Journal of Biological Dynamics
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tjbd20

Evaluating the efficacy of antimicrobial cycling programmes and patient isolation on dual resistance in hospitals

Karen Chow [a] , Xiaohong Wang [a] , R. Curtiss III [b] & Carlos Castillo-Chavez [a c d e]

[a] Mathematical, Computational Modeling Sciences Center , Arizona State University , PO Box 871904, Tempe, AZ, 85287, USA

[b] The Biodesign Institute, Arizona State University , Tempe, AZ, 85287, USA

[c] School of Human Evolution and Social Change, Arizona State University , Tempe, AZ, 85287, USA

[d] School of Mathematics and Statistics, Arizona State University , Tempe, AZ, 85287, USA

[e] Santa Fe Institute , 1399 Hyde Park Road, Santa Fe, NM, 87501, USA

Published online: 08 Jun 2010.

To cite this article: Karen Chow , Xiaohong Wang , R. Curtiss III & Carlos Castillo-Chavez (2011) Evaluating the efficacy of antimicrobial cycling programmes and patient isolation on dual resistance in hospitals, Journal of Biological Dynamics, 5:1, 27-43, DOI: 10.1080/17513758.2010.488300

To link to this article: http://dx.doi.org/10.1080/17513758.2010.488300

Journal of Biological Dynamics
Vol. 5, No. 1, January 2011, 27–43

Taylor & Francis
Taylor & Francis Group

Evaluating the efficacy of antimicrobial cycling programmes and patient isolation on dual resistance in hospitals

Karen Chow[a]*, Xiaohong Wang[a], R. Curtiss III[b] and Carlos Castillo-Chavez[a,c,d,e]

[a]*Mathematical, Computational Modeling Sciences Center, PO Box 871904, Arizona State University, Tempe, AZ 85287, USA;* [b]*The Biodesign Institute, Arizona State University, Tempe, AZ 85287, USA;* [c]*School of Human Evolution and Social Change, Arizona State University, Tempe, AZ 85287, USA;* [d]*School of Mathematics and Statistics, Arizona State University, Tempe, AZ 85287, USA;* [e]*Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501, USA*

(*Received 19 October 2009; final version received 16 April 2010*)

Antibiotic-resistant bacteria cause a number of infections in hospitals and are considered a threat to public health. A strategy suggested to curb the development of resistant hospital-acquired infections is antimicrobial cycling, in which antibiotic classes are alternated over time. This can be compared with a mixing programme in which, when given two drugs, half of the physicians prescribe one drug over the other. A mathematical model of antimicrobial cycling in a hospital *population* setting is developed to evaluate the efficacy of a cycling programme with an emphasis on reducing the emergence and significance of dual resistance. The model also considers the effects of physician compliance and isolating patients harbouring dual-resistant bacteria. Simulation results show that the optimal antimicrobial drug usage programme in hospital populations depends upon the type of resistance being targeted for treatment; a cycling programme is more effective against dual resistance compared with mixing. Patient isolation and high compliance to a cycling programme is also shown to dramatically decrease dual resistance in hospitalized populations. Ultimately, the exclusive use of antimicrobials in fighting nosocomial infection does not solve the problem but just slows down what appears to be a losing battle against drug resistance. We hope that this paper serves to instigate discussion on the many dimensions of the complex problem of drug resistance in hospital settings.

Keywords: nosocomial; model; antimicrobial; cycling; isolation; resistance

1. Introduction

Hospital-acquired (nosocomial) infections are dangerous; their increasing prevalence results in higher healthcare expenses, and facilitates the evolution of drug resistance. Nosocomial infections lengthen hospital stays and morbidity. The spread of infection is of particular concern in hospitals, where diseased people with weakened immune systems are situated in close proximity [31].

The problem of acquired hospital infections has gained prominence because of the tremendous growth of resistance to antibiotics. Antibiotic-resistant bacteria are transmitted between patients in hospitals primarily through contamination of hospital equipment, surfaces, and human

*Corresponding author. Email: kchow@asu.edu
Author emails: xiaohong.wang@asu.edu; rcurtiss@asu.edu; ccchavez@asu.edu

ISSN 1751-3758 print/ISSN 1751-3766 online

DOI: 10.1080/17513758.2010.488300
http://www.informaworld.com

vectors [24]. Antibiotic-susceptible bacteria are being replaced by resistant organisms. Further, the lack of new antimicrobials threatens a return to a pre-antibiotic era where current antibiotics are rendered useless [6,27]. The proper management of the limited number of antimicrobial drugs is central to our effort to sustain a viable and efficient drug supply.

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 antiseptics and disinfectants more effectively, developing antibiotics that do not select for resistance, reducing hospital stays, and monitoring healthcare workers that may be carrying antibiotic-resistant nosocomial pathogens [19], but the implementation of these tactics is challenging. Several interventions like these have been proposed for limiting nosocomial transmission, particularly with the goal of slowing down the spread of antibiotic-resistant bacteria through the reduction of bacterial transmission within a hospital. Some have proposed to stop the use of *all* antibiotics, though this is not considered a practical solution [20]. Using cocktails and synergistic combinations of drugs could be promising in changing treatment dosage, such as combining beta-lactams or aminoglycosides with vancomycin to treat methicillin-resistant *Staphylococcus aureus* strains, but more studies need to be done on this [25].

Additional factors that may contribute to resistant infections in hospitals include hospital architecture, patient movement and interaction, and exposure of patients to visitors and even plants and flowers. Single rooms with private bathrooms and priority assignments for infectious patients, as well as controlled air flow and movement, could be key to limiting the transmission to uninfected patients. Visitors have been identified as being the source of nosocomial infections and should perhaps be screened for infectious diseases prior to entering the ward [28]. Plants treated with antibiotics have led to the emergence of plant pathogens resistant to antibiotics such as streptomycin-resistant *Pseudomonas*. Although few studies have investigated the relevance of antibiotic use in plant agriculture to the problem of resistance in human medicine, it remains a concern in the medical community [21]. Hence, buying flowers at the hospital store before visiting a patient may not be safe. There are a multitude of issues involving the medical, cultural, and ethical aspects of the drug resistance problem in hospitals that need to be addressed, and this study hopes to provoke discussion of these concerns.

