Bacterial Resistance and
the Optimal Use of Antibiotics

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Abstract

The increasing resistance of harmful biological organisms (bacteria, parasites, and pests) to selection pressure from the widespread use of control agents such as antibiotics, antimalarials, and pesticides is a serious problem in both medicine and agriculture. Modeling resistance —or, conversely, the effectiveness of these control agents as a biological resource—yields insights into how these agents should be optimally managed to maximize their economic benefit to society. This paper uses a model of evolution of bacterial resistance to antibiotics—in which resistance places an evolutionary disadvantage on the resistant organism—to develop a simple sequential algorithm of optimal antibiotic use. Although the solution to this problem follows the well-recognized rule of using resources in the order of increasing marginal cost, the unique ways in which these economic costs arise from differing biological traits distinguishes this problem from others in the natural resources arena. This paper also examines the option of periodically rotating between two or more antibiotics and characterizes the economic and biological criteria under which a cycling strategy is superior to simultaneous use of two or more antibiotics.

Key Words: antibiotic resistance, natural resource, optimization.

JEL Classification Numbers: I0, Q0

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Introduction

There is a small but growing body of literature on the optimal use of drugs, pesticides, and other resources whose effectiveness may be conveniently modeled as a natural resource. There are three key features of this type of resource that distinguishes it from other natural resources such as fish, trees or copper. First, unlike in the case of these other resources, the use (or extraction of effectiveness) of biological control agents typically involves two dynamic externalities, one positive and the other negative. Take the case of antibiotics. On the one hand, antibiotic treatment cures an infected individual, thereby preventing disease from being transmitted to other uninfected individuals. On the other hand, using antibiotics reduces their effectiveness for future users, an externality that is not taken into consideration by the user. One can think of the analogous situation in the case of antimalarials, and pesticides as well. This type of dual externality is not frequently encountered in the natural resources arena and has important policy implications, as we shall soon encounter.

Second, we cannot readily classify antibiotic effectiveness as a renewable or a depletable resource. Whether effectiveness is renewable or not depends on a biological parameter called the fitness cost of resistance. Resistant parasites may bear an evolutionary disadvantage in the absence of antibiotics because they are specially adapted to survive in the presence of antibiotics. For instance, resistant bacteria may have a thicker cell wall to protect them from antibiotics, but the resources devoted to protective covering also makes them less fit for survival in an environment devoid of antibiotics. Although some studies have demonstrated that resistance does carry a fitness cost (Musher, Baughn et al. 1977; Bennett and Linton 1986; Bouma and Lenski 1988), others have shown that fitness cost is insignificant (Schrag, Perrot et al. 1997; Bjorkman, Hughes et al. 1998). The idea of fitness cost of

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resistance is central to this paper. The third difference between antibiotic effectiveness and other natural resources has to do with the functional form of intertemporal dynamics of resource extraction. For instance, the depletion of antibiotic effectiveness takes a peculiar logistic form in which the effect of harvest on the stock level is a function of the stock level (unlike in the case of fisheries, for instance). This difference is not trivial. It makes the antibiotic resistance problem both rich and complex and yields interesting results, including some that are counterintuitive from the standpoint of standard natural resource models.

In this paper, I focus on the specific question of optimal use of antibiotics. Antibiotic effectiveness may be conveniently modeled as a natural resource for the purpose of analyzing strategies for optimal use. Laxminarayan and Brown introduce this analytical framework to characterize the optimal use of two antibiotics that differ in economic costs, rate of evolution of resistance, and initial susceptibility (Laxminarayan and Brown 2001). That paper shows that if two antibiotics differ only with respect to the initial level of resistance, then the optimal treatment strategy is to use the more effective antibiotic initially until bacterial resistance to the two antibiotics is identical. From there on, both antibiotics are used simultaneously such that their effectiveness is always identical. The singular feature of this socially optimal decision rule is that it also is privately optimal for individual patients to use the most effective antibiotic at all times; therefore, theoretically, there is no need for a corrective policy intervention to ensure that the socially optimal rule is followed.

This paper differs from the Laxminarayan and Brown paper in two important respects. First, I relax the assumption that the fitness cost of resistance is zero or negligible.[3] Introducing fitness costs of resistance alters the results of the earlier paper substantially, and the case without fitness cost is simply a special case of the more general model that I discuss here. I find that when two drugs differ only with respect to the fitness cost of resistance and in no other respect (such as treatment costs or initial level of effectiveness), then it is optimal to first use the drug with the lower fitness cost of resistance until such time that the resistance to the two drugs is of the same ratio as their respective fitness costs. From this

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[3] Two other recent papers have approached the same problem, but from different directions. Wilen tackles the problem of optimal use of a single antibiotic and compares strategies that lower the overall transmission of infection through better infection control, with those that improve antibiotic use Wilen, J. E. and S. Msangi (2001). Dynamics of antibiotic use: ecological versus interventionist strategies. RFF Conference on the Economics of Antibiotic Resistance, Airlie House. Brown and Rowthorn use a two drug framework to characterize the optimal path of

point on, it is optimal to use both drugs at a steady state in which the loss of antibiotic effectiveness is just matched by the rate at which effectiveness recovers due to the fitness cost of resistance. Note that the coincidence of social and private incentives that one encounters in the Laxminarayan and Brown paper is no longer present. When fitness costs are present, it may sometimes be optimal to first use a drug even if it is of relatively lower effectiveness on some fraction of the infected population; such a strategy is not always compatible with the individual patient's desire to be treated with the most cost-effective drug.

Second, I examine the effect of nonconvexities in antibiotic treatment costs on the optimal antibiotic use strategy, particularly with respect to the use of cycling strategies that are the subject of close scrutiny in the medical literature. Although mathematical models and optimal control models are rarely, if ever, found in this literature, there has been much recent discussion of cycling or switching between two or more antibiotics as a potential strategy to address the problem of increasing antibiotic resistance (McGowan 1986; Niederman 1997; Bergstrom, Lipsitch et al. 2000; John and Rice 2000). The concept of cycling, as discussed in these papers, hinges critically on the fitness cost of resistance. If the fitness cost associated with bacterial resistance to antibiotics is high, then it is argued that one can conceive of periodically removing an antibiotic from active use to enable it to recover its effectiveness, before bringing it back into active use.[4] On the other hand, if fitness cost is insignificant, then antibiotic effectiveness always declines, and it makes no sense to cycle antibiotics.[5]

In a seminal paper on modeling the evolution of antibiotic resistance, Bonhoeffer et. al. use a simple mathematical model of evolution of drug resistance and infection to show that it is never optimal to cycle between two antibiotics that are identical, even if the fitness cost of resistance to the two antibiotics is large (Bonhoeffer, Lipsitch et al. 1997). They demonstrate that cycling is an inferior

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antibiotic use when all patients in the population receive treatment Rowthorn, B. and G. M. Brown (Ibid.). Using antibiotics when resistance is renewable.

[4] Among the few studies that have analyzed the effectiveness of cycling, one found that switching from gentamicin to other aminoglycosides reduced resistance to gentamicin. However, when gentamicin was reintroduced, resistance developed rapidly Gerding, D. N., T. A. Larson, et al. (1991). "Aminoglycoside resistance and aminoglycoside usage: Ten years of experience in one hospital." *Antimicrobial Agents and Chemotherapy* **35**(7): 1284-90. Another study noted a significant decrease in ventilator-associated pneumonia caused by antibiotic resistant bacteria when prescribed antibiotics were switched from third-generation cephalosporins to quinolones, but there was no switch back to cephalosporins Kollef, M. H., J. Vlasnik, et al. (1997). "Scheduled change of antibiotic classes: A strategy to decrease the incidence of ventilator-associate pneumonia." *Am. J. Respir. Crit. Care Med.* **156**: 1040-48.

