Economics of Antibiotic Resistance:
A Theory of Optimal Use

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Abstract

In recent years bacteria have become increasingly resistant to antibiotics, leading to a decline in the effectiveness of antibiotics in treating infectious disease. This paper uses a framework based on an epidemiological model of infection in which antibiotic effectiveness is treated as a nonrenewable resource. In the model presented, bacterial resistance (the converse of effectiveness) develops as a result of selective pressure on nonresistant strains due to antibiotic use. When two antibiotics are available, the optimal proportion and timing of their use depends precisely on the difference between the rates at which bacterial resistance to each antibiotic evolves and on the differences in their pharmaceutical costs. Standard numerical techniques are used to illustrate cases for which the analytical problem is intractable.

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Ramanan Laxminarayan and Gardner M. Brown[*]

1. Introduction

The issue of resistance is a recurring theme in any attempt to curb organisms that are harmful to humans and human enterprise. Bacteria develop resistance to antibiotics,[1] malarial parasites to antimalarial drugs, and pests to pesticides. The problem of resistance represents an externality associated with the use of antibiotics, antimalarial drugs, or pesticides. Associated with each beneficial application of these treatments is the increased likelihood that they will be less effective for oneself and for others when used in the future. Alexander Fleming, who discovered penicillin in 1928, was among the first to recognize the potential for bacteria to develop resistance. In recent times, with the evolution of multi-drug resistant strains of bacteria such as Vancomycin-resistant *Staphylococcus aureus* (VRSA) and multi-drug resistant *Streptococcus pneumoniae*, it is no longer possible to treat infections that were commonly treated using antibiotics only a few years ago. For instance gonorrhea, a disease that was commonly treated with penicillin, has now become almost completely resistant to that drug.

The prospect of a post-antibiotic era in which most common disease-causing bacteria are resistant to available antibiotics has been a topic of much speculation. In an address to the Irving Trust in 1994, Nobel laureate Joshua Lederberg declared,

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[1] We frequently alternate between referring to bacterial resistance and to antibiotic effectiveness; each is simply the converse of the other. Also note that antibiotic effectiveness is measured by the extent of bacterial "susceptibility" or "sensitivity" to the antibiotic.

> *"We are running out of bullets for dealing with a number of (bacterial) infections.*
> *Patients are dying because we no longer in many cases have antibiotics that*
> *work."* [2]

In fact, studies in the medical literature have shown conclusively that patients infected with drug-resistant organisms are more likely to require hospitalization, to have a longer hospital stay, and to die.[3]

Despite the huge potential consequences of antibiotic resistance to the treatment and cure of infectious diseases, the costs of resistance are not internalized during the process of antibiotic treatment. The evolution of antibiotic resistance is strongly influenced by the economic behavior of individuals and institutions. The more antibiotics are used (or misused), the greater the selective pressure placed on bacteria to evolve. The problem, therefore, arises from the lack of economic incentives for individuals to account for the negative impact of antibiotics use on social welfare. The economics literature on the topic of bacterial resistance is limited to a 1996 paper by Brown and Layton in which resistance is modeled as a dynamic externality (Brown and Layton 1996). Hueth et al. model pest susceptibility (to pesticides) as a stock of nonrenewable natural resource that is costless to use in the short run but extremely expensive to replace in the long run (Hueth and Regev 1974). Adopting this approach of treating susceptibility as an exhaustible resource in a study on the optimal management of pest resistance, Comins found that the cost of resistance is analytically equivalent to an increase in the cost of the pesticide (Comins 1977; Comins 1979).

Our purpose is to derive the optimal antibiotic treatment policy recognizing that both the rate of infection and the effectiveness of antibiotics decline with antibiotic use. The model presented in this paper has two physical components. First, there is a version of the Kermack-McKendrick SIS model of disease transmission in which individuals move between susceptible and infected states.[4] This model describes the dynamics of infection when antibiotic treatment is

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[2] J. Lederberg, speech before the Irvington Trust, New York City, February 8, 1994.

[3] According to the *Genesis Report*, a trade newsletter, "one of the consequences of allowing resistance to tuberculosis to develop is that, while the cost of treating a susceptible strain can be as low as $2,000, the cost of treating a resistant strain can be as high as $500,000, require major surgery, and result in high morbidity and increased mortality."

[4] The name SIS is used to describe the process of moving between the Susceptible and Infected states through infection and treatment (Susceptible->Infected->Susceptible.)

used (Kermack and McKendrick 1927). These equations were first used in 1915 by Sir Ronald Ross to describe the malaria epidemic (Ross 1915). Second, we derive the equations describing the evolution of antibiotic resistance by imposing certain biological attributes of resistant and sensitive strains of bacteria on the SIS model.

The problem we pose concerns the optimal use of a nonrenewable resource. In a simple nonrenewable resource model with variable costs of drugs omitted, the most effective drug should be used exclusively until the level of resistance (effectiveness) is the same for each antibiotic. Then each drug should be used in precise proportion to the rate that use deteriorates the respective capital stock of effectiveness. These results differ in general from those in the only comparable paper written by natural scientists (Bonhoeffer, Lipsitch et al. 1997).[5] Unlike their epidemiological model that simulates alternative treatment strategies, long-term benefits do depend on the policy of antibiotic use. For example, using two antibiotics in a 50/50 ratio is not an optimal proportion to propose in general.

We describe the circumstances under which resistance may be treated as a nonrenewable resource and also those circumstances under which a model applicable to a renewable resource is more relevant. We then use antibiotic use and bacterial resistance data from Harborview Medical Center in Seattle to estimate key parameters in the theoretical model. Results from the empirical section support the theoretical model. After a period of single drug use, it is optimal to use the two antibiotics simultaneously. One process analogous to the use of antibiotic effectiveness is ore extraction. In contrast to ores of different qualities, antibiotics with different vulnerabilities to resistance contribute equally (marginally) to the control of infection, and the optimal share keeps the resistance level of each drug in equality.

The organization of this paper is as follows. Section 2 provides an overview of the issue of resistance, its biological nuances and key features. Section 3 contains a description of the SIS model of disease transmission,[6] and a derivation of the antibiotic resistance. It also describes the economic problem of optimal antibiotic use when antibiotic effectiveness is treated as a nonrenewable resource. Section 4 presents the results obtained from numerical illustrations based on economic and biological parameters. Section 5 concludes the paper.

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[5] Personal communication with Dr. Bruce Levin, Emory University, August 5, 1999.

[6] The interested reader is referred to the standard text on this subject by Anderson and May (1991).

2. Antibiotic Resistance

Antibiotic resistance is usually an outcome of natural selection. Nature endows all bacteria with some low level of resistance. Thus a small fraction of the bacteria, in the order of one in a million, is naturally resistant to the antibiotic. Many studies have shown that the existence of these resistant strains predates the use of antibiotics as a treatment for infectious disease (Levy 1992). When an antibiotic is used to treat a bacterial infection, only the bacteria that are susceptible to the antibiotic are killed while the small fraction of resistant bacteria survive. Therefore, antibiotic use results in a selective advantage to the resistant bacteria and over time, the bacterial population is composed entirely of these resistant strains. Using antibiotics to treat these resistant populations is then quite ineffective.

Natural selection is not the only mechanism by which resistance evolves. Bacteria possess the ability to directly transfer genetic material between each other using a mechanism known as plasmid transfer. Plasmids are packets of genetic material that serve as a vehicle for the transfer of resistance between different bacterial species. They are believed to be responsible for the geographical spread of bacterial resistance from one region of the world to another. A third mechanism through which resistance is induced in bacteria is by mutation. By this process, bacteria spontaneously change their genetic composition in response to an attack by antibiotics. Over time, the continued use of antibiotics encourages greater levels of mutation, leading to high levels of bacterial resistance.

The increase in bacterial resistance in hospitals and communities has been attributed to a number of reasons. In hospitals, the use of broad-spectrum antibiotics and the use of antibiotics as prophylaxis, such as in preventing infections during surgery, have contributed to resistance. Since resistant bacteria spread in the same ways as those of normal bacteria, the failure to introduce sufficient infection-control methods has contributed to the quick spread of resistant strains. An important reason for the observed increase in antibiotic resistance has been the overuse of antibiotics in the community. This is partly due to the easy availability of antibiotics, sometimes even without a prescription in some parts of the world. Even in countries where antibiotics are sold only under prescription, there are few economic incentives for doctors to prescribe antibiotics responsibly. In addition, a patient's to complete a full cycle of antibiotic treatment allows a few bacteria in their system to develop a stronger resistance to antibiotics in the future. Finally, the use of antibiotics in cattle feed as growth promoters encourages antibiotic resistance (Levy 1992).

