{1-\epsilon Q})((1-\epsilon)Q),\\
\frac{dX}{dt} &= (1-m-m_1-m_2-m_{12}-X)\mu + (\tau_1+\tau_2+\gamma)S + (\tau_2+\gamma)R_1 + (\tau_1+\gamma)R_2\\
&\quad +\gamma R_{12} - \beta X(\tfrac{S}{1-\epsilon Q} + (1-c_1)\tfrac{R_1}{1-\epsilon Q} + (1-c_2)\tfrac{R_2}{1-\epsilon Q} + (1-c_{12})\tfrac{R_{12}+(1-\epsilon)Q}{1-\epsilon Q}).
\end{aligned} \tag{16}$$

This model incorporates an isolation class Q, where the isolation rate is η and the efficacy of isolation is ϵ. Patients who are identified to have dual-resistant strains are isolated within the hospital, thus reducing the overall population subject to the transmission rate β. Following standard incidence for dynamic models [25], the proportion of patients changes with ϵ since isolated individuals are no longer included in the adjusted population subject to patient contact. Additionally, leakage from Q into other compartments may occur if patients are not entirely effectively isolated. This is accounted for through the factor $(1-\epsilon)$, such that an isolation program that is 100% effective will entirely eliminate the Q class from contact with the rest of the patient population. From isolation, patients can be treated and discharged directly out of the hospital. The schematic diagram in Figure 10 reflects the incorporation of an isolation class. The impact of an isolation program on patients undergoing an antimicrobial cycling program is determined through simulation.

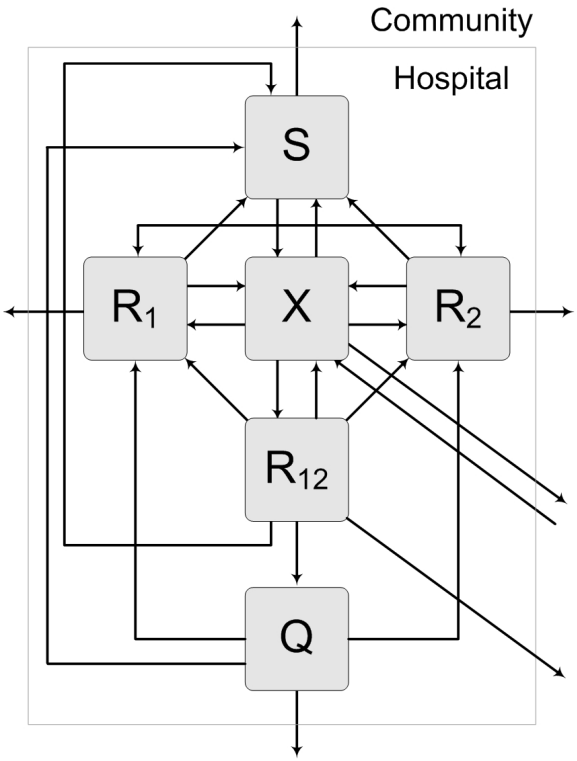

Figure 10: Schematic of the model incorporating isolation of patients with the dual-resistant strain.

4.1 Efficacy of Isolation Through Numerical Simulation of the Model

Isolation of patients colonized with the dual-resistant strain in the hospital is a possible intervention for controlling transmission by limiting patient contact. Numerical simulation of the model incorporating isolation in System 16 resulted in Figure 11, where efficacy of isolation ϵ was held constant at 90% and isolation rate η was varied from 0.01 to 0.025. This was done to examine the effects of varying the rate of isolation on the overall population of patients harboring resistant bacteria in the hospital.

As the isolation rate η increased, the isolation Q class increased, and the R_{12} proportion of the population decreased. Although the dual-resistant class is reduced as a result of increased isolation rate, the single-resistant classes R_1 and R_2 significantly increase. Since the total population of patients in the hospital remains constant, where the sum of the patient proportions equal one, the bacterial strains are constantly in competition with each other; therefore, a decrease in dual-resistant strains results in an increase in single-resistant strains. As the isolation rate increases, the proportion R_{12} is reduced, and thus the hospital population consists of more single resistance, where R_1 and R_2 are more inclined to flourish in a cycling regime.