[5] In some cases, resistant bacteria can acquire compensating mutations that restore their fitness *vis a vis* susceptible bacteria.

strategy when compared to simultaneously treating equal fractions of the population with the two antibiotics, or using a combination of the two antibiotics on all patients.

In this paper, I demonstrate that Bonhoeffer's results rest on the assumption that antibiotic treatment costs are convex.[6] This may not be the case in reality in a hospital setting. Often, there is a fixed cost of maintaining a drug on the hospital formulary, incurred by way of cost of shelf space, and the cost associated with returning unused or expired drug to the wholesaler. Further, some drug companies offer special prices for their products if they are put on the formulary and other substitutes are excluded, as well as volume discounts for their products.[7] Both of these factors introduce nonconvexities into the cost function, which may result in simultaneous use of two antibiotics being economically inefficient. Switching from one antibiotic to another also incurs its own set of costs. First, there is the administrative effort of taking one drug off the formulary and adding another one on. Second, there is a cost associated with educating physicians and nurse practitioners about a new drug. As will be shown in the rest of the paper, the cost of switching is critical in determining the length of time that an antibiotic should be used, before rotation to a second antibiotic.

This paper has two goals. The first is to derive a decision rule that describes the optimal strategy for using antibiotics when the fitness cost of resistance is positive. The second is to describe the conditions (if any) under which it may be optimal to cycle between two or more antibiotics. The simple model of evolution of antibiotic resistance and bacterial infection used in this paper is based on the modeling framework developed in Laxminarayan and Brown, modified by the assumption that fitness cost of resistance is non-zero (Laxminarayan and Brown 2001). In the interests of avoiding an elaborate discussion of the derivation of that model and its assumptions, I refer the interested reader to the earlier paper.

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[6] Typically, in economic analysis, marginal costs are assumed to convex, i.e. they increase with use, but at a decreasing rate. However, when there is a fixed cost associated with use, then the marginal cost of using the first unit is much greater than the marginal cost of each additional unit.

[7] For example, hospitals would be quoted the lowest price for Levofloxacin from Ortho-McNeil if ciprofloxacin (an antibiotic made by a rival firm) were not on the formulary. This discount is offered, regardless of how much levofloxacin is used. Therefore, having Ciprofloxacin on the formulary is costly in terms of increasing the price of levofloxacin to the hospital (personal communication, Professor Doug Black, Department of Pharmacy, University of Washington, Jan 30, 2000).

This paper is organized as follows: section 2 presents the basic model and describes the pattern of optimal antibiotic use, when biological fitness costs are present. Section 3 describes the conditions under which cycling antibiotics is optimal from an economic perspective. Section 4 concludes the paper.

Model

Natural selection is the most common mechanism by which antibiotic resistance develops. Most bacteria have a low level of resistance to antibiotics, in the order of one in a million. Repeated use of antibiotics places selection pressure on the susceptible bacteria, thereby favoring this small number of resistant bacteria for survival. Given enough time and antibiotic use, the bacterial population is composed entirely of these resistant strains. Treatment of these resistant populations using antibiotics is then quite ineffective.[8]

As one might imagine, the process of evolution of antibiotic resistance and the elements of human behavior that facilitate this process are incredibly complex. However, we can abstract from this degree of complexity to a level where we remain faithful to the essential elements of population genetics that govern how resistance evolves. We follow a model of evolution of resistance that is based on the well-known Kermack-McKendrick SIS model of evolution of infection (Kermack and McKendrick 1927).[9] The key element of the model used is that bacterial resistance to antibiotics increases in a logistic fashion to antibiotic use.[10] Although a number of other factors contribute to resistance, such as inappropriate use of antibiotics, lack of sufficient infection control methods, and failure by patients to complete a full cycle of treatment, an analysis of the economic incentives that influence these other factors lies outside the scope of this paper.

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[8] While natural selection is the most important mechanism for the spread of resistance, a less frequently occurring mechanism of resistance is through plasmid transfer. Bacteria possess the ability to directly transfer genetic material between themselves. These genetic materials, known as plasmids, frequently contain genetic material that codes for resistance, and enable the spread of resistance from bacterial species that have been exposed to antibiotics to other bacterial species.

[9] The interested reader is referred to the seminal text in this area by Anderson and May (Anderson, R. M. and R. M. May. 1991. *Infectious Diseases of Humans: Dynamics and Control*. New York: Oxford University Press).

[10] A number of studies have demonstrated conclusively that the development of bacterial resistance to antibiotics is correlated with the level of antibiotic use Cohen, M. L. 1992. Epidemiology of drug resistance: Implications for a post-antimicrobial era. *Science* 257: 1050-1055.

From a medical standpoint, the fundamental responsibility of the individual physician is to exercise good judgement in prescribing the optimal dose of the best antibiotic that would bring about a favorable clinical outcome (Gerding 2000). However, the overall objective of hospital infection control managers, who are charged with the well-being of all patients in the hospital both in the present and in the future, is to ensure that patients recover soon and that bacterial resistance is minimized, rather than just one or the other. Minimizing resistance, by itself, is a meaningless objective and is probably best achieved by not using antibiotics at all. Similarly, improving treatment outcomes in the short term is achieved by not imposing any restrictions on antibiotic use at the cost of increasing resistance in the future. It is because the infection control committee's objective is to tradeoff between treatment outcomes in the present, with the possibility of future resistance, that economic analysis plays a useful role in providing a metric for making comparisons between present and future benefits and costs of antibiotic treatment.

I follow the model and mathematical notation introduced in Laxminarayan and Brown. Complete derivations of the mathematical equations for evolution of infection and drug resistance are contained in that paper. The model presented here differs from the one in that earlier paper in two important respects. First, as discussed earlier, I permit the biological fitness cost of drug resistance to be non-zero. Second, I consider the case of N drugs, rather than two drugs, for reasons explained below.

Approximating to two drugs is a special case and not directly generalizable to the N drug case when fitness costs of resistance are involved.[11] As we shall soon see, at the steady state, the optimal fraction of the infected population that should be treated with each drug is equal to the fitness cost of resistance,[12] such that the decrease in effectiveness caused by selection pressure imposed by drug treatment is exactly offset by the evolutionary pressure exerted in the opposite direction by the fitness cost of resistance. Therefore, the necessary condition to ensure that it is optimal to treat *all* infected patients at

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[11] Considering the use of just one antibiotic is problematic for analytical reasons. Antibiotic resistance models are fairly complex to begin with, involving the simultaneous interplay between the effects of antibiotic use on lowering infection and on increasing resistance. Comparing the use of two or more antibiotics permits us to cancel out all terms related to the infection state equation and focus on the interplay between the costs and benefits of using two or more drugs and makes the model both analytically tractable, as well as realistic from a policy standpoint.

[12] To be more precise, the fraction treated is set equal to the fitness cost of resistance adjusted for the rate of recovery with drug treatment. We implicitly normalize this rate to one for analytical convenience.

the steady state is that the fitness cost of all of the individual antibiotics available for use be positive and that their sum be equal to one.

$$(1) \sum_{i=1}^{N} r_i = 1$$

If the sum of fitness costs was less than one, as it well might be if only two drugs were to be used, then we would leave some infected patients untreated at the steady state. Simultaneously imposing the simplifying assumption of two antibiotics with $r_1 + r_2 < 1$, as well as an exogenous constraint that all patients must be treated can be misleading, because the problem is implicitly reduced to one of depletable drug effectiveness, albeit at a slower pace of depletion than if the fitness cost were zero.