The problem of antibiotic resistance is complex and difficult to model in its entirety. In this paper, we rely on a few stylized facts about the mechanisms and issues that contribute to resistance. One such abstraction is that the increased use of antibiotics leads to increased resistance. This feature permits us to treat the problem of increasing resistance (or decreasing effectiveness) as a problem of optimal extraction of a nonrenewable natural resource (Carlson 1972; Hueth and Regev 1974). Although a number of other factors contribute to resistance, such as the reasons we mentioned in the previous paragraph, an analysis of the economic incentives that influence these other factors lies outside the scope of this paper.[7]

A number of studies have demonstrated conclusively that the development of bacterial resistance to antibiotics is correlated with the level of antibiotic use (Cohen and Tartasky 1997; Hanberger, Hoffmann et al. 1997; Muder, Brennen et al. 1997). In a comprehensive survey of the medical literature on antibiotic resistance, McGowan lists studies that have found associations between increased antibiotic use and increased resistance, as well as decreased antibiotic use and decreased resistance (McGowan 1983). He notes that resistance is more common in the case of hospital-acquired infections than in community-acquired infections. This is not surprising considering that antibiotic use in hospitals is relatively intensive compared to use in the community. Second, resistance bacteria are more likely to develop in areas in hospitals where antibiotic use is more intensive. Further, the likelihood that patients will be infected with resistant bacteria increases with a longer duration of hospitalization. These results indicate the presence of a causal relationship between antibiotic use and resistance. Moreover, studies have shown that the likelihood of resistance developing in a patient with a history of antibiotic use is greater than in a patient who has been unexposed to antibiotics. Strategies to improve antibiotic use include the use of "antibiograms" which provide information on the susceptibility of common bacteria to antibiotics; use of formularies, which restrict the menu of antibiotics available to the physician to prescribe from; sequestration of nursing staff; computerized monitoring of prescribing behavior; and physician education.

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[7] For the purpose of this analysis, we shall assume that bacterial resistance evolves through natural selection. The science and mechanisms for natural selection are reasonably well-understood in the biology literature. There is little understanding about the rate of transmission of transposons (plasmid transfer) and the environmental factors that encourage such transfers. In fact, a number of bacterial strains such as *Citrobacter freundii, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris,* and *Serratia*, do not acquire resistance by transfer of plasmids most of the time (Amabile-Cuevas 1996).

Should antibiotic effectiveness be considered a renewable or a depletable resource? Antibiotic resistant strains of bacteria are, by definition, more likely than sensitive strains to survive a treatment of antibiotics. Fortunately for humans, these resistant strains may be at a comparative disadvantage for survival in an environment free of antibiotics. This disadvantage is known as the fitness cost of antibiotic resistance. Mathematically, the fitness cost is a measure of the rate at which the bacteria regresses to susceptibility in the absence of antibiotic treatment.

The issue of evolutionary disadvantage imposed by resistance is important to analyze from the standpoint of natural resources modeling. If resistant strains are less able to survive when the use of antibiotics is suspended, then there may be a steady state in which the loss of antibiotic effectiveness is just matched by the rate at which it recovers due to the fitness cost of resistance.

This problem is analogous to an unresolved issue occurring in optimal fish harvesting. It is conceivable that an antibiotic may have cycles of useful life and some studies have demonstrated the possibility of cycling in the case of pesticide resistance. However, the time taken for antibiotics to recover their effectiveness is much longer than the time it took for the initial loss of effectiveness. Moreover, resistance evolves much faster when the antibiotic is reintroduced than during the initial cycle of use (Anderson and May 1991).

3. The Biology and Economics of Resistance

This paper examines the question of the optimal use of two antibiotics in a hospital setting. We find that the results obtained from an analysis of the economic problem of optimal antibiotic use differ from results that would be obtained from either biological models or ore extraction models alone. On the one hand, biological models ignore economic costs and suggest that it is optimal to use both antibiotics simultaneously at all times. On the other hand, ore extraction models suggest that one ought to use the less costly antibiotic to begin with, and switch to the more costly antibiotic when the effectiveness of the first antibiotic is fully exhausted.

Two essential building blocks in our model are setting forth the dynamics of both infection and antibiotic effectiveness (resistance) in a manner that is both faithful to epidemiological truth and amenable to economic analysis. That is the task to which we now turn, after which we add the economic components.

3.1 Biology

The basic SIS model of infectious disease was introduced by Kermack and McKendrick in 1920 and is commonly used in epidemiological studies of infectious diseases (Kermack and McKendrick 1927). We use a modified version of this model in order to incorporate the dynamics of resistance. There are two primary states in this model, Susceptible (S) and Infected (I) (see Figure 1). Patients move from S to I at a rate that is determined by pathogen virulence
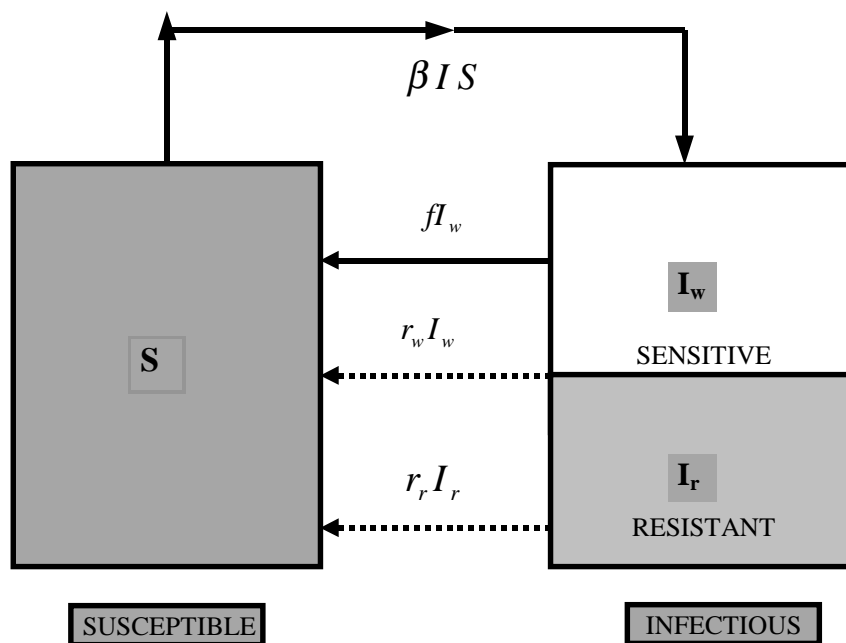
Figure 1. The SIS Model of Infection

and captured by the transmission coefficient, β. The infected patient population is characterized by infection either with a sensitive strain or with a resistant strain of bacteria. The fraction of individuals who are infected with the sensitive strain are cured faster through antibiotic treatment at a rate normalized to 1. Those with a resistant strain also recover, albeit at a slower rate defined as the spontaneous rate of recovery. For the case of a single antibiotic in a hospital inpatient population, these dynamics are described by the following equation (Bonhoeffer, Lipsitch et al. 1997):

$$(1) \qquad \frac{dS}{dt} = -\beta S \left(I_w + I_r \right) + r_w I_w + r_r I_r + f I_w$$

where S is the uninfected (healthy) fraction of the population. $\dot{I} = -\dot{S}$ since $I = 1 - S$, and $I = I_w + I_r$ where I_w denotes the fraction of the population infected with the sensitive (wild-type) strain and I_r refers to the fraction infected with the resistant strain. f is the fraction of the infected population treated with a single antibiotic. The spontaneous rate of recovery of the infected population is either r_w or r_r, depending on whether they are infected with a sensitive (w) or a resistant (r) organism respectively.[8] Due to the fitness cost imposed on resistant strains, the spontaneous rate of recovery from a sensitive strain is expected to not exceed the rate of recovery from a resistant strain. Thus fitness cost is denoted by $\Delta r = r_r - r_w \geq 0$[9].