A proposed strategy to slow the evolution and spread of resistant strains of pathogenic bacteria is to alternate antibiotics, using a policy where empiric, or first-line, antibiotics are alternated over a span of time from months to years. Typically, a primary treatment of infections by one class of antibiotics (e.g. aminoglycosides) is used for some period of time until resistance increases; then, the policy calls for switching to a second class of antibiotics for which resistance is rare or absent. This is particularly important in intensive care units (ICUs) where patients are in close contact with one another for prolonged periods of time and where they are often exposed to broad-spectrum antibiotics (e.g. levofloxacin). The cycling strategy is dependent upon the relationship between a particular antibiotic and the level of resistance to the drug. A mixing protocol, on the other hand, is a programme in which physicians will randomly prescribe one drug over the other, serving as a reasonable comparison with cycling [7,20].

The implementation of any intervention requires an adequate level of compliance by both patients and physicians. Physicians who have the authority to decide how a patient is treated in the hospital play a critical role. Typically, we isolate individuals who are symptomatic (confirmed) carriers. A successful isolation programme requires the implementation of strict hygiene practices to limit transmission to healthcare workers, who in turn can infect patients [16]. It can be difficult to quantify whether or not an intervention was successful or to compare interventions without any explicit quantitative approach. Such quantitative predictions and criteria for their evaluation can be offered through the investigation of mathematical models [7,20].

Mathematical models can be beneficial in evaluating solutions to problems involving infectious disease [1,2,4,5,9,10,12,14,17,22,23,26,30,32]. They provide insight into the underlying

mechanisms that influence the spread of disease at various levels of organization, including the population level. Simple models have been powerful tools in the identification and evaluation of control strategies. Models also help identify behaviour difficult to glean from experimental data [9].

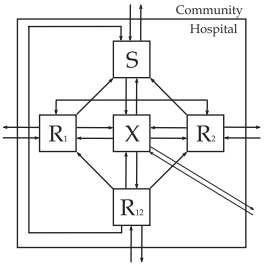
Bergstrom *et al.* [7] developed a model to determine whether antimicrobial cycling can be effective at controlling resistance in a hospital setting. The purpose of their study was to isolate and illustrate fundamental ecological processes responsible for the success or failure of antimicrobial cycling programmes. Two antimicrobial drugs were considered, and it was assumed that dual resistance had not emerged. Their model tracked populations of patients within the hospital according to their colonization status. By running several simulations of scenarios that compare mixing and cycling drug programmes, they were able to show that cycling is unlikely to reduce the carriage of resistant organisms when compared with alternative policies [7]. This manuscript builds on their model and some of the ideas in [30] as we explore the dynamics of resistance and dual resistance in a large population of hospitalized patients.

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 [7]. However, no work has been done on incorporating dual-resistant bacterial strains in a mathematical model of antimicrobial cycling. The rise in strains of pathogenic bacteria resistant to multiple antibiotics are of great concern in hospitals, as they result in more expensive drugs that may or may not be effective against infections. Investigating the effects of resistance to multiple antibiotics in hospitals and comparing them with the impact of focusing on a single resistance scenario may offer further insight into the dynamics and control of nosocomial infection transmission at the population level. Bergstrom *et al.*'s model implicitly looks at nosocomial infections over a rather 'short' temporal scale; that is, they assume 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 focus on the dynamics of dual resistance to antibiotics within hospital settings. Our model is used to evaluate the efficacy of a cycling versus mixing protocols as well as the effects of heterogeneous physician compliance and isolation interventions of various degrees of effectiveness at the population level. This paper is organized as follows: Section 2 formulates our mathematical model; in Section 3, model simulations are discussed with a focus on comparing our results with those of earlier research; in Section 4, we add isolation and explore its impact within the current dual resistance model; a discussion of our findings and their implications are discussed in Section 5.

2. Mathematical model

The transmission dynamics of infection in the presence of dual resistance to antibiotics are modelled by a system of ordinary differential equations that tracks several patient *populations* in hospital settings according to their colonization status, depicted in Figure 1. It is 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. In other words, the time scale and the organizational levels of interests are driven by scenarios where the emergence of newly resistant pathogens is unlikely. We are dealing with population level phenomena over time scales where evolutionary shifts can be neglected.



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

Figure 1. Schematic of the model incorporating dual resistance and the system of differential equations which corresponds to the compartmental model. All parameters are defined in Table 1. A detailed discussion of this model is found in the appendix.

Following the (non-classic) notation in [7] , we let X group represent 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 harbour 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 the proportions of 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’ is large (so that differential equations can be used) and that this population remains constant. Hence, 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 $\mu(1 - m - m_1 - m_2 - m_{12})$, 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, on average, for $1/\gamma$ days. Drugs 1 and 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 [18]. 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, since bacteria may have the capacity to mutate in response to their environmental conditions [3]. This applies to the interaction between the single-resistant R_1, R_2 strains, and the dual-resistant R_{12} strain. As a result, a patient can move from any resistance class to the other, though the least likely would be from dual resistance to single resistance only, reflected in the fitness costs. The parameter σ is multiplied by the fitness cost according to [7] since the fitness cost of the bacteria also affects secondary colonization. The parameter α represents physician compliance to an antibiotic therapy programme and is equal to the fraction of patients receiving the currently indicated drug; this parameter will be used only in numerical simulations. Figure 1 includes not only the flow diagram but also the nonlinear system of differential equations used to model the transmission dynamics of four bacteria types in a large population of hospitalized individuals.

3. Comparison of antimicrobial cycling and mixing programmes through numerical simulation

Numerical simulations of this model are used to explore the effects of policies for antibiotic usage for populations in hospitals. In this paper, we focus on the effects of antimicrobial cycling programmes relative to mixing regimes, with further assessment of the impact of physician compliance and isolation interventions. Preliminary analysis of the model in the simplest case is provided in the appendix.

An antimicrobial cycling programme alternates empiric classes of antibiotics over a given span of time in an attempt to control the spread of resistant bacteria. An antimicrobial mixing programme describes physicians prescribing drugs 1 and 2 to patients at random, meaning about half of the physicians use drug 1 to treat patients and the other half of the physicians prescribe drug 2 to patients receiving treatment. This scheme serves as a reference against which cycling is compared.

In order to assess the impact under different usage policies, the equations are simulated using MATLAB® under appropriate ranges for the parameter values (Table 1). Most parameter ranges were obtained from previously published work [7,15,20], whereas other parameters were 'guessed' from what we considered to be reasonable values.

Table 1. The definition of parameters and references that highlight acceptable ranges are listed in this table.