The model variables are as follows. $I(t)$ denotes the stock of infection and refers to the fraction of the hospital population that is infected. r is the spontaneous or no-treatment rate of recovery from a resistant infection. The fraction of the infected population that carries a susceptible strain (treatable using antibiotic i) is denoted by $w_i(t)$. The fitness cost associated with resistance to antibiotic i is represented by r_i. The rate of recovery from a susceptible infection with antibiotic treatment is assumed to be identical for both antibiotics, and normalized to one. The equations of motion for the $N+1$ state variables in the model, $I(t)$, $w_i(t)$, $i = 1..N$ are given by

$$(2) \frac{\dot{I}(t)}{I(t)} = \beta(1 - I(t)) - r - \sum_i w_i(t)(f_i(t) - r_i)$$

$$(3) \frac{\dot{w}_i(t)}{w_i(t)} = (f_i(t) - r_i)(w_i(t) - 1) \quad i = 1..N$$

The objective is to choose $f_i(t)$, the fraction of the infected population to treat with antibiotic i in each period, so as to maximize the discounted net present value of benefits of antibiotic use. The benefit of successful (and expedited) recovery through antibiotic treatment is given by $bw_i f_i I$, where b is the benefit associated with each successful treatment using antibiotics (measured in dollars per person), scaled by the infected population that is treated $f_i(t)I(t)$, and the effectiveness of the antibiotic

treatment, $w_i(t)$. The cost of the infected population borne by society is $c_i I$. The intertemporal objective functional can be written as[13]

$$(3.1)\max\int_0^\infty\left[bI(t)\left(\sum_i w_i(t)f_i(t)\right)-c_I I(t)\right]e^{-\delta t}\,dt,$$

subject to equations (2.1) and (2.2) and the following constraints

$$(3.2)\,I(t)\le 1$$

$$(3.3)\,0\le f_i(t)\le 1$$

$$(3.4)\sum_i f_i(t)\le 1$$

     Antibiotic treatment costs are assumed to be identical for all drugs and therefore normalized. Infection enters both the benefit and cost function, and acts as capacity constraint on the extraction of antibiotic effectiveness in any given period. This feature of a moving capacity constraint distinguishes the antibiotic problem from other problems of natural resource extraction. Although infection is undesirable and is reflected in the term $c_I I(t)$, a higher level of infection also implies a greater number of patients reap the benefits of successful antibiotic treatment for any given $f_i(t)$. We assume that

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[13] An alternative objective could be to minimize the sum of the cost of infection and the cost of treatment, $cfI + c_I I$. However, the function presented is a more general version of this total cost approach for the following reason. Consider the benefit of recovery from the infected state, the analytical twin of the cost of treatment cfI. The benefit to those who are infected with a susceptible infection and who get antibiotics can be written as $b_1 wfI$. Patients who get an antibiotic but have a resistant infection get benefit of $b_2 fI(1-w)$. Patients who do not get any antibiotic at all recover at the spontaneous rate of recovery, r, and get a benefit given by $b_3 rI$. Net benefit (NB) of recovery either at faster or slower rate is given by the sum, $NB = b_1 wfI + b_2(1-w)fI + b_3 rI - c_I I$. Now, if patients care only about being treated and have no preference between recovering faster from a susceptible infection and slowly from a resistant infection, then $b_1 = b_2 = b$ and $b_3 = 0$, then we get $NB = bfI - c_I I$, which is essentially equivalent to the total cost approach. However, if the hospital administrator cares only about recovering faster, and the cost of infection, $b_1 \ne b_2$ and $b_2 = b_3 = 0$, then we get $NB = x_1 wfI - c_I I$ which what we use in the model. This approach also allows us to focus on the role of antibiotic effectiveness as part of the planner's objective function.

$b\left(\sum_i w_i(t)f_i(t)\right) - c_I < 0$ to ensure that the objective function is non-increasing in the level of

infection. We also assume that no patient receives more than one antibiotic.

In the interest of clarity, time subscripts are suppressed hereon. The current value Hamiltonian to maximize (3.1) subject to constraints is given by

$$(4) \quad H = bI\left(\sum_i w_i f_i\right) - c_I I + \varphi\left[\beta I(1-I) - rI - I\left(\sum_i w_i(f_i - r_i)\right)\right] + \sum_i \left(\mu_i(f_i - r_i)w_i(w_i - 1)\right)$$

where δ is the social discount rate and costate variables φ and μ_i are associated with I and w_i respectively.

The necessary first order conditions for a maximization of (7) are:

$$(5.1)\ f_i\begin{pmatrix} =0 \\ \in [0,1] \\ =1 \end{pmatrix} as\ (b-\varphi)Iw_i - \mu_i w_i(1-w_i)\begin{pmatrix} < \\ = \\ > \end{pmatrix} 0\ \ for\ i=1..N$$

$$(5.2)\ (b-\varphi)If_i + \varphi Ir_i - \mu_i(f_i - r_i)(1-2w_i) = \delta\mu_i - \dot\mu_i\ \ for\ i=1..N$$

$$(5.3)\ b\sum_i w_i f_i - c_I + \varphi\left[\beta - 2\beta I - r - \sum_i w_i(f_i - r_i)\right] = \delta\varphi - \dot\varphi$$

$$(5.4)\ \lim_{t\to\infty} \mu_{it}w_{it}e^{-\delta t} = 0$$

$$(5.5)\quad \lim_{t\to\infty} \varphi_t I_t e^{-\delta t} = 0$$

According to the first order condition represented by equation (5.1), our decision on whether or not to use antibiotic i is determined by whether the sum of the private (bIw_i)and social benefit of treatment ($-\varphi Iw_i$) equals or exceeds the cost to society of decreased antibiotic effectiveness. The cost to society is given by the marginal user cost of antibiotic i, (μ_i), scaled by the impact of treating another infected patient on the overall level of effectiveness, ($w_i(1-w_i)$). φ is the marginal cost to society of

another infected individual and is therefore non-positive (see Appendix 1 for proof). The divergence between the socially optimal benchmark on whether to use a particular antibiotic from the privately optimal decision is apparent. In contrast to the social planner who takes both the social benefit of treatment in terms of reduced infection transmission as well as the social cost of treatment in terms of reduced future effectiveness into account, the individual decision maker will use an antibiotic as long as the private marginal benefit of use exceeds the private marginal cost.

Hereon, I shall take the following approach. First, I characterize the steady state in which all antibiotics are in use. Then, working backwards from the steady state, I examine the N-jointly singular path along which all N antibiotics are being used. We will see that the steady state lies on the N-jointly singular path. Finally, I examine the case in which only one antibiotic is being used to the exclusion of all others. Having proceeded thus far in a reverse fashion, I illustrate the results shown with an example—which we will move forward in time—to reconstruct the optimal pattern of antibiotics use from time zero until the steady state is reached.

At the steady state, $\dot{w}_i = 0$, $\dot{I} = 0$. From equations (2.1) and (2.2), we have

(6) $f_i^* = r_i$ for all $i = 1..N$

which implies that all available antibiotics are used at steady state, as long as their fitness cost of resistance is non-zero. We can then solve for the steady state stocks of infection, I^* and antibiotic effectiveness, w_i^*. From equation (1), at steady state, $I^* = \dfrac{\beta - r}{\beta}$.

From equation (5.2), and the steady state condition $\dot{\mu}_i = 0$, we get

(6.1) $bIf_i = \delta \mu_i$

Substituting for $(b - \varphi)I^*$ into equation (5.1), we get

(6.2) $(b - \varphi)I^* = \dfrac{bIf_i}{\delta}\left(1 - w_i^*\right)$ for all $i = 1..N$

Since the term on the left hand side is identical for all antibiotics, we have at the steady state

(7) $$\left(1 - w_1^*\right)f_1 = \left(1 - w_2^*\right)f_2 = \ldots = \left(1 - w_N^*\right)f_N$$

Equation (7) represents the social optima, which equates the probability that an infected patient will be treated with drug 1 and that such treatment will be unsuccessful, with the corresponding probabilities for any other drug in the available portfolio of drugs. Note that at the steady state, the socially optimal treatment strategy is independent of considerations of infection or of future antibiotic resistance.