The dynamic changes in the population infected with sensitive and resistant strains are represented by the following equations, which are related to (1) and the definitions above:

$$(2) \qquad \frac{dI_w}{dt} = \beta S I_w - r_w I_w - f I_w,$$

$$(3) \qquad \frac{dI_r}{dt} = \beta S I_r - r_r I_r,$$

and antibiotic effectiveness expressed as a fraction, given by

$$(4) \qquad w = \frac{I_w}{I} = \frac{I_w}{I_w + I_r}.$$

Thus w is good capital in the sense that it is used to treat the consequences of infection whereas infection is taken to be bad capital. Making appropriate substitutions using equations (1)-(4) yields

$$(5.1) \qquad \frac{dI}{dt} = \frac{dI_w}{dt} + \frac{dI_r}{dt} = (\beta S - r_r - wf)I,$$

$$(5.2) \qquad \frac{dw}{dt} = (f - \Delta r)w(w-1).$$

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[8] An alternative perspective of the equation is in terms of duration of colonization where $1/r_r$ and $1/r_w$ represent the duration of colonization by the antibiotic resistant and sensitive strains of the bacteria normalized with respect to the duration of colonization by the sensitive strain under antibiotic therapy.

[9] The notion of fitness cost may be captured by using different transmission rates, β_r and β_w, for resistant and sensitive organisms (Massad et al. 1993).

For the purpose of this paper, we assume in the text that $\Delta r = 0$ because we want to analyze the case when antibiotic effectiveness is a depletable resource. This scenario is described in a recent study that showed that while bacterial strains resistant to antibiotics are initially less virulent than their susceptible counterparts, they acquire virulence rapidly without any loss of their resistance (Bjorkman, Hughes et al. 1998). The natural rate of recovery of an infected individual from a resistant strain is therefore the same as his/her rate of recovery from a susceptible strain. A static overall absolute size of population is assumed, without loss of generality.

Equation (5.2) indicates that w decreases with antibiotic use. The decrease in w is analogous to the case of declining ore quality in mineral extraction. It is well-known that declining ore quality is the conceptual twin of the case of increasing cost of extraction. Resistance can therefore be thought of as a cost associated with the use of antibiotics. However, unlike the case of oil, the decline of antibiotic effectiveness, represented by (5.2), is a non-linear (specifically, logistic) function of use (Figure 2). We see that $\partial \dot{w}/\partial w$ is positive until $w = 0.5$ and is negative thereafter.[10]
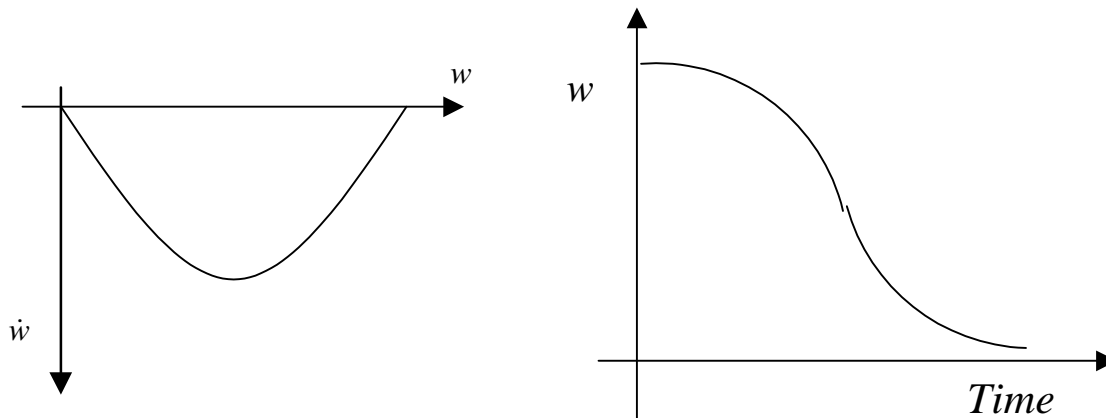
Figure 2. Logistic Decrease of Antibiotic Effectiveness

Further assumptions are necessary in order to shape the analytical model so that key ideas have prominence. We also assume that both cross-resistance (the effect of using antibiotic 1 on bacterial resistance to antibiotic 2) and multi-drug resistance (simultaneous resistance to both

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10 $\dfrac{\partial \dot{w}}{\partial w} = f(2w - 1)$. Therefore, $sign\left(\dfrac{\partial \dot{w}}{\partial w}\right) = sign\left(w - \dfrac{1}{2}\right)$

antibiotics) are negligible. Two standard assumptions that accompany the basis SIS model are applicable here. Immunity is ruled out and an individual is susceptible to infection immediately after successful treatment. We also rule out super-infection, thereby assuming that an infected individual is not at risk for a secondary infection. This assumption is reasonable for a small, infected population (Bonhoeffer, Lipsitch et al. 1997). We further assume that resistance has already been introduced into the infected population and that a small sub-population of infected individuals carries the resistant strain. The initial effectiveness of the antibiotics is denoted by w_0 where $w_0 \approx 1$. The model is generally applicable to infections such as tuberculosis, *Pseudomonas*, and gonorrhea, in which the organism that causes infection is not normally present in the host.[11]

3.2 Economics

The benefit for each antibiotic i used is $bw_i(t)f_i(t)I(t)$, where b is the benefit associated with each successful treatment using the antibiotic measured in \$/person, scaled both by the fraction of $I(t)$ treated and the effectiveness, $w_i(t)$, of such treatment.[12] The cost associated with the infection is represented by $c_I I(t)$. The intertemporal net benefit function is

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[11] Some infection-causing organisms such as *E. Coli* and *Pneumococci* are present in the intestine, nasal cavity, and other areas without infecting the host. A different model is applicable to the evolution of resistance in these "commensal" organisms.

[12] At least one reviewer suggested that the objective function could be more succinctly represented by the total cost of infection and the cost of treatment, given by $cfI + c_I I$. However, our formulation is a more general version of this total cost approach, as explained below. 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 a 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 are indifferent to whether they recover faster from a susceptible infection or slower 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 about the cost of infection, then $b_1 \neq b_2$ and $b_2 = b_3 = 0$, and so we get $NB = x_1 wfI - c_I I$ which is 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.

$$\max \int_0^\infty \left[b\left(\sum_i w_i(t) f_i(t) I(t) \right) - \bar{c} f_2(t) I(t) - c_I I(t) \right] e^{-\rho t} dt \,,$$

where $\bar{c}$ is the unit cost of treatment with antibiotic 2, and the cost of antibiotic 1 is assumed to be 0.[13] Time subscripts are suppressed for clarity in the following analysis.

We treat potentially with two antibiotics, whose resistance dynamics are derived in Appendix 1 and modified by the assumption that $\Delta r = 0$ are described by

(7.1) $$\dot{w}_1 = f_1 k w_1 (w_1 - 1)$$

(7.2) $$\dot{w}_2 = f_2 w_2 (w_2 - 1)$$

Here $k \, (<1)$ is a factor introduced to distinguish the resistance profile of antibiotic 1 from antibiotic 2. Thus using antibiotic 1 decreases future effectiveness less than treating an identical fraction of patients with antibiotic 2.

The current value Hamiltonian to be maximized combining (6), (7.1), (7.2), and (5.1)[14] is

(8)
$$H = bI\left(\sum_i w_i f_i \right) - c_I I - \bar{c} f_2 I + \varphi \left[\beta I (1 - I) - rI - I \left(\sum_i w_i f_i \right) \right]$$
$$+ \mu_1 \left[f_1 k w_1 (w_1 - 1) \right] + \mu_2 \left[f_2 w_2 (w_2 - 1) \right] \,,$$

where $I \le 1$ and $0 \le f_i \le 1$ and ρ is the social discount rate and costate variables μ_1, μ_2, and φ are associated with w_1, w_2, and I respectively. We further assume that no patient is treated with both antibiotics simultaneously. Therefore, $f_i \le 1$ and $\Sigma f_i \le 1$ are constraints harmlessly omitted from (8), which will become clear in the ensuing discussion. Relevant necessary conditions for a maximization of (8) are as follows:

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[13] We assume that $b\left(\sum_i w_i(t) f_i(t) \right) - \bar{c} f_2(t) - c_I > 0$ to ensure that the objective function is non-increasing in the level of infection.

[14] wfI becomes $I \sum w_i f_i$ when more than one antibiotic can be used. Further, in the absence of fitness costs, r_r in equation (5.1) is denoted by r.