Parameter	Description	Value	References
β	*Per capita* primary transmission rate (colonization rate)	$1\,\text{day}^{-1}$	[7]
σ	Relative rate of secondary colonization to that of the primary colonization $\in (0, 1)$	$0.25\,\text{day}^{-1}$	[7]
τ_i	*Per capita* treatment rate of drug i, $i = 1, 2$	$0.38\,\text{day}^{-1}$	
γ	*Per capita* clearance rate of bacteria due to immune response	$0.03\,\text{day}^{-1}$	[7,20]
μ	*Per capita* patient turnover rate in the hospital	$0.10\,\text{day}^{-1}$	[7,20]
m	Proportion of admitted already colonized with sensitive bacteria	0.70	[7,20]
μm_i	Rate at which patients colonized by bacterial strains resistant to drug i enter the hospital	$0–0.07\,\text{day}^{-1}$	[7]
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 programme	0.80	[7]
η	*Per capita* isolation rate of patients colonized by bacterial strains resistant to both drugs 1 and 2	$0.01–0.025\,\text{day}^{-1}$	
ϵ	Proportion of patients effectively isolated	0.5–1	[15]

Note: The parameters listed without references were explored via simulations.

3.1. *Comparison of cycling and mixing programmes*

In order to determine whether cycling is an effective strategy for reducing the spread of antibiotic-resistant bacteria, a cycling protocol is compared with a random mixing regime. In other words, the case when $\tau_1 = \tau_2$ (mixing regime) is compared with the cycling regime where piece-wise continuous functions are used to model a regular alternating drug treatment cycle 2.

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

Figure 3 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 relatively constant, that is, the *fraction* of the population infected with a resistant type is around 0.7 regardless of the treatment regimes. This is significantly higher fraction than that of just R_1+R_2 and it is maintained for each cycling period length. These results further suggest that dual resistance has a greater impact on the fraction of patients colonized by any resistant bacteria.

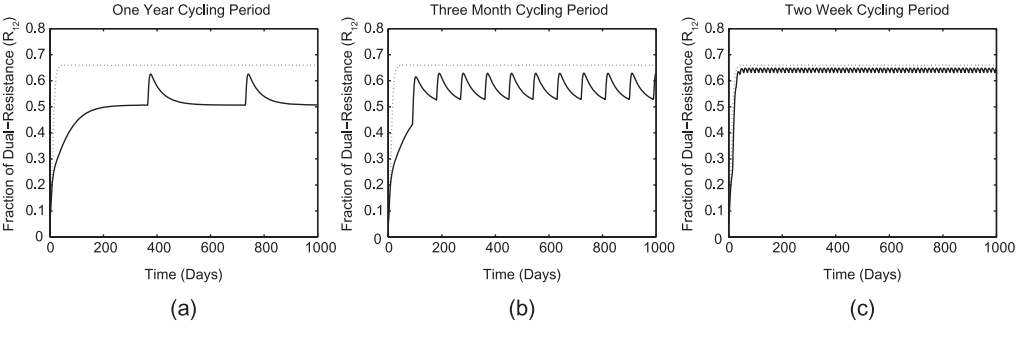


Figure 2. Fraction of patients carrying only dual-resistant bacteria R_{12} for cycle lengths of (a) 1 year, (b) 3 months, and (c) 2 weeks. The solid lines indicate the total fraction of patients colonized with dual-resistant bacteria under cycling, and the dashed lines indicate the total fraction of patients colonized with dual-resistant bacteria under a 50–50 mixing regime. Parameter values are as in Table 1.

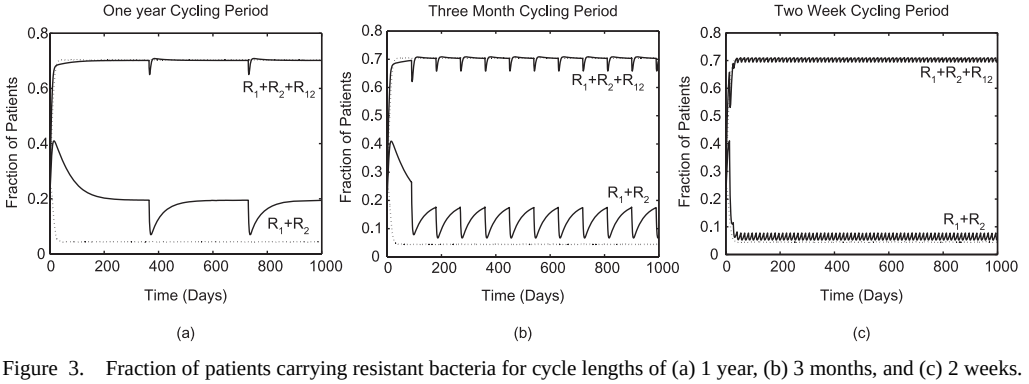


Figure 3. Fraction of patients carrying resistant bacteria for cycle lengths of (a) 1 year, (b) 3 months, and (c) 2 weeks. Parameter values are as in Table 1.

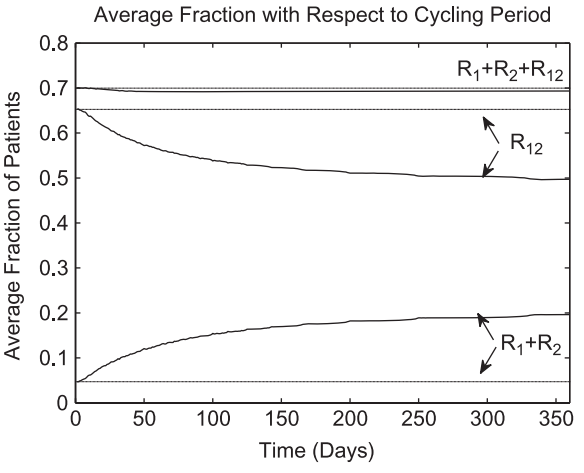


Figure 4. Average fractions of patients colonized by resistant bacteria as a function of cycle period. The dashed line indicates a mixing programme, and the solid line indicates a cycling programme. Parameter values are as in Table 1.