When condition (1) is met, the above steady state is one in which the rate at which antibiotic effectiveness is depleted through use is exactly offset by the rate of growth of effectiveness due to the fitness cost of resistance.[14] A similar state, albeit for a single stock, exists in the case of optimal fish harvesting. Furthermore, the steady state lies along the N-jointly singular path. Therefore, we can reasonably assume that it is possible to reach this steady state.

What is the economic intuition that underlies this steady state? First of all, the first order condition for the maximization problem stipulates that that marginal private benefit of antibiotic use plus the marginal social benefit in terms of a reduced stock of infection is identical for all antibiotics that are in use. For each antibiotic that is being used, the marginal benefit of use (private plus social) is exactly equal to the marginal social cost measured by the adjusted rental rate on the stock of effectiveness of that antibiotic. Since the first order condition stipulates that the fractions treated with any given antibiotic is such that the marginal benefit of all antibiotics in use is identical, the marginal rental cost of all antibiotics also is the same at the steady state.

We now turn to the problem of characterizing the optimal path of antibiotic use leading up to the steady state. The optimization problem is linear in the control variables $f_i(t)$, where

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[14] This, of course, rests on the assumption that equation (1) holds. Suppose $\sum_{i=1}^{N} r_i > 1$, then all drugs would be used in the steady state, but $f_i = \dfrac{r_i}{\sum_i r_i}$. Therefore, there would be a steady state in which the rate of depletion was lower than the rate of growth of effectiveness, in which the effectiveness of all drugs that were being used was rising slowly.

the N switching functions are given by the coefficients of N $f_i(t)$ controls. We consider various combinations of singular and bang-bang controls:

Case 1: All f_i's are singular

Assume that all N drugs are being used, and that we are on the N-jointly singular path. From equation (5.1),

$$(8)\,(b-\varphi)I = \mu_i(1-w_i) \text{ for all } i = 1..N$$

Therefore,

$$(9)\,\mu_j(1-w_j) = \mu_k(1-w_k) \text{ for } i = j, k.$$

We demonstrate the condition for joint use of any two antibiotics j and k, obtained by synthesizing the control. Differentiating equation (9) with respect to time, we have

$$(10.1)\,(b-\varphi)\dot{I} - \dot{\varphi}I = \dot{\mu}_i(1-w_i) - \mu_i \dot{w}_i$$

We can substitute for $\dot{\mu}_i$ and $\dot{w}_i$ from equations (2.2) and (5.2) and equate for drugs j and k, to show that (see Appendix 2 for mathematical derivation)

$$(10.2)\,r_j(1-w_j) = r_k(1-w_k)$$

We refer to equation (10.2) as the joint use condition. It describes the simple mathematical condition for simultaneous use of any two antibiotics to be optimal. The key feature of this joint use condition is that it may be socially optimal to use two antibiotics simultaneously, even if bacterial resistance to one drug is greater than to the other.

At the steady state, when all N drugs are being used and $f_i = r_i$ for all $i = 1..N$, the joint use condition defines the steady state as represented by equation (7). From this, we infer that the steady state lies along the jointly singular path.

From equations (2.1) and (10.2), along the doubly singular path,

$$(11)\ \frac{\dot{w}_j}{w_j}\left(\frac{r_j}{f_j - r_j}\right) = \frac{\dot{w}_k}{w_k}\left(\frac{r_k}{f_k - r_k}\right)$$

Differentiating the equation (10.2) with respect to time yields, and combining with equation (11), we have

$$(12)\ w_j\left(f_j - r_j\right) = w_k\left(f_k - r_k\right)$$

Therefore, the joint use condition is always satisfied if $f_j = r_j$ and $f_k = r_k$.

Case 2: $f_j = 1$ and $f_k = 0\ \forall\ k \neq j$.

From the first order conditions, we have the necessary conditions for antibiotic j to be used alone,

$$(13)\ (b - \varphi)I - \mu_j\left(1 - w_j\right) = 0$$

and

$$(14)\ (b - \varphi)I - \mu_k\left(1 - w_k\right) < 0\ \forall\ k \neq j$$

Therefore,

$$(15)\ \mu_k\left(1 - w_k\right) < \mu_k\left(1 - w_k\right)\ \forall\ k \neq j$$

This condition can be interpreted as follows: μ_j is the shadow cost of effectiveness of antibiotic j. Under a conventional resource use criterion, we would want to use the resource with the lowest marginal cost, first. In the case of antibiotics, the user cost of an antibiotic is reflected in the rental rate on antibiotic effectiveness. Therefore, we would want to use the antibiotic with the lowest rental rate, and the highest level of effectiveness first, as shown by the above inequality.

In order to represent this optimal path in terms of measurable epidemiological and economic parameters, we can differentiate the above inequality with respect to time to obtain,

$$(16)\ \dot{\mu}_j\left(1-w_j\right)-\mu_j\dot{w}_j < \dot{\mu}_k\left(1-w_k\right)-\mu_k\dot{w}_k \quad \forall \ k \neq j$$

We can substitute for $\dot{\mu}_j$ and $\dot{\mu}_k$ from equations (5.2), and make the following substitution

$$(17)\ \mu_k\left(1-w_k\right)-\mu_k\left(1-w_k\right)=\theta \ \text{ where } \theta > 0$$

to arrive at the following condition[15]

$$(18.1)\ bI\left[\mu_j\left(1-w_j\right)-\mu_k\left(1-w_k\right)\right]< 0$$

The simple decision rule is to use antibiotic j before using antibiotic k , as long as

$$(18.2)\ r_j\left(1-w_j\right)< r_k\left(1-w_k\right)$$

In words, we would use a drug with a combination of relatively low fitness cost and relatively high level of effectiveness. In order to understand the economic intuition underlying this rule, we need to translate these biological criteria into economic costs. We can interpret the biological fitness cost of resistance, r_i, in economic terms as an inverse measure of the cost of using antibiotic i in terms of declining future effectiveness. The greater the value of r_i, the less effect that antibiotic use has on eroding future drug effectiveness. An antibiotic with a larger value of r_i is more valuable and, therefore, the rental rate associated with each unit of effectiveness of this drug also is relatively greater. Hence, our optimal policy is to use the drug that is both the most effective as well as "least costly" in terms of user cost of foregone antibiotic effectiveness. This policy is in keeping with the general wisdom of using resources in the order of increasing marginal cost of extraction (Weitzman 1976). Note that a drug with a low fitness cost of

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[15] This holds when $w_k > \dfrac{r_k-\delta}{r_k}$, a condition that is met as long as the fitness cost of resistance of each antibiotic is smaller than the discount rate, or effectiveness is sufficiently large.

resistance is inherently a "cheaper" drug, not from the standpoint of treatment effectiveness (because effectiveness only depends on level of resistance), but from an economic opportunity–cost standpoint. Therefore, all else equal, it pays to use this drug first.

When $r_j = r_k$, then the condition for using drug j alone is that $w_j > w_k$. This is the specific case addressed in the earlier paper by Laxminarayan and Brown.[16] If two antibiotics have identical fitness costs of resistance, then the necessary condition to use drug j only before drug k is that resistance to drug j is lower. Interestingly enough, this coincides perfectly with private incentives. Individuals who act in a self-serving manner ignore both the positive social impact of getting treated (in reducing the chance that they will transmit the infection to someone else), as well as the negative social impact of getting treated (in decreasing future antibiotic effectiveness for the rest of society). While choosing the right antibiotic for their needs, individuals (or, more likely, their physicians) equate the probability of successful treatment using any one of the antibiotics available to them and therefore set equal the expected probability of treatment cure from all available antibiotics. Therefore, the socially optimal policy is compatible with private incentives for this special case alone.