(8.1)
$$f_1 \begin{pmatrix} = 0 \\ \in [0,1] \\ = 1 \end{pmatrix} as \ (b-\varphi)I - \mu_1 k(1-w_1) \begin{pmatrix} < \\ = \\ > \end{pmatrix} 0 \quad \text{for } w_1 \neq 0 \ ,$$

(8.2)
$$f_2 \begin{pmatrix} = 0 \\ \in [0,1] \\ = 1 \end{pmatrix} as \ (b-\varphi)I - \frac{\overline{c}I}{w_2} - \mu_2(1-w_2) \begin{pmatrix} < \\ = \\ > \end{pmatrix} 0 \quad \text{for } w_2 \neq 0 \ ,$$

(8.3)
$$(b-\varphi)If_1 - \mu_1 k f_1(1-2w_1) = \rho\mu_1 - \dot{\mu}_1$$

(8.4)
$$(b-\varphi)If_2 - \mu_2 f_2(1-2w_2) = \rho\mu_2 - \dot{\mu}_2$$

(8.5)
$$b\left(\sum_i w_i f_i\right) - c_I - \overline{c}f_2 + \varphi\left[\beta - 2\beta I - r - \sum_i w_i f_i\right] = \rho\varphi - \dot{\varphi}$$

plus the transversality conditions

(9.1)
$$\lim_{t \to \infty} \mu_{it} w_{it} e^{-\rho t} = 0$$

and

(9.2)
$$\lim_{t \to \infty} \varphi_t I_t e^{-\rho t} = 0.$$

The economic interpretation of (8.1) after rewriting as

(10)
$$bIw_1 - \varphi I w_1 = \mu_1 w_1(1-w_1)$$

is that the marginal benefit of changing the fraction of the population treated using antibiotic 1 equals its marginal cost. Since φ is the costate variable for infection, a bad, $\varphi < 0$, which is proved in Appendix 2 along with the conditions under which $\dfrac{\dot{\varphi}}{\varphi} \overset{>}{\underset{<}{=}} 0$.

      The relevant marginal unit here is not a person but a fraction of the infected population treated. Marginal use of an antibiotic does two good things. It cures infection, conferring the benefit of b to the individual, scaled by the effective fraction successfully treated, (Iw_1). It also reduces the stock of infection, conferring a benefit of $|\varphi Iw_1|$ to society. The user cost or rental rate for a unit of "effectiveness" capital is μ_1 for antibiotic 1. In traditional renewable resource models, there is an opportunity cost of reducing resources by a unit. In this model, changing the

fraction of people treated reduces the growth equation of effectiveness by $\dot{w}$ when $f_1 = 1$, so the population effectively treated must see this cost, $\mu_1 \dot{w}_1$. When $f_2 = 1$, the economic interpretation of (8.2) is the same, but for the addition of a cost term.

To understand the economic anatomy of this model, it is useful to move from simpler to more complex cases.

Case 1: $c_I = \bar{c} = 0$

There are two important segments along the optimal path in this model, when the effectiveness of the two antibiotics is the same, $w_1 = w_2$, and when they differ. We prove in Appendix 3 that the necessary condition for both the antibiotics to be used simultaneously is $w_1 = w_2$. This condition holds along the optimal path as the effectiveness of each drug declines asymptotically towards zero.

When, say $w_2 > w_1$, it pays to draw down w_2 as rapidly as possible until it reaches w_1, setting $f_2 = 1$. There are three explanations in support of this reasoning. First, the value of the marginal product of each antibiotic, $(b - \varphi)Iw_i$, decreases as w_i decreases, so it pays to use the antibiotic with the highest effectiveness first. Second, since from (5.1), $\dot{I}$ is inversely and linearly related to antibiotic effectiveness (w_i), the biggest impact on reducing infection is achieved by using the antibiotic with the biggest w. Note that there is a capacity constraint with a maximum value of $f_2 = 1$ and hence $f_1 = 0$. The length of time T, during which only drug 2 is used, is readily calculated from antibiotic 2's resistance dynamics in (7.2) and our knowledge of $w_1(0)$, $w_2(0)$, and when both are used, $w_1(0) = w_2(T)$. Solve for

$$(11) \qquad w_1(0) = w_2(T) = \frac{1}{1 + ce^{kT}} \quad \text{where } c = \frac{1 - w_2(0)}{w_2(0)}$$

Finally, if the lower effectiveness drug (w_1) is used first, w_1 would decrease asymptotically toward zero and there never would be a time when $w_1 = w_2$. Consequently, the most effective drug would never be used. Moreover, μ_2 rises at the rate of interest when antibiotic 2 is not in use (evaluate (8.4) for $f_2 = 0$) so the transversality conditions for w_2 are violated.

How should each antibiotic be used when $w_1 = w_2 = w$? From (7.1) and (7.2),

$$(12) \qquad \frac{\dot{w}}{w - 1} = f_1 k = f_2$$

and therefore,

(13)
$$\frac{f_1}{f_2} = \frac{1}{k}, \ f_1 = \frac{1}{1+k}, \text{ and } f_2 = \frac{k}{1+k}$$

since $f_1 + f_2 \leq 1$ where the equality holds because the Hamiltonian is linear in f_i. Therefore, use should be the maximum permissible. Following the ore analogy, k is a parameter that represents the 'thickness' of an ore grade. When extracting from two mines with different ore grade thickness, it is optimal to extract a smaller quantity from the mine with less grade thickness to ensure that marginal costs of extraction are identical throughout the extraction period. Similarly, since $k < 1$, a greater fraction of the infected population is treated with drug 1 because a given dose reduces effectiveness (increases resistance) less than does drug 2. For this reason, the rental rate on w_1 exceeds the rental rate on w_2, as manipulation of (8.1) and (8.2) demonstrates.

When both antibiotics are in use, the rental rate rises slower than the discount rate. Using (8.1)-(8.4) and (13), we get

(14.1)
$$\frac{\dot{\mu}_1}{\mu_1} = \rho - kf_1 w_1 = \frac{\dot{\mu}_2}{\mu_2} = \rho - f_2 w_2$$

The result follows naturally from recognizing that antibiotics are Ricardian resources with the quality of each decreasing with use over time.

Figure 3 summarizes the optimal path of w_1 and w_2, when $w_1 = w_2$. Combining (7.1) or (7.2) with (13) yields

(14.2)
$$\dot{w} = \frac{-k}{1+k} w(1-w)$$

along the path of joint use, and so the level of effectiveness, at any time t after joint use has started at a time normalized at $t = 0$, is

(14.3)
$$w(t) = \frac{1}{1 + \left(\frac{1-w(0)}{w(0)}\right) e^{\frac{k}{1+k}t}}.$$

It is a little curious that the amount each antibiotic should be used (equation (13)) and the optimal paths of effectiveness (given by equation (14.3)) are independent of economic variables. Natural scientists, such as Bonhoeffer et al., do not use dynamic optimization, but rather use
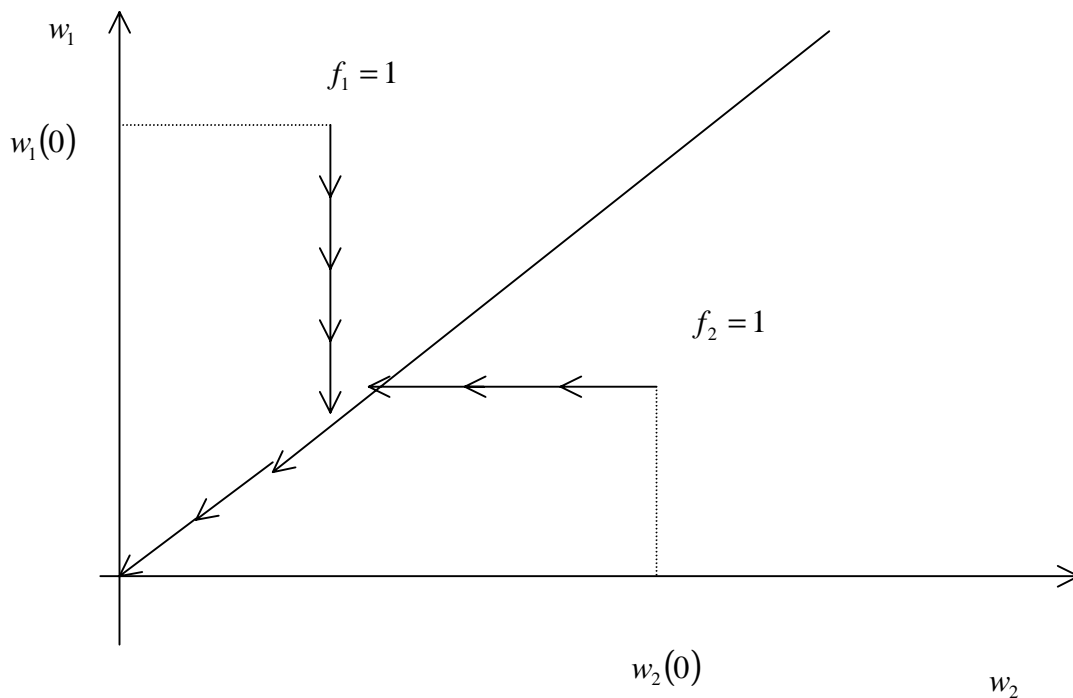
Figure 3: Singular Paths of Effectiveness

static optimization and simulations to choose protocols such as equal proportions of infected persons receiving each drug instead of cycling or multiple drug use simultaneously. Such a protocol varies in general from the results of our optimization procedure. Put differently, inter-temporal optimization—not economic parameters—drive the results in this problem; these results differ from treatments of the same problem by non-economists.