To examine the effects of varying isolation efficacy, η was held constant at 0.025 while ϵ was varied between 50%, 90%, and 100%. The results of the simulation are shown in Figure 12. The efficacy of isolation significantly affects the outcome of the persistence of the R_{12} population; as ϵ increased, both Q and R_{12} decreased. The more effectively isolated the patients are, the lower

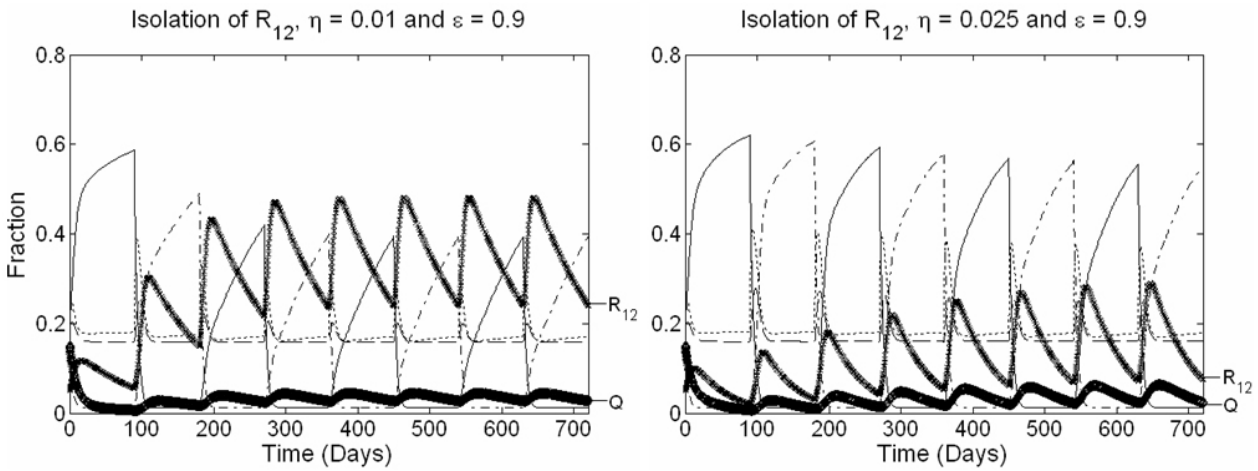

Figure 11: The effect of varying isolation rate η on fraction of patients colonized with dual-resistant bacteria. Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0$; $c_1 = 0.05$; $c_2 = 0.05$; $c_{12} = 0.15$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; $\gamma = 0.03$; $\eta = 0.01$, 0.025; and $\epsilon = 0.9$.

the levels of R_{12} are, and the higher the single-resistant populations R_1 and R_2 become. At 25% efficacy of isolation, R_{12} is controlled but still maintains a fairly high fraction level of around 0.3, outcompeting the single-resistant populations. At 100% efficacy of isolation, the R_{12} population is controlled and maintained at a modest fraction level of less than 0.1.

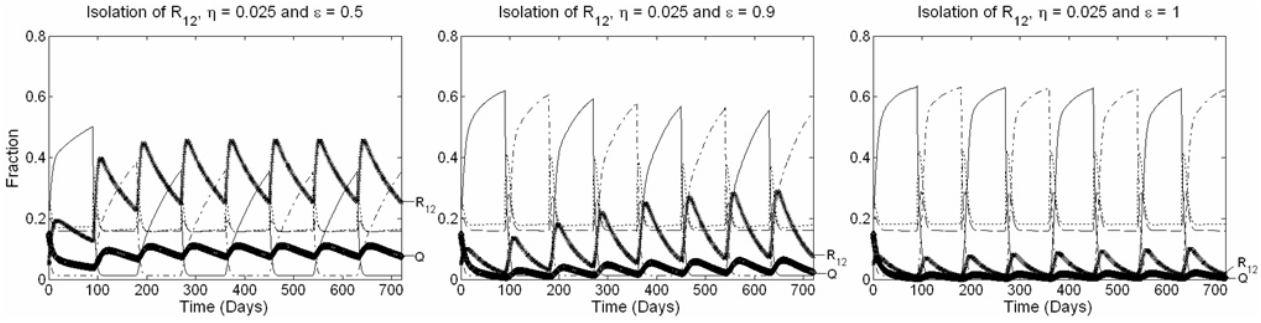

Figure 12: The effect of varying isolation efficacy ϵ on fraction of patients colonized with dual-resistant bacteria. Parameter values: $m = 0.7$; $m_1 = 0.05$; $m_2 = 0.05$; $m_{12} = 0$; $c_1 = 0.05$; $c_2 = 0.05$; $c_{12} = 0.15$; $\beta = 1$; $\mu = 0.1$; $\sigma = 0.25$; $\gamma = 0.03$; $\eta = 0.025$; and $\epsilon = 0.5$, 0.9, 1.