When $r_j > r_k$, then the necessary condition to use antibiotic j alone is $w_j > w_k$. In other words, if the fitness cost of resistance of drug j is greater than that of drug k, then it is absolutely necessary that the effectiveness of drug j exceed that of drug k for the following reason: since drug j has the higher fitness cost of resistance, it is the more costly drug to use, from an economic opportunity cost standpoint. Therefore, its effectiveness will have to be greater in order to compensate for the higher cost of using this antibiotic.

When $r_j < r_k$, it is possible that we may want to first use drug j alone even if $w_j < w_k$. This is completely counterintuitive to the medical viewpoint that the patient must be treated with the best available drug at the lowest cost. This strange result is easily explained, once the user cost of antibiotic effectiveness is taken into consideration. A drug with the lower fitness cost of resistance is naturally the less "costly" drug from a resistance cost standpoint since *ceteris paribus,* the shadow value, on this drug

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[16] In fact, they assume that the fitness costs of resistance to the two drugs are not just equal to each other, but also equal to zero.

will always be lower than for other drugs. Therefore, this drug should be used first. If r_j is sufficiently less than r_k, the user cost advantage afforded by drug j may be large enough to outweigh a disadvantage in terms of its lower level of effectiveness. Therefore, our optimal policy would be to use the "less costly" drug, j, even if the level of resistance to this drug is greater. We continue using drug j until the level of resistance increases sufficiently so as to ensure that equation (13) holds. From this point on, it is optimal to use both j and k drugs simultaneously, as shown in Case 1.

Based on the above discussion, we can characterize the optimal pattern of antibiotic use as shown in Figure 1. Consider three drugs, j, k and l such that $r_j + r_k + r_l = 1$. The initial level of effectiveness of the two drugs is given by $w_j(0), w_k(0)$ and $w_l(0)$ respectively, such that $(1 - w_j(0)) r_j < (1 - w_k(0)) r_k < (1 - w_l(0)) r_l$.

Initially, it is optimal to use antibiotic j exclusively for a period of time, before drug k is also brought into use. During this time, the effectiveness of the drugs k and l which are not being used rises at a rate determined by r_k and r_l while the effectiveness of drug j declines in response to its use. This continues until time, τ_k, when $\left[1 - w_j(\tau_k)\right] r_j = \left[1 - w_k(\tau_k)\right] r_k$.

By integrating equation (2.1), we can rewrite the above condition as

$$(19) \quad \left[1 - \frac{1}{1 - \dfrac{w_j(0)}{1 - w_j(0)} e^{(1 - r_j)\tau_k}} \right] r_j = \left[1 - \frac{1}{1 - \dfrac{w_k(0)}{1 - w_k(0)} e^{-r_k \tau_k}} \right] r_k$$
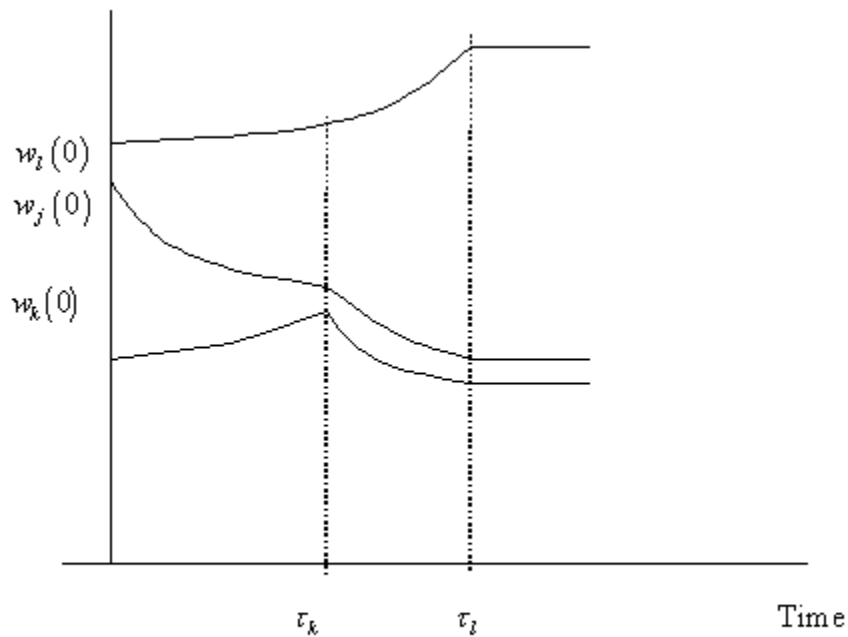
Figure 1: Pattern of optimal antibiotic use

From our knowledge of $w_j(0)$, $w_k(0)$, r_j, and r_k, we can solve for the optimal period τ_k, during which only antibiotic j is used. After time τ_k, both antibiotics are used simultaneously in the fractions proportional to their respective fitness costs.

The optimal fraction to treat once the joint use condition between any two drugs has been reached is identically equal to the fitness cost of resistance of each drug adjusted for the rate of recovery. It is obvious that one would want to use all available antibiotics at the steady state as long as their fitness cost of resistance was positive. If any single antibiotic were not being used, then its effectiveness would rise due to the fitness cost of resistance until such time that condition (18.2) was satisfied. At this time, it would be optimal to include that antibiotic in our menu of drugs. From condition (1), at the steady state, the entire population of infecteds receives treatment, and the effectiveness of each antibiotic used remains constant. Imagine for a moment that condition (1) does not hold and $\sum_{i=1}^{N} r_i < 1$. We then either have to settle for treating less than the entire population of patients in order to remain at a steady state, or forgo the steady state in favor of one where the effectiveness of all drugs is declining. It is for this reason that

the notion of thinking of a world in which only two drugs are available is a spurious approximation, and could lead to incorrect policy solutions.

Cycling Antibiotics

A topic of current interest related to managing antibiotic resistance is that of cycling between two or more antibiotics that are therapeutic substitutes for one another. In some bacterial populations, it has been documented that drug resistance declines once the drug has been withdrawn from active use. However, the time taken for antibiotics to recover their effectiveness is longer than the time it takes for the initial loss of effectiveness, a fact that is easily explained by equation (3). A great deal of uncertainty persists about the conditions under which cycling is optimal, and the optimal rotation or switching time between two or more antibiotics (McGowan 1986; McGowan and Gerding 1996; Bergstrom, Lipsitch et al. 2000). Finally, there is little empirical that promotes using cycling strategies to successfully manage resistance in hospitals. (McGowan and Gerding 1996).

Bonhoeffer and colleagues make it clear that biology confers no advantage on the cycling strategy (Bonhoeffer, Lipsitch et al. 1997). They suggest, "When more than one antibiotic is employed, sequential use of different antibiotics in the population or cycling is always inferior to treatment strategies where, at any given time, equal fractions of the population receive different antibiotics." Extending their argument to the economic dimension, we can see that, unless the cost of stocking two antibiotics is substantial enough to outweigh the biological benefits of simultaneously employing two antibiotics, the issue of cycling between two antibiotics, though interesting, may not be an important one.