Figure 4 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 the cycle period length increases, R_1+R_2 under the cycling programme increases. The simulation outcomes for R_{12} go in the opposite direction, demonstrating an advantage of a cycling programme over a mixing programme when attempting to reduce dual resistance in hospitals. As the cycle period length increases, the fraction of patients colonized with total resistance under a cycling programme is *slightly* lower than that under a mixing programme. We did not carry out a formal sensitivity analysis but our extensive simulations always support this pattern. Hence, we arrive at the following qualitative (based on simulations) conclusion:

Table 1 provided some idea of an adequate range for most of the parameters used in our simulations. However, careful studies that measure not only the values of these parameters but also assess their variability at the population level are still missing. Hence, our simulation results can only be used to gauge the overall patterns of resistance as a function of the treatment regime and not as specific quantitative recommendations. Specifically we conclude that as the cycling period decreases we recover the mixing treatment regime. The overall levels of resistance are uniformly high (over 60%) regardless of the treatment regime; the distribution of resistant types is a function of the treatment regime; and that if the goal is to reduce dual resistance, then cycling is better than mixing, a point missed by single resistance models [7]; if the priority is to first treat patients suffering from single-resistant bacterial infections, then a mixing protocol would be better.

3.2. *Physician compliance*

Clearly, the exclusive use of treatment regimes even if 'properly' managed, are insufficient to drastically change the levels of resistance. Unfortunately, there are additional sources of uncertainty including the level of physicians' compliance.

Compliance is described as the fraction of patients that receive the currently recommended drug under a pre-selected treatment regime. When $\alpha = 1$ (perfect compliance), all treated patients are assumed to receive the recommended drug while when $\alpha = 0$, half of the patients receive drug 1 and the other half receives drug 2.

Figure 5(a) shows the effect of varying the physician compliance parameter α on patients colonized by bacteria resistant to either drug 1 or 2 over a 2-year period. The level of physicians'

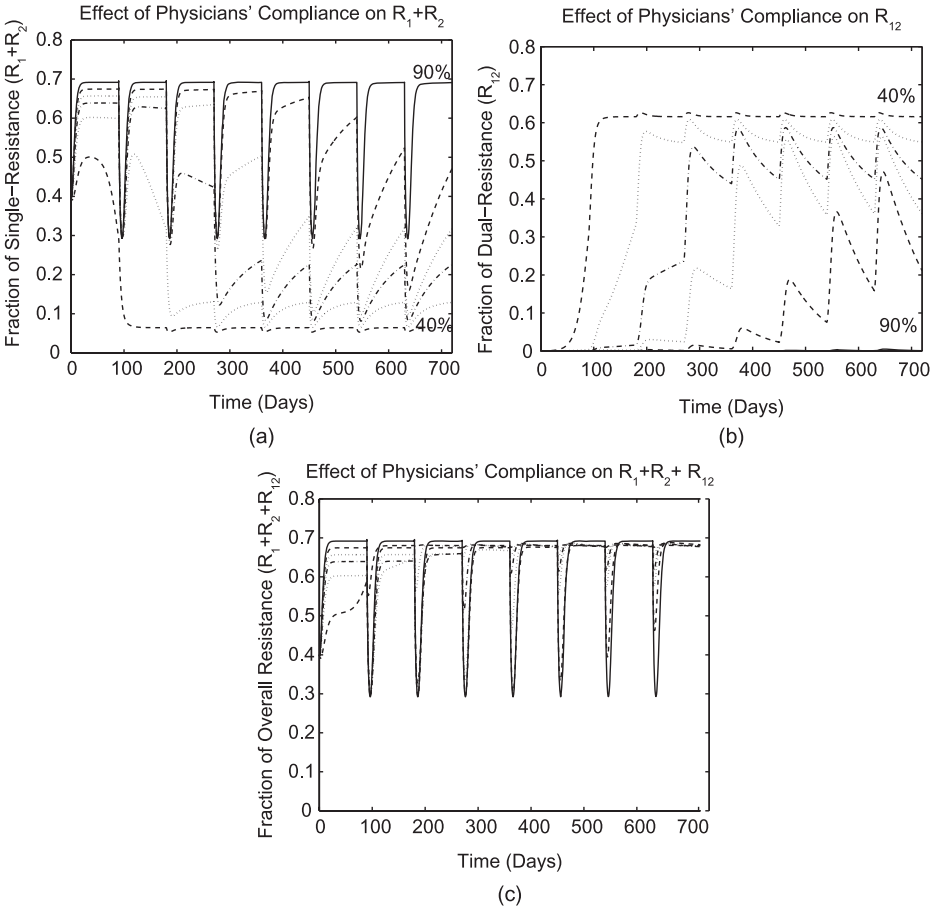


Figure 5. The effect of varying physician compliance α on (a) $R_1 + R_2$, (b) R_{12}, and (c) $R_1 + R_2 + R_{12}$. Physician compliance was varied from 40 to 90% so as to compare the long-term effects of low compliance versus high compliance over 2 years. Parameter values are as in Table 1.

compliance results in potentially dramatic shifts in resistant types. In fact, in our settings, resistance levels increase when physicians are more compliant with the cycling programme. A lower compliance level (α closer to zero) in the cycling programme essentially moves in closer to the mixing (50–50 by nature). Thus, by administering each drug at 'random' (too many mistakes), the level of $R_1 + R_2$ increases.

Figure 5(b) shows the effect of varying the physician compliance parameter α on patients colonized by bacteria resistant to both drugs 1 and 2. As expected, lower compliance results in a lower fitness cost. Hence, dual-resistant strains spread more easily at lower physicians' compliance levels. Again, this reinforces the idea that a cycling programme is more effective in reducing dual resistance.

Figure 5(c) shows the effect of varying the physician compliance parameter α on total resistance in hospital settings. Increasing compliance results in slightly increased resistance levels. The curves seem to converge (in our simulations). We see that 90% compliance results in the highest resistance level, a fraction approaching 0.7. With regards to total resistance, physician compliance with a cycling programme does not result in a dramatic shift in the number of patients colonized with resistance in hospital settings.

4. Isolation of patients with dual-resistant strains

Obviously, treatment is *not* the solution. In fact, the lack of development of new antimicrobial drugs over the last few decades [6,27] means that our current polices are exhausting the usefulness of a limited resource, namely antimicrobial drugs. We need a sustainable policy that extends the life of the current fixed set of antimicrobial drugs and the only way to preserve their usefulness is through the careful management of this limited drug supply. Hence, alternative mechanisms must be implemented that reduces our need to deal with the challenges posed by the potential spread of dual resistant types.