According to our revised model, which incorporates isolation of R_{12}, both isolation rate and isolation efficacy are significant factors to consider when implementing an isolation program. Isolation appears to be a potentially effective intervention technique for controlling and maintaining lower levels of dual resistance in a hospital.

5 Discussion

The basis of cycling is in the fluctuating selection pressures induced by regularly switching antimicrobials, thereby reducing the rate of bacterial adaptation through variations in its habitat and landscape changes generated by an evolving population. By varying the currently indicated antimicrobial drug in a hospital ward such as the ICU, the emergence of antibiotic resistance can be minimized because pathogenic organisms would become continually exposed to varying environments, consequently limiting their ability to quickly adapt and develop resistance.

However, as Bergstrom *et al.* previously discussed, the scale of heterogeneity of bacterial clones in a hospital must be considered in order to assess the impact of mixing and cycling on levels of resistance. At a scale appropriate for bacterial populations, mixing likely induces greater fluctuation than cycling in selective conditions, since mixing results in continual fluctuations over shorter periods of time, while cycling offers consistent selective conditions for an extended period of time [21].

Our model investigates cycling versus mixing antimicrobial usage policies in a hospital setting by incorporating transmission of dual resistance, resulting in a model that can describe a more realistic situation: the threat of multiple-resistant pathogens in an era where only so many classes of antibiotics are available for treating patients. Previous work assumed that dual resistance had not yet emerged and therefore did not consider the dynamics of transmission of resistance to both drugs. Our model assumes that dual resistance is already present in the hospital, making it possible to consider the effects of spreading.

Numerical simulations of our model clearly demonstrate the significant impact that dual-resistant strains have on an antimicrobial cycling program in a contained hospital setting. It was evident, as expected, that cycling of antimicrobial therapies results in a cyclic incidence of strain frequencies. Just after switching drugs, the fraction of uncolonized patients surges upward, demonstrating a temporary effectiveness of the antibiotic therapy; this, however, diminishes over time, as do fractions of patients resistant to only a single drug. After a year of a 90-day cycling program at 80% physician compliance, the number of patients colonized with the strain resistant to both drugs dramatically and rapidly increases, persisting as the highest fraction level of patients.

Our model demonstrates that the fraction of patients colonized by strains resistant to both drugs remains highest regardless of cycling period length. Also, each switch of the drug causes a brief increase in the R_{12} and a comparable decrease in $R_1 + R_2$; the discrepancy between the two populations increases with smaller cycle period length. The total resistance levels remain relatively constant regardless of the length of cycle period, as indicated in Figure 3.

Current practices in prescribing antibiotic therapies are approximated to be essentially random mixing. Our model simulated a mixing regime under the assumption that dual resistance is already present in the hospital. Since mixing implies the usage of both drugs 1 and 2 at the same time, part of the strains that are resistant to only one drug are still targeted, whereas the strain resistant to both is able to thrive. Simulated results show R_{12} clearly dominating at a high fraction throughout any cycling or mixing program, where mixing seems to result in a higher fraction of patients infected with the dual-resistant strain than longer cycling time period lengths.

Another simulation was run to show the different outcomes when varying physician compliance. There is great variation in the rate of increase in patients acquiring dual-resistant bacteria, with a threshold value somewhere in between 85-90% compliance. At 90% physician compliance, as shown in Figure 9, there is only a slight oscillation of R_{12} close to a fraction of zero. It is expected that higher physician compliance would result in a lower fraction of patients colonized with resistant

bacteria, but it is interesting to note the wide range of fractions as a result of varying physician compliance. It is also interesting to note that the results are the opposite for R_1+R_2, meaning that higher compliance with a cycling program is not effective in curbing single resistance, since mixing would be the more useful protocol in that case.