Specifically, we can demonstrate that cycling is an optimal strategy only when two essential conditions are satisfied. First, there must be non-convexities in antibiotic costs. For instance, there may be a fixed cost associated with maintaining an antibiotic on the hospital formulary. If there is no fixed cost of storing keeping an antibiotic on the formulary, then it makes sense to maintain the greatest diversity of antibiotics on the formulary. This minimizes the likelihood that selective pressure to any single drug or class of drugs would be great enough to lead to bacterial resistance to that drug. Second, it is necessary that there be a cost of switching from one antibiotic to another. If this second condition is not satisfied, then the optimal switching strategy may be to instantaneously switch back and forth between the two or more antibiotics. Although economic considerations determine whether or not a cycling strategy is optimal, biological considerations, such as the fitness cost of resistance, play an important role

in determining the optimal rotation time (the length of the interval during which one antibiotic is used) before switching to the other. In short, in the absence of economic considerations, there is no rationale to implement a cycling strategy in place of a simultaneous use strategy, in which all available antibiotics are used. Although the fitness cost of resistance does not determine whether or not cycling is an optimal strategy, it does determine the fraction of time devoted to using each antibiotic during a single rotation.

There are important parallels between the question of cycling antibiotics and the long-studied questions in natural resources economics, such as those of crop rotation, and cycling between two or more stocks of fish for harvesting (Niederman 1997).[17] These analogies can be useful in understanding the theoretical underpinnings of cycling strategies for antibiotics. The most general theoretical analysis of cycling is by Lewis and Schmalensee (Lewis and Schmalensee 1977; Lewis and Schmalensee 1979). In these papers, they formally characterize the economic conditions under which cyclical harvesting is a superior strategy to continuous harvesting. The most direct analogy of the essence of the optimal rotation of antibiotics is represented by the Faustman solution to the problem of optimal rotation in tree harvesting (Clark 1976). In that model, the principle of stationarity is invoked to determine the optimal period of time that a tree is grown before it is harvested and the land is reforested.[18] The cost of planting a new tree in the Faustman solution is similar to the cost of switching from one antibiotic to another. In the absence of this planting cost, the optimal solution in the Faustman problem is to cut trees

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[17] The literature on cycling in natural resource economics is derived from the Ss model of inventory stocking Reed, W. J. (1974). A stochastic model for the economic management of a renewable animal resource. Mathematical Biosciences 22: 313-37. Under this model, there is a fixed cost of harvesting a renewable resource (an activity that is the analytical twin of replacing a low effectiveness antibiotic with a more effective one.) Harvesting is initiated if the stock of the resource exceeds some level, s, and continued until the stock reaches a lower bound value of S, where $S < s$. At this point, harvesting is stopped and the resource is allowed to regenerate. If the fixed cost incurred by harvesting the resource is zero, then $S = s$, in which case, continuous harvesting is the optimal strategy. Other research in this area has shown that, in addition to fixed costs, non-convexities in the optimization problem such as those introduced by non-linear cost functions, and positive stock externalities can facilitate cycling. Clark, C. W., F. H. Clarke, et al. (1979). "The optimal exploitation of renewable resource stocks: Problems of irreversible investment." *Econometrica* 47: 25-47.

Wirl, F. (1995). "The cyclical exploitation of renewable resource stocks may be optimal." *Journal of Environmental Economics and Management* 29: 252-61.

[18] The principle of stationarity, which is described in greater detail in the next section, essentially refers to a condition in which the optimal strategy is a function only of the state variables (infection and resistance levels in the hospital setting) and is independent of the time period during which the strategy is to be executed.

down instantaneously after planting, a strategy that bears resemblance to the simultaneous use of two antibiotics.[19]

In the analysis presented, I examine the economic wisdom of cycling between antibiotics. As is typical in such rotation models, stationarity is assumed. In other words, if the pattern of antibiotic use, given by $f_1, f_2 \ldots f_N$, is optimal for the state variables $I(t_1)$, $w_1(t_1), w_2(t_1)$, ..., $w_N(t_1)$ at time t_1, then the same pattern of use must be optimal when the same states are encountered at some time $t_2 \neq t_1$. Therefore, the optimal rotation rule can be expressed as a function of the state variables alone.

We can show that the necessary condition for cycling (using sliding control) to be preferable to continuous optimal control is that cost of treatment is non-convex. Furthermore, the optimal fraction of time devoted to each drug is directly proportional to the fitness cost of resistance to that drug. The proof is as follows. Consider an infinitesimally small time interval ε. During this time interval, infection level is assumed to be constant. Under a chattering (or sliding) control strategy, we use each drug i for a fraction of time α_i of the interval ε.

$$(20)\ f_1 = 1 \text{ and } f_{i \neq 1} = 0 \text{ for } 0 \leq t \leq \alpha_1 \varepsilon$$

$$f_2 = 1 \text{ and } f_{i \neq 2} = 0 \text{ for } \alpha_1 \varepsilon \leq t \leq (\alpha_1 + \alpha_2)\varepsilon$$

.

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$$f_N = 1 \text{ and } f_{i \neq N} = 0 \text{ for } (\alpha_1 + \alpha_2 + ... + \alpha_{N-1})\varepsilon \leq t \leq \varepsilon$$

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[19] The idea that the cost of planting (or tree harvesting) is critical to obtaining a finite rotation time in the Faustman solution is not often recognized by resource economists. Indeed, many papers completely leave these costs out of the optimal tree rotation model without acknowledging their importance. In the Faustman model if there were no planting or harvesting costs, the optimal rotation formula would be to instantaneously harvest trees immediately after planting to reap a return to capital that approaches infinity. I am grateful to Gardner Brown for pointing this out to me.

Further,

$$(21) \sum_i \alpha_i = 1$$

With chattering (or sliding control),[20] the equilibrium state for drug i can be written as

$$(22) \Delta w_i^* = \left(f_i^c \alpha_i \varepsilon - r_i \varepsilon \right) w_i^* \left(w_i^* - 1 \right)$$

Since this is a steady state,

$$(23) \alpha_i = \frac{r_i}{f_i^c}$$

Benefit of chattering is

$$(24) V^c = \sum_i \alpha_i \varepsilon \left(w_i^* f_i^c - c \left(f_i^c \right) \right)$$

We compare the benefit of chattering over the time interval ε with the benefit of continuous control given by

$$(25) V^* = \sum_i \varepsilon \left(w_i^* f_i^* - c \left(f_i^* \right) \right)$$

where

$$(26) f_i^* = r_i$$

Chattering (using drugs individually in temporal sequence) is preferable to continuous control (when all drugs are used simultaneously in fractions proportional to their fitness cost of resistance), if

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[20] In optimization theory, chattering has two meanings. The first deals with situations in which optimal control does no exist, or rather a minimizing sequence of controls does not tend to any limit in a given class of admissible controls. This is more commonly referred to as *sliding* control. In chattering, optimal control has an infinite number of switches on a finite time interval Zelikin, M. I. and V. F. Borisov. 1994. *Theory of Chattering Control with applications to astronautics, robotics, economics and engineering*. Boston: Birkhauser..

$$(27) \sum_i \alpha_i \varepsilon \left(w_i^* f_i^c - c \left(f_i^c \right) \right) > \sum_i \varepsilon \left(w_i^* f_i^* - c \left(f_i^* \right) \right)$$

Substituting for f_i^c and f_i^* from above, we can write this condition as

$$(28) \sum_i c(r_i) - \alpha_i c \left(\frac{r_i}{\alpha_i} \right) > 0$$

It is easy to show that the sufficient condition for the above inequality to hold is that the cost of treatment is non-convex.[21]

Our next task is to determine the optimal value of α_i.

$$(29.1) \text{Minimize} \sum_i \alpha_i c \left(\frac{r_i}{\alpha_i} \right)$$

$$(29.2) \text{Subject to:} \sum_i \alpha_i = 1$$

And

$$(29.3) \, 0 \le \alpha_i \le 1$$

The i first order conditions for the Lagrangian are

$$(30) \frac{r_i}{\alpha_i} c' \left(\frac{r_i}{\alpha_i} \right) - c \left(\frac{r_i}{\alpha_i} \right) = \lambda$$

Let $c(x) = x^k$ where $k < 1$. Then

$$(31) \, \alpha_i = \left(\frac{1-k}{\lambda} \right)^{\frac{1}{k}} r_i$$

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[21] Hint: Let $c(x) = x^k$, then $k < 1$ will ensure that the inequality holds.