Since nosocomial transmission of antibiotic-resistant bacterial strains is driven by contact with patients in hospitals, the isolation of infected patients may be highly effective. That is, identified carriers of resistant bacteria can be treated in single rooms with barrier precautions [8] to restrict contact with the rest of the patient population in hospitals. With the addition of a new class of isolated individuals Q, our mathematical model is updated to include the isolation effect, as shown in the following system of nonlinear differential equations:

$$
\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= (m-S)\mu - (\tau_1+\tau_2+\gamma)S + \sigma\beta \\
&\quad \times \left(c_1\frac{R_1}{1-\epsilon Q} + c_2\frac{R_2}{1-\epsilon Q} + c_{12}\frac{R_{12}+(1-\epsilon)Q}{1-\epsilon Q}\right) S + \beta S\frac{X}{1-\epsilon Q}, \\
\frac{\mathrm{d}R_1}{\mathrm{d}t} &= (m_1-R_1)\mu - (\tau_2+\gamma)R_1 + \beta(1-c_1)R_1\frac{X}{1-\epsilon Q} + \sigma\beta c_{12}\frac{R_{12}+(1-\epsilon)Q}{1-\epsilon Q}R_1 \\
&\quad - \sigma\beta\left(c_1\frac{S}{1-\epsilon Q} + (c_1-c_2)\frac{R_2}{1-\epsilon Q}\right)R_1, \\
\frac{\mathrm{d}R_2}{\mathrm{d}t} &= (m_2-R_2)\mu - (\tau_1+\gamma)R_2 + \beta(1-c_2)R_2\frac{X}{1-\epsilon Q} + \sigma\beta c_{12}\frac{R_{12}+(1-\epsilon)Q}{1-\epsilon Q}R_2 \\
&\quad - \sigma\beta\left(c_2\frac{S}{1-\epsilon Q} + (c_2-c_1)\frac{R_1}{1-\epsilon Q}\right)R_2, \\
\frac{\mathrm{d}R_{12}}{\mathrm{d}t} &= (m_{12}-R_{12})\mu - \eta R_{12} - \gamma R_{12} + \beta(1-c_{12})(R_{12}+(1-\epsilon)Q)\frac{X}{1-\epsilon Q} \\
&\quad - \sigma\beta c_{12}\left(\frac{S+(1-c_1)R_1+(1-c_2)R_2}{1-\epsilon Q}\right)R_{12}, \\
\frac{\mathrm{d}Q}{\mathrm{d}t} &= -\mu Q + \eta R_{12} - \sigma\beta c_{12}\left(\frac{S+(1-c_1)R_1+(1-c_2)R_2}{1-\epsilon Q}\right)((1-\epsilon)Q), \\
\frac{\mathrm{d}X}{\mathrm{d}t} &= (1-m-m_1-m_2-m_{12}-X)\mu + (\tau_1+\tau_2+\gamma)S + (\tau_2+\gamma)R_1 + (\tau_1+\gamma)R_2 \\
&\quad + \gamma R_{12} - \beta X\left(\frac{S}{1-\epsilon Q} + (1-c_1)\frac{R_1}{1-\epsilon Q} + (1-c_2)\frac{R_2}{1-\epsilon Q}\right. \\
&\quad \left. + (1-c_{12})\frac{R_{12}+(1-\epsilon)Q}{1-\epsilon Q}\right).
\end{aligned}
\tag{1}
$$

The above model incorporates an isolation class Q. The *per capita* isolation rate η and the efficacy of isolation ϵ are used to modulate the effect and efficacy of isolation policies. Patients who are identified to have *dual-resistant* strains are isolated within the hospital. Following standard incidence for dynamic models [11], the proportion of patients changes with ϵ since isolated individuals are no longer included in the adjusted population subject to patient contact (unfortunately,

possibly increasing the likelihood of getting infected by single-resistant strains). Additionally, leakage from Q into other compartments may occur if patients are not entirely effectively isolated. This is accounted by the factor $(1-\epsilon)$, such that an isolation programme 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 impact of an isolation programme on patients undergoing an antimicrobial cycling programme is explored through simulation.

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 is shown in Figure 6, where the efficacy of isolation parameter ϵ was held constant at 90%, and the isolation rate η was varied from 0.01 to 0.025. This was done to examine the effects of varying the *per capita* rate of isolation on the overall population of patients harbouring 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 (not surprisingly, given that the isolation of dual resistant types increased the likelihood of infection of single-resistant types). 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 7. 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 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.

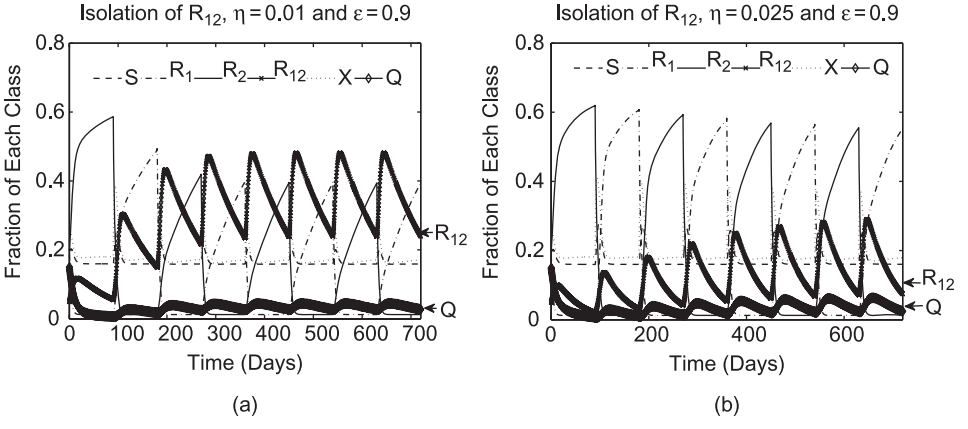


Figure 6. The effect of varying isolation rate η on fraction of patients colonized with dual-resistant bacteria. Parameter values are as in Table 1, with $\eta = 0.01, 0.025$ and $\epsilon = 0.9$.