Physician compliance is particularly important when studying antibiotic resistance in developing countries. In many developing countries, several factors contribute to the development and pervasiveness of antibiotic resistance, including a lack of regulation on drugs, quality control, patient access to quality health care, patient non-compliance and self medication, lack of reliable information sources for physicians, and physician misuse of antibiotics. When a patient needs antibiotics, physicians have a choice of which antibiotic(s) to prescribe. However, especially in developing countries, physicians tend to be overworked, underinformed, and pressured to prescribe certain treatments based on availability or cost [26]. Even in developed countries, physicians still face pressure from pharmaceutical companies or even the patients themselves to prescribe certain drugs. Thus, when evaluating the effects of an antimicrobial usage policy, it is important to consider the effects of varying physician compliance.

The potential impact of an isolation protocol was also considered in this paper, and the model was revised to incorporate an isolation compartment where the R_{12} class is subject to removal from the contact population. By increasing the rate of isolation η in an antimicrobial cycling program, the proportion of patients colonized with dual-resistant bacterial strains was significantly reduced. Consequently, the proportion of patients colonized with single-resistant bacteria increased. Additionally, an increase in isolation efficacy ϵ was shown to have a significant impact on maintaining lower levels of R_{12} in the hospital, again at the cost of higher levels of R_1 and R_2.

These results further demonstrate the importance of establishing priorities when it comes to treating antibiotic resistance in hospitals. Since dual-resistant bacteria are untreatable by the two drugs available in this particular model, it would likely be most advantageous to isolate patients with dual-resistant bacteria, even at the cost of a rise in single resistance. It is also important to keep in mind that the effectiveness of an isolation program depends on the timely detection of patients eligible for isolation. Rapid diagnostic testing of those suspected to be infected with the dual-resistant strain is necessary. Also, a major problem with nosocomial infections is asymptomatic carriers. Patients entering the hospital may be colonized but unaware of their infectiousness, making it difficult for the patient to be admitted into isolation. An effective patient isolation program must consider these issues.

The bottom line, evident throughout this investigation, is that dual resistance simply cannot be ignored. In our model, R_1+R_2 and R_{12} are competing over the susceptible population. Controlling dual resistance is more significant in this day and age since we face a limited supply of antibiotics; outbreaks of pathogens resisted to multiple antibiotics could cause a significant amount of damage, especially to the health and lives of fragile patients as in the ICU. The current mixing policy is not a bad idea, however, as it seems to have a positive effect in reducing resistant strains, especially in the case of resistance to only one drug. According to simulations of the model we have developed, an antimicrobial cycling program is still more useful in reducing overall drug resistance, especially dual resistance, and should be considered for implementation in hospital settings.

6 Conclusions

Antimicrobial usage programs can be effective in the fight against rising antibiotic resistance in hospitals, but our results show that the battle against multiple resistance levels is important to consider when evaluating drug usage policies. It is shown throughout this paper that an antimicrobial cycling program is more useful in reducing dual resistance when compared to a random mixing regime. Additionally, an intervention involving the isolation of patients colonized with dual-resistant bacteria is effective in maintaining lower levels of dual resistance in the hospital setting.

The model presented in this paper may be useful for understanding short-term dynamics of resistant bacterial transmission in a hospital, but it must be stated that the model's predictions cannot necessarily be used to understand trends in antibiotic resistance on a longer-term or global scale. Resistance does not end at two drugs; if the dynamics of dual-resistant strains are so different from those of single-resistant strains, it may be prudent to investigate higher orders of resistance. Nevertheless, the further insight into the problem of nosocomial transmission of antibiotic-resistant bacteria offered by this model allows for discussion of potential interventions and policies, either locally or globally, for reducing the prevalence of hospital patients infected with organisms resistant to multiple therapies.

7 Acknowledgements

Endless thanks to Dr. Xiaohong Wang for her patience and wisdom in guiding me through my project and to Professor Carlos Castillo-Chávez for giving me the opportunity to conduct research at the Mathematical & Theoretical Biology Institute. Thanks to Christopher Kribs-Zaleta for his insightful feedback on my work as well as to my honors thesis committee, Dr. Priscilla Greenwood and Dr. Jonathan Weisbuch, for their ongoing support. The MTBI/SUMS Summer Undergraduate Research Program is supported by the National Science Foundation (DMS-0502349), the National Security Agency (DOD-H982300710096), the Sloan Foundation, and Arizona State University.