From equations (18) and (21), we have

$$(32)\ \alpha_i = \frac{r_i}{\sum_i r_i}$$

The optimal fraction of chatter time devoted to any single drug is proportional to the fitness cost associated with resistance to that drug. Using this simple rule one can arrive at a chattering strategy that is superior to continuous optimal control from an economic perspective. If there is no cost of switching between the drugs, chattering is instantaneous for extremely short intervals of length $0 \le \alpha_i \le 1$. However, if there is a cost of switching, then it may be optimal to linger longer with each drug, as we demonstrate below.

Consider the following switching problem. We can assume that costs are nonconvex so that sliding control is an optimal strategy. However, we leave these costs out of the math that follows, so as to focus our attention on the dependence of switching time, ε on switching costs. Consider a finite time horizon, T. Then the number of times we will rotate fully between all available drugs (two in the case under discussion) is given by $\frac{T}{\varepsilon}$. Fractions treated are chosen to ensure return to the steady state at the end of each full rotation. The benefit associated with $\frac{T}{\varepsilon}$ such rotations is given by

$$(33)\ V^R = \frac{T}{\varepsilon}\left(G(\varepsilon) - n\tilde{c}\right)$$

where $\tilde{c}$ is the cost of switching between the n drugs for one complete rotation.[22] We can then choose the optimal ε, by setting $\dfrac{\partial V^R}{\partial \varepsilon} = 0$

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[22] It is relatively easy to set up the problem with discounting and to show that the optimal rotation time for an infinite horizon problem is given by the condition $\dfrac{G'(\varepsilon)}{G(\varepsilon) - n\tilde{c}} = \dfrac{\rho}{1 - e^{-\rho\varepsilon}}$. From this expression we can verify that

$$(34)\ G'(\varepsilon) = \frac{G(\varepsilon) - n\tilde{c}}{\varepsilon}$$

This equation implies that completing a full rotation at time ε maximizes the average per period economic yield. We can verify the necessary second-order condition for concavity is satisfied when $G''(\varepsilon) < 0$ (see Appendix 3 for proof). Fully differentiating the above expression with respect to $\tilde{c}$, we get

$$(35)\ \frac{d\varepsilon}{d\tilde{c}} = \frac{-n}{\varepsilon G''(\varepsilon)} > 0$$

Therefore, the optimal length of each full rotation is increasing in the cost of switching from one drug to the other.

Discussion

Antibiotic effectiveness is a unique natural resource. Although the optimal use strategy broadly conforms to the standard intuition of using the lowest marginal cost resource before turning to resources with higher marginal costs, it is not always clear in what form these costs will arise. The real challenge is to interpret different biological traits as economic costs so that we are able to arrange these biological resources in the order of increasing marginal cost. In the problem described in this paper, a low–cost resource is one for which the fitness cost of resistance is relatively low. This may seem counter-intuitive from a medical practitioner's standpoint, since using a drug with a relatively high fitness cost has the lowest effect on future resistance to that drug. From that perspective, it appears to make sense to use such a drug in preference over others that develop resistance more rapidly in response to use. However, from an economic standpoint, a drug with a high fitness cost of resistance is also a more valuable one. The rental rate on the effectiveness of such a drug is higher, and so it makes sense to delay the use of this drug.

$\dfrac{d\varepsilon}{d\tilde{c}} = \dfrac{-n\rho}{\left(1 - e^{-\rho\varepsilon}\right)\left(G''(\varepsilon) - \rho G'(\varepsilon)\right)} > 0$. Furthermore, we can show that $\dfrac{d\varepsilon}{d\rho} < 0$. A higher discount rate implies a shorter rotation time.

The results in this paper diverge from those in the Laxminarayan and Brown paper in two important ways. In that paper, the optimal treatment strategy was to use the most effective drug first at all times, and to use two antibiotics simultaneously only if they were of identical effectiveness. This strategy is perfectly compatible with individual patients' desire to be treated with the most effective available drug. Introducing fitness cost of resistance does more than simply add a steady state to the analytical model by converting a non-renewable resource problem to one of renewable resources. It alters this neat coincidence of social and private incentives in a significant way. When bacterial resistance entails an evolutionary cost, it may be optimal to use drugs that have different effectiveness at the same time, even if they cost the same, as long as the drug that is of greater effectiveness also has a higher fitness cost of resistance. Needless to say, this conclusion is dramatically different from that reached by medical practitioners and health economists.

If one were to follow the standard cost–effectiveness approach, the economic paradigm most commonly used in the health economics literature, the optimal first choice of drug is always the one with the lowest ratio of cost to effectiveness. In fact, many papers in the medical literature use the private-cost approach to determine the optimal treatment for a communicable disease. As it turns out, this approach to arriving at an optimal treatment strategy is valid as long as the fitness cost of resistance is zero. However, the very nature of a communicable disease means there is a potentially large externality associated with drug treatments. Therefore, when bacterial resistance entails a fitness cost, the optimal solution is to use a mixed variety of drugs, even if the cost-effectiveness of some of these drugs is unfavorable to certain individual patients.

Cycling of antibiotics has been proposed as a suitable strategy for reducing the pressure on resistant organisms. However, I find that cycling is appropriate only when costs of using antibiotics are non-convex, and there is a cost of switching from one antibiotic to another. Further, the usual conditions associated with the SIS model of infection, such as static population, no super-infection, no immunity must hold. Although the fitness cost of bacterial resistance to the two antibiotics does not determine whether or not it is optimal to use cycling, it is critical in determining the optimal rotation time. If the half-life of resistant organisms in the absence of antibiotic selection pressure is high, then antibiotics can be cycled more rapidly.

The economic analysis presented in this paper has important implications that should be considered in antibiotics policy. In general, the optimal policy when reached from an economist's perspective sharply differs from that in the medical literature where economic costs play no role and a

convenient framework for thinking about inter-temporal tradeoffs (such as between the benefits of current use and the costs of future bacterial resistance) does not exist.[23] Economics, while helping determine the optimal social policy, can help attain that solution when social optima are not compatible with the incentives of individual patients acting in their self-interest. For instance, when bacterial resistance bears a fitness cost, the socially optimal algorithm for using antibiotics differs from that of a myopic individual agent. A case can then be made for a corrective policy prescription, such as a tax on antibiotic treatment, or a subsidy on certain antibiotics that should be included in a socially optimal menu, but are not cost-effective from an individual's perspective.

Without a doubt, the model presented in this paper is highly abstracted from reality. I have conveniently swept under the carpet important secondary considerations such as cross-resistance, multiple pathogens, drug dosages, compliance, and treatment side effects, among others, in order to focus on key issues related to infection and drug resistance. Empirical studies that are able to estimate key parameters such as fitness cost of resistance and the virulence of the pathogen could be valuable in translating economic analyses of the kind presented in this paper into practice. One hardly need emphasize that the problem of antibiotic resistance is a critical one and is likely to seriously compromise our ability to treat infectious diseases in coming years. Innovating new antibiotics is a very expensive proposition and there may be great economic benefit in efficiently using the antibiotics that we currently have.[24] Economic analysis, in conjunction with models of mathematical epidemiology, could play an important role in designing innovative policies to address this problem.

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[23] There are similar examples of divergence between epidemiological and economic policy conclusions. See, for instance, work by Tomas Philipson Philipson, T. 1999. *Economic epidemiology and infectious diseases*. Cambridge, MA: NBER..