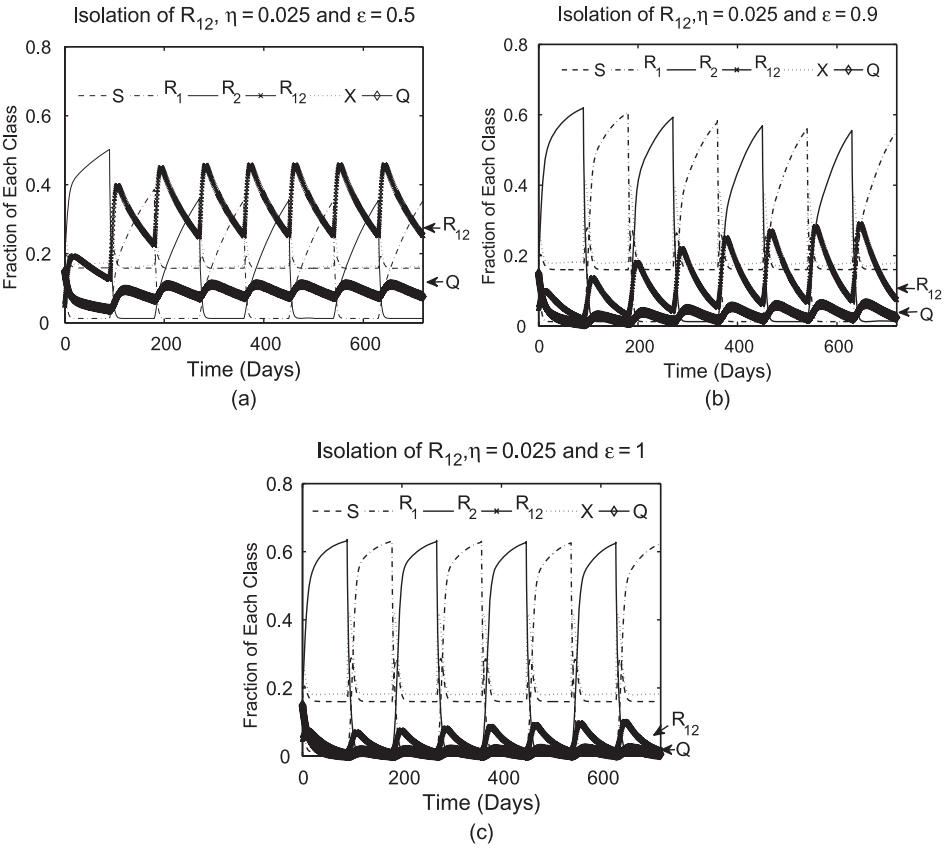


Figure 7. The effect of varying isolation efficacy ϵ on fraction of patients colonized with dual-resistant bacteria. Parameter values are as in Table 1, with $\eta = 0.025$ and $\epsilon = 0.5, 0.9, 1$.

According to our isolation model, which incorporates isolation of R_{12} into the Q class, both the isolation rate and the isolation efficacy parameter are significant factors to consider when implementing such a programme. Isolation appears to be a potentially effective intervention technique for controlling and maintaining lower levels of dual resistance in hospital settings, but of course, we did not incorporate the costs or difficulties of implementing such policies in current hospital settings.

5. Discussion

Antimicrobial usage programmes can be effective in the fight against rising antibiotic resistance in hospitals. Our results show in addition 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 programme is more useful in reducing dual resistance when compared with a random mixing regime, a fact that could not be assessed with existing models [7]. Additionally, we found that isolation dramatically reduces the persistence of dual resistance but we did not address the costs and logistics associated with the implementation of such programmes.

The basis of cycling is in the fluctuating selection pressures induced by regularly switching antimicrobials, thereby affecting the ability of resistant bacteria to replace commensal bacteria through variations in habitat and landscape changes generated by an evolving population. It is

an issue of competition and displacement; drugs eliminate sensitive bacteria to effectively make room for resistant ones. 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 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 the 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 extended periods of time [7].

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 the spread of resistance for which there is no treatment.

Numerical simulations of our model clearly demonstrate the significant impact that dual-resistant strains have on an antimicrobial cycling programme in contained hospital settings. 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 colonized by bacteria resistant to only a single drug. After a year of a 90-day cycling programme 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. In other words, the evolutionary landscape changes dramatically with the evolution of dual resistance and the policies or paradigms that support the implementation of treatment regimes geared towards the reduction of single-drug resistance must be clearly re-evaluated in the context of dual-resistance.

The bad news is that our model demonstrates that the fraction of patients colonized by strains resistant to both drugs remains highest regardless of cycling period length. In fact, 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.

Current practices in prescribing antibiotic therapies are approximated by random mixing. Our model simulated a mixing regime under the assumption that dual resistance is already present in hospital settings. Since mixing implies the simultaneous usage of drugs 1 and 2, 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 programme, where mixing seems to result in a higher fraction of patients infected with the dual-resistant strain than longer cycling time period lengths.

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 [29]. 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.

Simulations were performed to show the outcomes that result from 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 and 90% compliance. At 90% physician compliance, as shown in Figure 5, 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 programme is not effective in curbing single resistance, since mixing would be the more useful protocol in that case. We cannot solve the resistance problem just with the treatment.

The potential impact of an isolation protocol was also considered, 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 programme, 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 programme 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 programme must consider these issues and extended models should be used to evaluate their role.

The bottom line, evident throughout this investigation, is that dual resistance simply cannot be ignored and cannot be controlled effectively via treatment alone. 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 resistant 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 programme is more useful in reducing overall drug resistance, especially dual resistance, and should be considered for implementation in hospital settings.

These results are based on a very particular set of assumptions. In this study, overall resistance levels will not change, but the distribution of the proportions of resistance types will. It should be noted that we are not focusing on any specific pathogen; specific models would be needed to address the transmission dynamics and control of specific pathogens.

Model outcomes come from studying a simple and general scenario. We are aware that the problem of hospital-acquired infections is complex, involving not only medical treatment, but cultural norms and ethical issues. Some of the heterogeneities found in hospitals can have a substantial impact on nosocomial infections. Hospital architecture can dictate the flow of patients, healthcare workers, and visitors, as well as their interactions with each other and the inanimate environment. At large, many patients in hospitals are already undergoing antibiotic therapy, so

synergistic effects of drugs should be considered. Cultural norms play a role as well, evident in the customary practice of bringing fresh flowers and plants to friends and family in hospitals. These plants could be covered with resistant pathogens, possibly contributing to selective pressure in hospital settings. Ethical issues should also be considered, such as the responsibility of a physician to treat the individual as opposed to looking at the welfare of the entire population. The role of physicians in distributing drugs must also be addressed [13,27].