References

[1] Wenzel, R. P. & Edmond, M.B. (2001) *Emerg Infect Dis.* **7**, 174-177.

[2] Okeke, I. N., et al. (2005) *Lancet Infect Dis.* **5**, 481-93.

[3] Baquero, F. & Blazquez, J. (1997) *TREE.* **12** (12), 482-487.

[4] Selgelid, M. J. (2007). *Bioethics.* **21** (4), 218-229.

[5] Levin, B. R. & Bonten, M. J. (2004) *Proc Natl Acad Sci.* **101** (36), 13101-13102.

[6] Lipsitch, M., Bergstrom, C. T., & Levin, B. R. (2000) *Proc Natl Acad Sci.* **97** (4), 1938-1943.

[7] Gumel, A. B., et al. (2004) *Proc R Soc Lond.* **271**, 2223-2232.

[8] Ross, R. (1911) *The Prevention of Malaria.* London, 2nd Edition.

[9] Aron, J. & May, R. (1982) *The Population Dynamics of Malaria.* Chapman and Hall.

[10] Bailey, N. (1975) *The Mathematical Theory of Infectious Diseases.* Griffin.

[11] Anderson, R.M. & May, R. M. (1979) Population Biology of Infectious Diseases, *Nature* **280**, 361-367.

[12] Anderson, R.M. & May, R. M. (1991) *Infectious Diseases of Humans: Dynamics and Control*, Oxford Univ. Press, Oxford, U.K.

[13] Nowak, M. & May, R. (1994) Superinfection and the evolution of parasite virulence. *Proceedings of the Royal Society of London B*, **255**, 81-89.

[14] Castillo-Chávez, C. & Feng, Z. (1998) Global stability of an age-structure model for TB and its applications to optimal vaccination strategies. *Mathematical Biosciences*, **151** (2), 135-154.

[15] Hethcote, H. (2000) The mathematics of infectious diseases. *SIAM Review*, **42** (4), 599-653.

[16] Chowell, G., Fenimore, P., Castillo-Garsow, M., & Castillo-Chávez, C. (2003) SARS outbreaks in Ontario, Hong Kong and Singapore: the role of diagnosis and isolation as a control mechanism. *Journal of Theoretical Biology*, **224**, 1-8.

[17] Feng, Z., Castillo-Chávez, C., & Capurro, A. (2000) A model for tuberculosis with exogenous reinfection. *Theoretical Population Biology*, **57**, 235-247.

[18] Wu, J. & Feng, Z. Mathematical models for schistosomiasis with delays and multiple definitive hosts. Mathematical Approaches for emerging and re-emerging infectious diseases, Part II, IMA, **126**, 215-229.

[19] Nuno, M., Feng, Z., Martcheva, M., & Castillo-Chávez, C. (2005) Dynamics of two-strain influenza with isolation and cross-protection. *SIAM Journal of Applied Mathematics*, **65** (3), 964-982.

[20] Brauer, F. & Castillo-Chávez, C. (2000) Mathematical Models in Population Biology and Epidemiology. *Texts in Applied Mathematics 40*, Springer.

[21] Bergstrom, C. T., Lo, M., & Lipsitch, M. (2004) *Proc Natl Acad Sci.* **101** (36), 13285-13290.

[22] Laxminarayan, R. (2001) Bacterial resistance and optimal use of antibiotics. *Resources for the Future.*

[23] Fraser, C., et al. (2004) *Proc Natl Acad Sci.* **101** (16), 6146-6151.

[24] Bootsma, M.C.J., Diekmann, O., & Bonten, M.J.M. (2006) *Proc Natl Acad Sci.* **103** (14), 5620-5625.

[25] Castillo-Chávez, C., et al. (2002) *Mathematical Approaches for Emerging and Reemerging Infectious Diseases: Models, Methods, and Theory.* Springer.

[26] Sosa, A. & Travers, K. (2002) *Physician Antibiotic Prescribing Practices and Knowledge in Seven Countries in Latin America and the Caribbean.* Pan American Health Organization.