    Case 2: $k = 1, \quad \bar{c} > 0$

The case when $\bar{c} > 0$ is importantly different for two reasons. Letting $k = 1$, and starting out with $w_1(0) = w_2(0)$, resource 1 is cheaper to use initially and so should be used first. In the initial stages, the results resemble the solution for ores of different qualities (Hartwick 1978). However, using antibiotic 1 reduces its effectiveness, which in turn reduces benefit such that $bw_1 < bw_2$. When this loss cannot compensate for the higher marginal cost $\bar{c}$, it pays to introduce drug 2 as well, a result that is compatible with the policy of using two ores of different qualities. These qualitative results are illustrated in the next section using a case study.

The second reason this case is potentially important is that it contrasts with the Bonhoeffer et al. result that two drugs should *always* be used, a conclusion reached by limiting

the model to biological variables, such as omitting economic variables. The interpretation of (8.2) with variable costs is straightforward. In each time period, the marginal benefit of treatment with antibiotic 2 (represented by the first term) should equal the marginal out of pocket expense, $\bar{c}I$, plus the marginal user cost of drawing down the stock of antibiotic 2's effectiveness capital. The marginal user cost of treatment captures the future opportunity cost of increasing resistance. If the marginal benefit of antibiotic treatment is less than the user cost of antibiotics, then that antibiotic should not be used.

4. Case Study: Aminoglycoside Use at Harborview Medical Center

We extend our demonstration of the divergence between results obtained from purely epidemiological models and other models that combine economics with epidemiology, to include cases that are more complex than the ones considered so far, such as when the economic cost of using antibiotics is non-zero. In order to do this, we use numerical computations to trace out the optimal extraction paths of antibiotic effectiveness and the paths of costate variables. Parameter values used in the numerical computations were estimated in an earlier study and are contained in Table I (Laxminarayan and Brown 1998). These estimates were based on monthly data on the resistance of *Pseudomonas aeruginosa* (PSAR) to two commonly used antibiotics, Gentamicin (GENT) and Tobramycin (TOB), over a 12-year period from January 1, 1985 through December 31, 1996. These data from Harborview Medical Center in Seattle were complemented by pharmacy data on antibiotic prescriptions during this period. Although the fitness cost of resistance (Δr) was positive and statistically significant in these estimates, Δr was assumed to be equal to zero for the purpose of the numerical computation, in order to stay consistent with our treatment of antibiotic effectiveness as a depletable resource in the analytical model. In contrast to the infinite time horizon used in the analytical section, a finite time horizon was used for the numerical computations. Data on antibiotic prices were obtained from the MediSPAN$^{©}$ database.

The following equations describe the discrete time version of the model replicating (5.1), (7.1), (7.2), and (8.3)-(8.5). h represents the rate of recovery from a susceptible infection under antibiotic treatment; both antibiotics have costs and recall that $S = 1 - I$.

(15.1)
$$I_{t+1} = I_t \left[1 + \beta - r - w_{t,1} f_{t,1} h - w_{t,2} f_{t,2} h \right] - \beta I^2{}_t$$

(15.2)
$$w_{1,t+1} = w_{1,t} \left[1 + f_{1,t} k h w_{1,t} - f_{1,t} k h \right]$$

(15.3)
$$w_{2,t+1} = w_{2,t} \left[1 + f_{21,t} h w_{1,t} - f_{2,t} h \right]$$

$$(15.4) \qquad \begin{aligned} \varphi_{t+1} &= \varphi_t \left[1 + \rho - \beta + r + 2\beta I_t + h\left(w_{1,t} f_{1,t} + w_{2,t} f_{2,t} \right) \right] \\ &\quad - b\left(w_{1,t} f_{1,t} + w_{2,t} f_{2,t} \right) + c_1 f_{1,t} + c_2 f_{2,t} + c_I \end{aligned}$$

$$(15.5) \qquad \mu_{1,t+1} = \mu_{1,t} \left[1 + \rho - f_{1,t} kh\left(2w_{1,t} - 1 \right) \right] - \left[b - \varphi_t h \right] I_t f_{1,t}$$

$$(15.6) \qquad \mu_{2,t+1} = \mu_{2,t} \left[1 + \rho - f_{2,t} h\left(2w_{2,t} - 1 \right) \right] - \left[b - \varphi_t h \right] I_t f_{2,t}$$

In the benchmark experiment, we consider two antibiotics with $k = 1$ and identical costs. The initial effectiveness of antibiotic 1 (GENT) is assumed to be 0.81 (the 12-year median level of antibiotic effectiveness in our data set (see Table 1)), in contrast with an assumed initial effectiveness of antibiotic 2 (TOB) of 0.96 (again, see Table 1). The optimal treatment rule is to use only antibiotic 2, until the level of resistance to the two antibiotics is identical (Figure 4).

Table I: Parameters used in numerical computations

Coefficient of disease transmission, β	0.01
Social discount rate,[*] ρ	0.004
Rate of recovery from antibiotic treatment[**], h	2.55
Initial effectiveness of GENT, $w_{GENT}(0)$	0.81
Initial effectiveness of TOB, $w_{TOB}(0)$	0.96
Marginal benefit of successful antibiotic treatment, x	\$200 (Low) \$2,000 (High)
Marginal cost of GENT, c_{GENT}	\$0.96
Marginal cost of TOB, c_{TOB}	\$43

*We used an annual social discount rate of 5% that corresponds to the monthly rate expressed in the table.
** This parameter is the inverse of the mean duration of bacterial colonization under antibiotic treatment for susceptible infections and corresponds to a mean of 11 days of colonization.
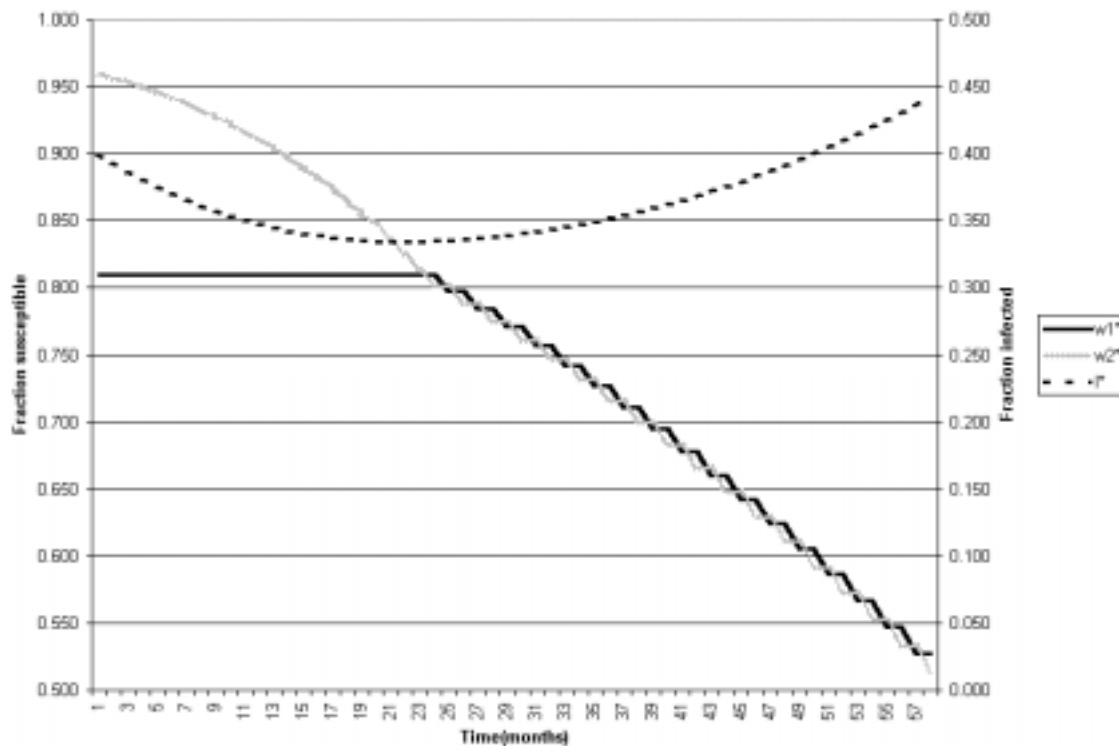
Figure 4: Antibiotic effectiveness and infection, k=1, $c_1 = c_2 = 0$.