This study raises certain questions about the problem of resistant pathogens in hospitals. These questions can be addressed through mathematical models, and the greater purpose of this paper is to instigate discussion about the many dimensions of this complex problem and the wealth of possible methods that can be implemented to mitigate it. We will never win the battle against antimicrobial resistance through the exclusive use of integrated microbial management approaches that focus entirely on the prescription of antibiotics. In other words, drugs provide no silver bullet, and policies that reward their judicious use can only attempt to slow down what appears to be a losing battle. If we insist on the exclusive use of antimicrobials to fight nosocomial infections, then it is only a matter of time before we begin to run out of effective antibiotics.

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 types of 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, 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.

Acknowledgements

This research was supported by the National Science Foundation (DMS-0502349), the National Security Agency (DOD-H982300710096), the Sloan Foundation, and Arizona State University.

References

[1] R.M. Anderson and R.M. May, *Population biology of infectious diseases*, Nature 280 (1979), pp. 361–367.
[2] R.M. Anderson and R.M. May, *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, Oxford, UK, 1991.
[3] D.I. Andersson and B.R. Levin, *The biological cost of antibiotic resistance*, Curr. Opin. Microbiol. 2 (1999), pp. 489–493 (http://dx.doi.org/10.1016/S1369-5274(99)00005-3).
[4] J. Aron and R. May, *The Population Dynamics of Malaria*, Chapman and Hall, London, UK, 1982.
[5] N. Bailey, *The Mathematical Theory of Infectious Diseases*, Griffin, London, UK, 1975.
[6] F. Baquero and J. Blazquez, *Evolution of antibiotic resistance*, TREE 12(12) (1997), pp. 482–487.
[7] C.T. Bergstrom, M. Lo, and M. Lipsitch, *Ecological theory sugggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals*, Proc. Natl. Acad. Sci. 101(36) (2004), pp. 13285–13290.
[8] M.C.J. Bootsma, O. Diekmann, and M.J.M. Bonten, Proc. Natl. Acad. Sci. 103(14) (2006), pp. 5620–5625.
[9] F. Brauer and C. Castillo-Chávez, *Mathematical Models in Population Biology and Epidemiology*, Texts in Applied Mathematics 40, Springer, 2000.
[10] C. Castillo-Chávez and Z. Feng, *Global stability of an age-structure model for TB and its applications to optimal vaccination strategies*, Math. Biosci. 151(2) (1998), pp. 135–154.
[11] C. Castillo-Chávez, S. Blower, P. Driessche, D. van de Kirschner, A.A. Yakuba (eds) *Mathematical Approaches for Emerging and Reemerging Infectious Diseases: Models, Methods, and Theory*, Springer, 2002.
[12] G. Chowell, P. Fenimore, M. Castillo-Garsow, and C. Castillo-Chávez, *SARS outbreaks in Ontario, Hong Kong and Singapore: The role of diagnosis and isolation as a control mechanism*, J. Theor. Biol. 224 (2003), pp. 1–8.
[13] J. Coast, R.D. Smith, and M.R. Millar, *An economic perspective on policy to reduce antimicrobial resistance*, Soc. Sci. Med. 46(1) (1998), pp. 29–38.
[14] Z. Feng, C. Castillo-Chávez, and A. Capurro, *A model for tuberculosis with exogenous reinfection*, Theor. Popul. Biol. 57 (2000), pp. 235–247.

[15] C. Fraser, S. Riley, R.M. Anderson, N.M. Ferguson, *Factors that make an infections disease oubreak uncontrollable*, Proc. Natl. Acad. Sci. London, UK, 101(16) (2004), pp. 6146–6151.
[16] A.B. Gumel, S. Ruan, T. Day, J. Watmough, F. Brauer, P. van den Driessche, D. Gabrielson, C. Bowman, M.E. Alexander, S. Ardal, J. Wu and B.M. Sahai, *Modelling Strategies for controlling SAKS outbreaks*, Proc. R. Soc. Lond. Winnipeg, Canada, 271 (2004), pp. 2223–2232.
[17] H. Hethcote, *The mathematics of infectious diseases*, SIAM Rev. 42(4) (2000), pp. 599–653.
[18] R. Laxminarayan, *Bacterial resistance and optimal use of antibiotics*, Resources for the Future, Washington, D.C., 2001.
[19] B.R. Levin and M.J. Bonten, *Cycling antibiotics may not be good for your health*, Proc. Natl. Acad. Sci. 101(36) (2004), pp. 13101–13102.
[20] M. Lipsitch, C.T. Bergstrom, and B.R. Levin, *The epidemic of antibiotic resistance in hospitals: paradoxes and Prescriptions*, Proc. Natl. Acad. Sci. 97(4) (2000), pp. 1938–1943.
[21] P.S. McManus, V.O. Stockwell, G.W. Sundin, and A.L. Jones, *Antibiotic use in plant agriculture*, Ann. Rev. Phytopathol. 40 (2002), pp. 443–465.
[22] M. Nowak and R. May, *Superinfection and the evolution of parasite virulence*, Proc. R. Soc. Lond. B 255(1994), pp. 81–89.
[23] M. Nuno, Z. Feng, M. Martcheva, and C. Castillo-Chávez, *Dynamics of two-strain influenza with isolation and cross-protection*, SIAM J. Appl. Math. 65(3) (2005), pp. 964–982.
[24] I.N. Okeke, R. Laxminarayan, Z.A. Bhutta, A.G. Duse, P. Jenkins, T.F., O'Brien, A. Pablos-Mendez, and K.P. Klugman, *Antimicrobial resistance in developing countries. Part I: recent trends and current status*, Lancet Infect. Dis. 5 (2005), pp. 481–93.
[25] S. Rochon-Edouard, M. Pestel-Caron, J.-F. Lemeland, and F. Caron, *In vitro synergistic effects of double and triple combinations of beta-lactams, vancomycin, and netilmicin against methicillin-resistant Staphylococcus aureus strains*, Antimicrob. Agents Chemother. 44(11) (2000), pp. 3055–3060.
[26] R. Ross, *The Prevention of Malaria*, 2nd ed., Murray, London, 1911.
[27] M.J. Selgelid, *Ethics and drug resistance*, Bioethics 21(4) (2007), pp. 218–229.
[28] J.D. Siegel, E. Rhinehart, M. Jackson, and L. Chiarello, *Guideline for isolation precautions: Preventing transmission of infectious agents in health care settings*, Am. J. Infect. Control 35(10, Suppl 2) (2007), pp. S65–S164.
[29] A. Sosa and K. Travers, *Physician Antibiotic Prescribing Practices and Knowledge in Seven Countries in Latin America and the Caribbean*, Pan American Health Organization, Boston, MA, 2002.
[30] G. Webb, E.M.C. D'Agata, P. Magal, and S. Ruan, *A model of antibiotic resistant bacterial epidemics in hopsitals*, Proc. Natl. Acad. Sci. 102(37) (2005), pp. 13343–13348.
[31] R.P. Wenzel and M.B. Edmond, *The impact of hospital-acquired bloodstream infections*, Emerg. Infect. Dis. 7 (2001), pp. 174–177.
[32] J. Wu and Z. Feng, *Mathematical models for schistosomiasis with delays and multiple definitive hosts. Mathematical approaches for emerging and re-emerging infectious diseases*, Math. Appl. IMA, Vol. 126, pp. 215–229.