[24] The cost of innovating and introducing a new antibiotic is estimated to be in the order of $1 billion. This number is increasing as the most easily discoverable antibiotics have all been discovered.

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Appendix 1

When antibiotic 1 is being used along the singular path, from equation (5.2), we have

$$\dot{\mu}_1 = \rho\mu_1 - (x-\varphi)f_1 I - \varphi r_1 I - \mu_1(f_1 - r_1)(2w_1 - 1)$$

$$\dot{\mu}_1 = \rho\mu_1 - \mu_1(1-w_1)f_1 - \varphi r_1 I - \mu_1(f_1 - r_1)(2w_1 - 1)$$

$$\dot{\mu}_1 = \rho\mu_1 - f_1\mu_1 w_1 - \varphi r_1 I - r_1(2w_1 - 1)$$

$$\dot{\mu}_1 = \rho\mu_1 - f_1\mu_1 w_1 - r_1[xI - \mu_1 w_1]$$

$$\dot{\mu}_1 = \rho\mu_1 - (f_1 - r_1)\mu_1 w_1 - xI r_1$$

Differentiating the FOC with respect to time, we get

$$\dot{\mu}_1 = \frac{(x-\varphi)\dot{I} - \dot{\varphi}I - \mu_1 \dot{w}_1}{(1-w_1)}$$

From the two equations above, we can synthesize the control to get

$$I = \frac{x(\beta - r - \rho + r_1 + w_2 r_2)}{\beta(x+\varphi)}$$

φ is the co-state variable associated with infection in a maximization problem. Therefore, we would expect it to be negative. If at any point along the optimal path, if $\varphi > 0$ this would imply that we would better off with a higher initial stock of infection, which makes no sense. Note that $\varphi < 0$ as long as $I > \tilde{I}$, where

$$\tilde{I} = \frac{\beta - r - \rho + r_1 + w_2 r_2}{\beta}$$

Note that when only one drug is being used

$$I = \frac{\beta - r - \rho - w_1 + w_1 r_1 + w_2 r_2}{\beta}$$

However, in order for this level of infection to exceed the minimum level needed to keep the shadow price of infection negative, we require that

$$-w_1 + w_1 r_1 + w_2 r_2 > r_1 + w_2 r_2$$

or

$$\frac{1}{w_1} + \frac{1}{r_1} < 1$$

which can never hold since both w_1 and r_1 are less than one. Therefore, by backward induction, we have shown that it is never optimal to use just one drug along the steady state path.

At the steady state, the level of infection is given by

$$I^{ss} = \frac{\beta - r - \rho}{\beta}$$

At the initial equilibrium, when no antibiotics are being used, infection is given by

$$\bar{I} = \frac{\beta - r - \rho + \overline{w}_1 r_1 + \overline{w}_2 r_2}{\beta}$$

We can see that

$$\bar{I} > \tilde{I} > I^{ss}$$

As we approach the steady level of infection, note that we would never choose to use one drug alone.

Appendix 2

For any drug 1, the right hand side of equation (10.2) can be written as

$$(1-w_1)\left[\rho\mu_1 - (b-\varphi) f_1 I - \varphi r_1 I - \mu_1 (f_1 - r_1)(2w_1 - 1)\right] - \mu_1 (f_1 - r_1) w_1 (w_1 - 1)$$

$$\Rightarrow (1-w_1)\left[-(b-\varphi) f_1 I - \varphi r_1 I - \mu_1 (f_1 - r_1)(2w_1 - 1) + \mu_1 (f_1 - r_1) w_1\right] + \rho(b-\varphi) I$$

$$\Rightarrow (1-w_1)\left[-(b-\varphi) f_1 I - \varphi r_1 I - \mu_1 (f_1 - r_1)(w_1 - 1)\right] + \rho(b-\varphi) I$$

$$\Rightarrow (1-w_1)\left[-(b-\varphi) f_1 I - \varphi r_1 I + (x-\varphi) I (f_1 - r_1)\right] + \rho(b-\varphi) I$$

$$\Rightarrow (1 - w_1)[-bIr_1] + \rho(b - \varphi)I$$

Appendix 3

$$w_1(t) = \frac{1}{1 + ke^{(f_1^c - r_1)t}}$$

The gross benefit of adopting strategy for a single rotation can be written as

$$G(\varepsilon) = \int_0^{\alpha\varepsilon} \frac{f_1^c}{1 + k_1 e^{(f_1^c - r_1)t}} dt + \int_{\alpha\varepsilon}^{\varepsilon} \frac{f_2^c}{1 + k_2 e^{(f_1^c - r_1)t}} dt$$

where $k_i = \dfrac{1 - w_i^*}{w_i^*}$, $f_1^c = \dfrac{r_1}{\alpha}$ and $f_2^c = \dfrac{r_2}{1 - \alpha}$

Therefore,

$$G(\varepsilon) = \frac{r_1}{\alpha} \int_0^{\alpha\varepsilon} \frac{1}{1 + k_1 e^{r_1\left(\frac{1-\alpha}{\alpha}\right)t}} dt + \frac{r_2}{1 - \alpha} \int_{\alpha\varepsilon}^{\varepsilon} \frac{1}{1 + k_2 e^{r_2\left(\frac{\alpha}{1-\alpha}\right)t}} dt$$

$$= \frac{r_1}{\alpha}\left[\alpha\varepsilon - \frac{\log\left(1 + k_1 e^{r_1\left(\frac{1-\alpha}{\alpha}\right)\alpha\varepsilon}\right)}{r_1\left(\frac{1-\alpha}{\alpha}\right)}\right] + \frac{r_2}{1-\alpha}\left[\varepsilon - \frac{\log\left(1 + k_2 e^{r_2\left(\frac{\alpha}{1-\alpha}\right)\varepsilon}\right)}{r_2\left(\frac{\alpha}{1-\alpha}\right)} - \alpha\varepsilon + \frac{\log\left(1 + k_2 e^{r_2\left(\frac{\alpha}{1-\alpha}\right)\alpha\varepsilon}\right)}{r_2\left(\frac{\alpha}{1-\alpha}\right)}\right]$$

$$= \left[r_1\varepsilon - \frac{\log\left(1 + k_1 e^{r_1\left(\frac{1-\alpha}{\alpha}\right)\alpha\varepsilon}\right)}{(1-\alpha)}\right] + \left[r_2\varepsilon - \frac{\log\left(1 + k_2 e^{r_2\left(\frac{\alpha}{1-\alpha}\right)\varepsilon}\right)}{\alpha} + \frac{\log\left(1 + k_2 e^{r_2\left(\frac{\alpha}{1-\alpha}\right)\alpha\varepsilon}\right)}{\alpha}\right]$$

As derived earlier, let $\alpha = \dfrac{r_1}{r_1 + r_2}$. Then

$$G(\varepsilon) = (r_1 - r_2)\varepsilon + (r_1 + r_2)\left[-\frac{\log(1 + k_1 e^{r_2\alpha\varepsilon})}{r_2} - \frac{\log(1 + k_2 e^{r_1\varepsilon})}{r_1} + \frac{\log(1 + k_2 e^{r_1\alpha\varepsilon})}{r_1}\right]$$

For the simplest case in which $r_1 = r_2$, where $k_1 = k_2$ and $\alpha = 0.5$, we can show that

$$\frac{dG(\varepsilon)}{d\varepsilon} = -\frac{kre^{r\varepsilon}}{0.5(1+ke^{r\varepsilon})} < 0, \text{ and}$$

$$\frac{d^2G(\varepsilon)}{d\varepsilon^2} = -\frac{kre^{r\varepsilon}}{0.5(1+ke^{r\varepsilon})} < 0.$$