After this point, both antibiotics are used simultaneously. The level of infection drops in response to the introduction of antibiotics, but swings upwards as resistance increases. Initially, μ_1 increases at the discount rate (Figure 5). $\mu_1 = \mu_2$ at the point in time when antibiotic 1 is brought into use. After this, both μ_1 and μ_2 decrease over time. Furthermore, the absolute value of φ increases as the level of infection goes down. When the rate of infection starts increasing (with decreasing antibiotic effectiveness), the cost of infection given by φ decreases in absolute value.

The behavior of w_1 and w_2 when $k = 0.1$ in the second numerical computation is almost identical to that in the previous experiment (Figure 6). Here too, antibiotic 1 is used only after resistance to the two antibiotics is identical. Once antibiotic 1 is brought into use, the ratio of use of antibiotic 1 to that of antibiotic 2 is roughly ten to one, as one would expect. The rental rate for antibiotic 1 is higher than the rental rate for antibiotic 2 when both are used, because each treatment draws down w_1 less ($k = 0.1$) than it does w_2. The movement of the co-state variables over time is plotted in Figure 7.
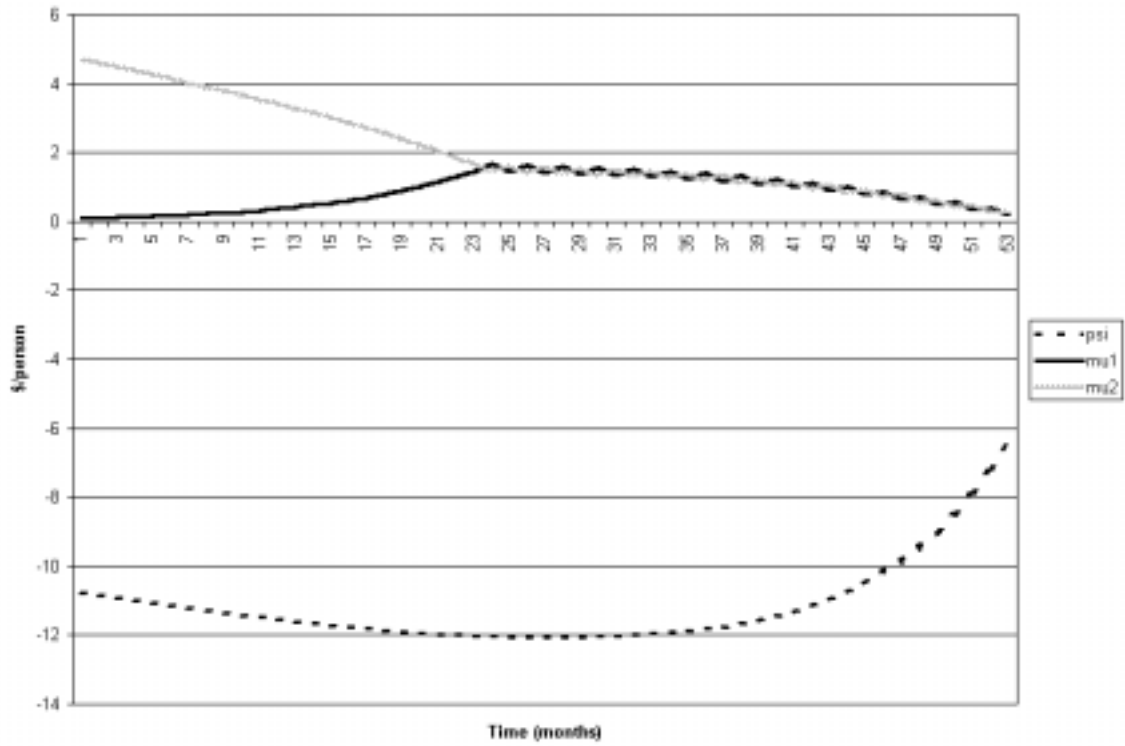
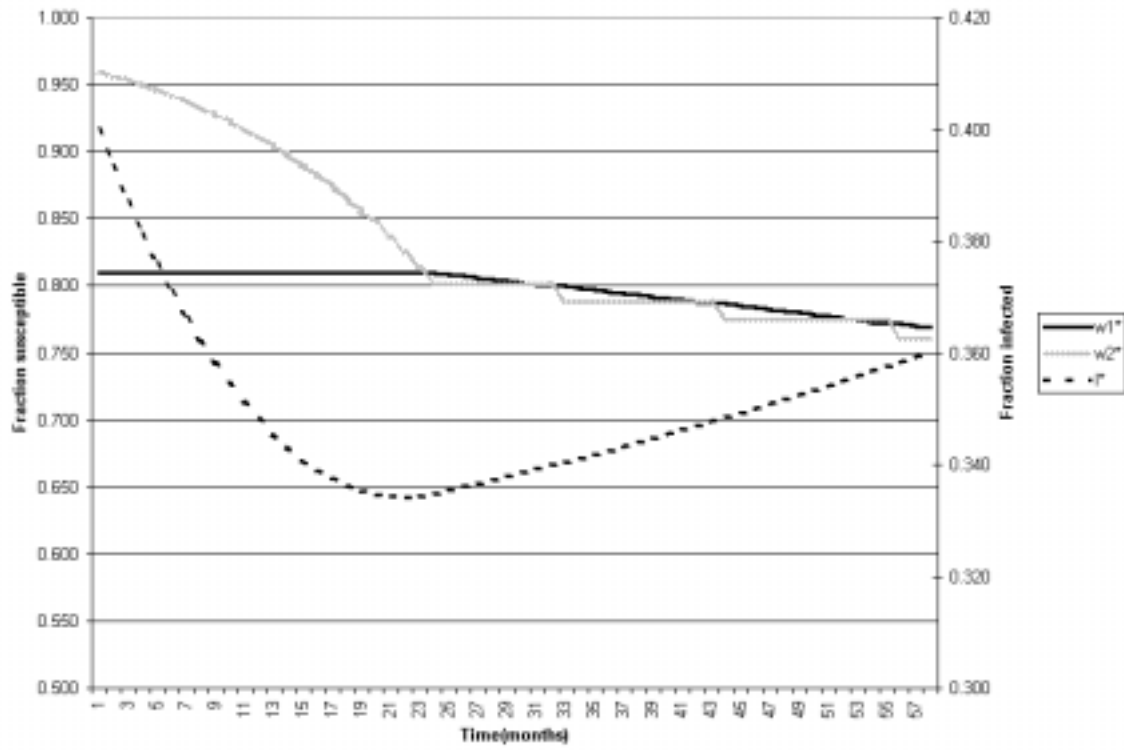**Figure 5: Costate variables, k<1,** $c_1 = c_2 = 0$