Appendix

In this appendix, we provide a limited analysis of the simplest model used in the simulations. The following constitutes the equilibrium and stability analyses of the equations shown in Figure 1. 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

$$\Re_S = \frac{\beta}{\tau_1 + \tau_2 + \mu + \gamma}. \tag{A1}$$

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

$$\Re_{R_1} = \frac{\beta(1 - c_1)}{\tau_2 + \mu + \gamma}, \tag{A2}$$

$$\Re_{R_2} = \frac{\beta(1 - c_2)}{\tau_1 + \mu + \gamma}, \tag{A3}$$

$$\Re_{R_{12}} = \frac{\beta(1 - c_{12})}{\mu + \gamma}. \tag{A4}$$

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 USA, 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, the system in Figure 1 can be reduced to

four dimensions. Hence, we only need to study the following system of ordinary differential equations:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= (m-S)\mu - (\tau_1+\tau_2+\gamma)S + \sigma\beta(c_1R_1 + c_2R_2 + c_{12}R_{12})S \\
&\quad + \beta S(1-S-R_1-R_2-R_{12}), \\
\frac{\mathrm{d}R_1}{\mathrm{d}t} &= -R_1\mu - (\tau_2+\gamma)R_1 + \beta(1-c_1)R_1(1-S-R_1-R_2-R_{12}) + \sigma\beta c_{12}R_{12}R_1 \\
&\quad - \sigma\beta(c_1S + (c_1-c_2)R_2)R_1, \\
\frac{\mathrm{d}R_2}{\mathrm{d}t} &= -R_2\mu - (\tau_1+\gamma)R_2 + \beta(1-c_2)R_2(1-S-R_1-R_2-R_{12}) + \sigma\beta c_{12}R_{12}R_2 \\
&\quad - \sigma\beta(c_2S + (c_2-c_1)R_1)R_2, \\
\frac{\mathrm{d}R_{12}}{\mathrm{d}t} &= -R_{12}\mu - \gamma R_{12} + \beta(1-c_{12})R_{12}(1-S-R_1-R_2-R_{12}) \\
&\quad - \sigma\beta c_{12}(S + (1-c_1)R_1 + (1-c_2)R_2)R_{12}
\end{aligned} \tag{A5}$$

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

$$S^* = \frac{\beta - (\mu+\tau_1+\tau_2+\gamma) + \sqrt{(\mu+\tau_1+\tau_2+\gamma-\beta)^2 + 4m\beta\mu}}{2\beta}. \tag{A6}$$

The Jacobian at E_0 can be computed as follows:

$$J_0 = \begin{pmatrix} \beta - (\mu+\tau_1+\tau_2+\gamma) - 2\beta S^* & \sigma\beta c_1 S^* - \beta S^* & \sigma\beta c_2 S^* - \beta S^* & \sigma\beta c_{12} S^* - \beta S^* \\ 0 & J_0(2,2) & 0 & 0 \\ 0 & 0 & J_0(3,3) & 0 \\ 0 & 0 & 0 & J_0(4,4) \end{pmatrix}, \tag{A7}$$

where

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

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 [9]. Since J_0 is an upper triangular matrix, it is easy to obtain the eigenvalues of J_0, namely

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

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

$$\begin{aligned}
\lambda_{02} < 0 &\Leftrightarrow \beta(1-c_1)(1-S^*) < \sigma c_1\beta S^* + \mu + \gamma + \tau_2 \\
&\Leftrightarrow \frac{\beta(1-c_1)(1-S^*)}{\mu+\gamma+\tau_2} < \frac{\sigma c_1\beta S^*}{\mu+\gamma+\tau_2} + 1 \\
&\Leftrightarrow \Re_{R_1} < \frac{\sigma c_1\beta S^*}{(1-S^*)(\mu+\gamma+\tau_2)} + \frac{1}{1-S^*}.
\end{aligned} \tag{A8}$$

This can also be expressed as

$$\lambda_{02} < 0 \Leftrightarrow \left[(1-S^*) - \sigma S^* \frac{c_1}{1-c_1}\right] \Re_{R_1} < 1, \tag{A9}$$

where $(1-S^*)$ is the proportion available for primary colonization at E_0 and $\sigma S^*(c_1/1-c_1)$ 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

$$\lambda_{03} < 0 \Leftrightarrow \Re_{R_2} < \frac{\sigma c_2 \beta S^*}{(1-S^*)(\mu+\gamma+\tau_1)} + \frac{1}{1-S^*} \tag{A10}$$

$$\Leftrightarrow \left[(1-S^*) - \sigma S^* \frac{c_2}{1-c_2}\right] \Re_{R_2} < 1, \tag{A11}$$

$$\lambda_{04} < 0 \Leftrightarrow \Re_{R_{12}} < \frac{\sigma c_{12} \beta S^*}{(1-S^*)(\mu+\gamma)} + \frac{1}{1-S^*} \tag{A12}$$

$$\Leftrightarrow \left[(1-S^*) - \sigma S^* \frac{c_{12}}{1-c_{12}}\right] \Re_{R_{12}} < 1. \tag{A13}$$

Therefore, we have the following:

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

$$R^S = \max\left(\left[(1-S^*) - \sigma S^* \frac{c_1}{1-c_1}\right] \Re_{R_1}, \left[(1-S^*) - \sigma S^* \frac{c_2}{1-c_2}\right] \Re_{R_2}, \left[(1-S^*) - \sigma S^* \frac{c_{12}}{1-c_{12}}\right] \Re_{R_{12}}\right), \tag{A14}$$

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.