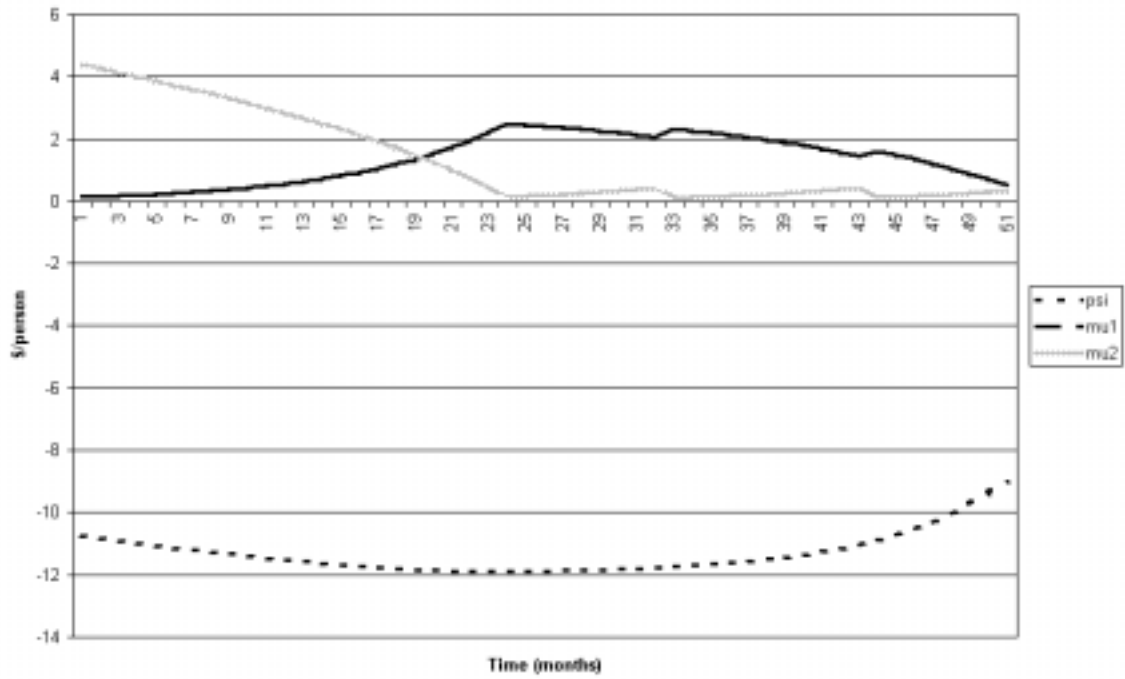**Figure 6: Antibiotic effectiveness and infection, k=0.1,** $c_1 = c_2 = 0$

Figure 7: Costate variables, k=0.1, $c_1 = c_2 = 0$

The time paths for infection and its shadow cost can be explained as follows. Initially, the infection level drops in response to the introduction of antibiotics in the hospital. The shadow cost of infection, given by φ, increases in response to the decrease in infection level.[15] This is because with fewer infections, the marginal cost (both in terms of the direct cost and the cost associated with decreasing the number of secondary infections) to the hospital of an additional infected individual is greater. However, as antibiotics lose effectiveness, the infection level starts to go back up again, and the shadow cost of infection declines.

Costs are introduced in the third experiment (Figures 8-9). Following the MediSPAN® data, the cost of antibiotic 2 is assumed to be $43 and the cost of antibiotic 1 is assumed to be $0.96.[16] The marginal benefit of each successful treatment, b, is assumed to be $200.[17] In order to focus on the role of costs, we assume the initial effectiveness of the two antibiotics to be identical. Figure 7, which is provided for comparison, illustrates the optimal extraction path when the cost of the two antibiotics is identical and set equal to zero. Here, the optimal policy is to use both antibiotics simultaneously since they are perfect substitutes in both resistance profile and economic costs.

Introducing economic costs modifies the biologically optimal solution in two respects. First, if the cost of using one antibiotic is less than that of the second, then *ceteris paribus*—in other words, the lower cost antibiotic will be used first. The high cost antibiotic will be introduced only when the marginal benefit of its superior effectiveness is equal to its relatively higher marginal cost of use. This policy diverges from the conclusion in Bonhoeffer *et al.* that two antibiotics should be used simultaneously. When the role of costs is considered (in Figure 8),

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[15] Note that φ is non-positive.

[16] The average wholesale price of gentamicin was $0.11/80mg and the average wholesale price of tobramycin was $4.95/80mg, over the period from 1986-1997. The mean aminoglycoside dose at Harborview Medical Center during this period was approximately 700 mg. Therefore, the total drug cost of treatment using gentamicin was $0.96. The drug cost of treatment using tobramycin was nearly 45 times as great at $43.31. The costs of intravenously administering the two drugs were similar.

[17] We used this figure (b=$200) as a lower bound estimate in order to compare the optimal path for this case with the optimal path when b=$2,000. The $2,000 figure was mentioned by doctors at Harborview Medical Center as the lump-sum reimbursement to the hospital from Medicare for treating most illnesses related to infectious diseases.
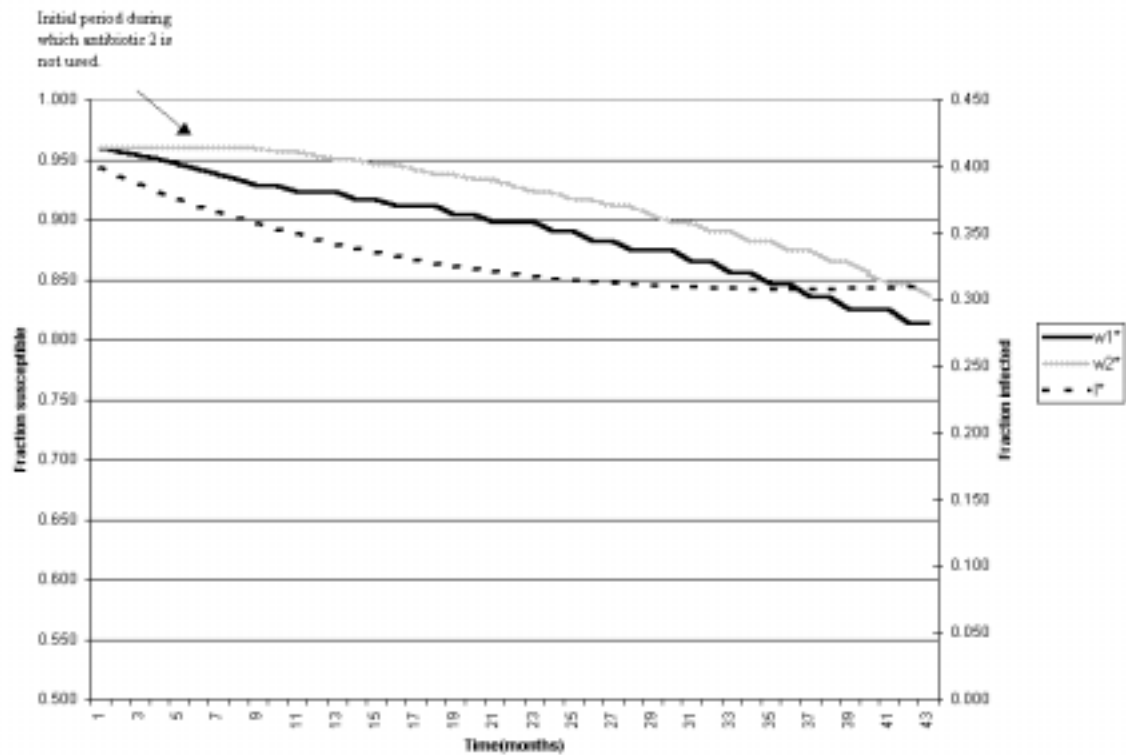
Figure 8: Antibiotic effectiveness and infection, k=1, $c_1, c_2 > 0$, b=200.

there is an initial period of time (nine months in this case) during which only antibiotic 1 (lower cost antibiotic) is used.[18] Following this, both antibiotics are used simultaneously.

Second, the extent to which the low cost antibiotic will be preferred over the high cost antibiotic is determined by the marginal net benefit of successful antibiotic treatment. The divergence between the path of effectiveness of the two antibiotics when variable costs differ is unmistakable in Figure 8, where b is assumed to be \$200. On the other hand, if b is large relative to antibiotic costs, then antibiotic costs play only a minor role. In this case, both antibiotics will be used simultaneously, even if the cost of using one antibiotic exceeds that of the other. When antibiotic costs, c_1 and c_2, are relatively small compared to the benefit of

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[18] The length of this initial period, T, is sensitive to the value of k. The elasticity of T with respect to k is –1, calculated from (11).

successful therapy, b (see Figure 9), the role of variable costs in selecting the less expensive antibiotic over the more expensive one is somewhat diminished.
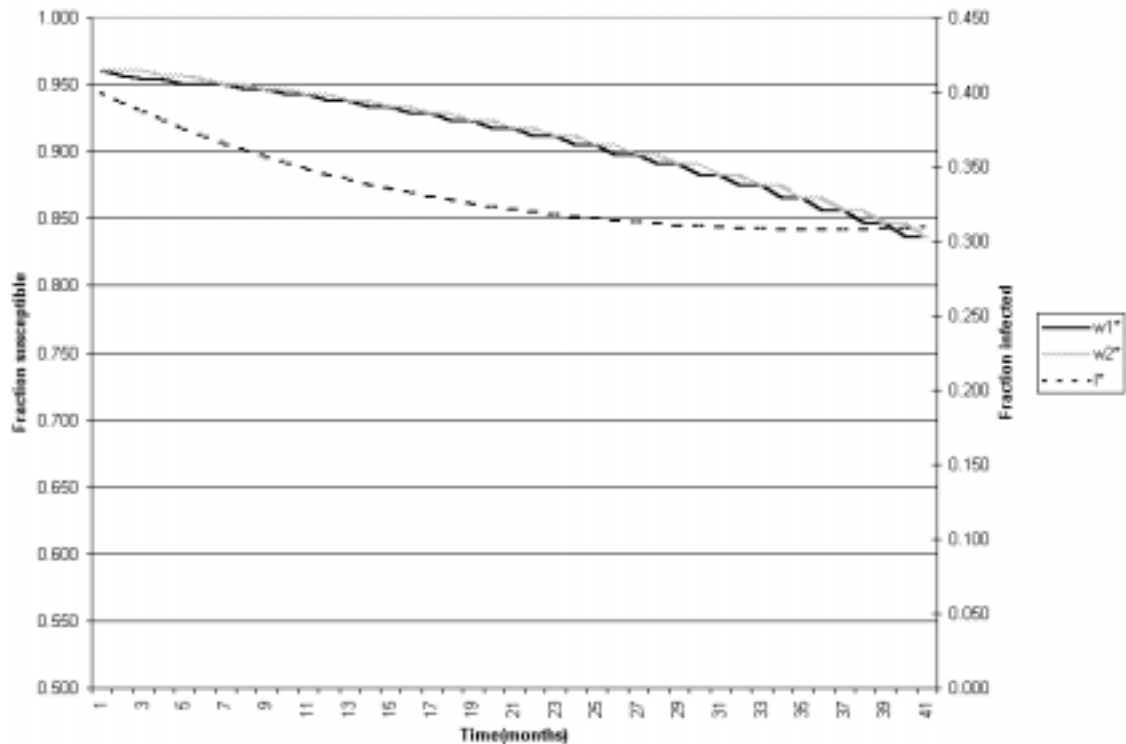

Figure 9: Antibiotic effectiveness and infection, k=1, $c_1, c_2 > 0$, b=2000.

5. Conclusions and Extensions

The problem of declining antibiotic effectiveness presents a classic case of resource extraction. Antibiotic effectiveness can be treated as renewable or nonrenewable depending on biological and biochemical attributes of the bacteria and antibiotics under consideration. When we apply the economic objectives of intertemporal optimization to the biological model of resistance dynamics, a number of results become apparent.

Antibiotics with greater effectiveness will be used before those with lesser effectiveness in the same manner that low cost deposits will be extracted before high cost deposits (Weitzman 1976). This result contrasts with the conclusion in Bonhoeffer *et al.* that both antibiotics should be used simultaneously, a result obtained by disregarding economic costs. In general, antibiotics differ from each other, both in the rate at which they lose effectiveness and with respect to the marginal cost of use. The policies formulated in this paper recognize these features and hence

are distinct from conclusions drawn in biology and epidemiological literature on population, in which economic considerations play no role.[19]

It is perhaps prudent to remind the reader that this analysis rests on two important caveats. First, we have assumed that there is no fitness cost associated with resistance.[20] A forthcoming paper examines the case when the fitness cost is significant and antibiotic effectiveness is treated as a renewable resource. Second, our model treats a hospital as a closed system and is therefore applicable only to nosocomial or hospital-acquired infections. Therefore, antibiotic effectiveness is, for all practical purposes, a private access resource from the perspective of the hospital administrator. In the case of community-acquired infections, antibiotic effectiveness is more akin to an open access resource and a different model would be applicable under those circumstances.

At the heart of the problem of antibiotic resistance is the issue of the externality imposed by each beneficial use of antibiotics on their future effectiveness. One potential economic solution to the problem of divergence between the rate of antibiotic use in a decentralized situation and the optimal rate can be corrected by imposing an optimal tax on antibiotics. However, taxes may not be the only mechanism at the social planner's disposal. Most hospitals use a formulary, a list of antibiotics that are stocked in the pharmacy based on recommendations from the infection-control committees. The purpose of formularies is to give the hospital administration some control over the prescribing patterns of its physicians. Since the menu of antibiotics available to a physician is based on the composition of the formulary at that time, a central (hospital) planner can alter the fraction of patients treated with a given antibiotic by altering the composition of the formulary.

The above measures to encourage the optimal use of antibiotics are distinct from those that discourage the misuse of antibiotics for unnecessary prophylaxis or for the treatment of viral infections (which cannot be cured using antibiotics). The absence of incentives for pharmaceutical firms to take antibiotic resistance into account when making pricing decisions in a competitive market—characterized by threat of entry by similar antibiotics—is a subject for

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[19] The potential for divergence between economic results and results from purely epidemiological models has been noted by other researchers in this field Philipson, T. (1999). Economic epidemiology and infectious diseases. Cambridge, MA, NBER..

[20] Although Bonhoeffer et al. introduce the notion of fitness cost in their model, fitness cost is set equal to zero throughout.

another paper. Finally, the use of antibiotics in cattle and poultry feed continues to be a contentious issue that is unlikely to be resolved any time soon.

Appendix 1

Let I_1, I_2, and I_{12} represent fractions of the infected population that are resistant to only antibiotic 1, only antibiotic 2, and both antibiotics 1 and 2, respectively. Then,

A.1.1
$$I = I_1 + I_2 + I_{12} + I_w$$

where I_w is the fraction of the infected population that is susceptible to both antibiotics. The equations of motion that describe the four categories of the infected population are as follows:

A.1.2
$$\dot{I}_w = \beta S I_w - r_w I_w - (f_1 + f_2) I_w$$

$$\dot{I}_1 = \beta S I_1 - r_1 I_1 - f_2 I_1$$

$$\dot{I}_2 = \beta S I_2 - r_2 I_2 - f_1 I_2$$

$$\dot{I}_{12} = \beta S I_{12} - r_{12} I_{12}$$

where f_1 and f_2 are the fractions of the infected population treated with antibiotics 1 and 2. We assume that no one is treated using both antibiotics. The effectiveness of antibiotic 1 is given by,

$$w_1 = 1 - \frac{I_1 + I_{12}}{I} = \frac{I_2 + I_w}{I}.$$

Similarly,

$$w_2 = 1 - \frac{I_2 + I_{12}}{I} = \frac{I_1 + I_w}{I} \quad \text{and} \quad w_{12} = \frac{I_w}{I}.$$

Therefore,

$$\frac{I_{12}}{I} = 1 - \frac{I_1 + I_2 + I_w}{I} = 1 - (w_1 - w_{12}) - (w_2 - w_{12}) - w_{12} = 1 - w_1 - w_2 + w_{12}.$$

We know that

$$\dot{I} = \dot{I}_1 + \dot{I}_2 + \dot{I}_{12} + \dot{I}_w.$$

Substituting for I_w, I_1, I_2, and I_{12} we get

A.1.3 $$\frac{\dot{I}}{I} = \beta S - w_1 f_1 - w_2 f_2 - r_1(w_2 - w_{12}) - r_2(w_1 - w_{12}) - r_w w_{12} - r_{12}(1 - w_1 - w_2 + w_{12})$$

and

$$\text{A.1.4} \quad \frac{\dot{I}}{I} = \beta S - w_1 \left(f_1 + r_2 - r_{12} \right) - w_2 \left(f_2 + r_1 - r_{12} \right) + w_{12} \left(r_1 + r_2 - r_{12} - r_w \right) - r_{12} .$$

If $r_1 = r_2 = r_{12} = r_w = r$, then

$$\text{A.1.5} \qquad\qquad\qquad\qquad\qquad\qquad \frac{\dot{I}}{I} = \beta S - w_1 f_1 - w_2 f_2 - r .$$

The rate at which effectiveness declines over time is given by

$$\dot{w}_1 = \frac{\partial \left(\dfrac{I_2 + I_w}{I} \right)}{\partial t}$$

$$= \frac{\dot{I}_2}{I} + \frac{\dot{I}_w}{I} - \left(\frac{I_2 + I_w}{I} \right) \left(\frac{\dot{I}}{I} \right)$$

$$\text{A.1.6} \qquad\qquad = \left[\beta S - r_w - \left(f_1 + f_2 \right) \right] w_{12} + \left[\beta S - r_2 - f_1 \right] \left[w_1 - w_{12} \right]$$

$$- w_1 \left[\beta S - w_1 f_1 - w_2 f_2 - r_1 \left(w_2 - w_{12} \right) - r_2 \left(w_1 - w_{12} \right) - r_w w_{12} - r_{12} \left(1 - w_1 - w_2 + w_{12} \right) \right] .$$

If $r_1 = r_2 = r_{12} = r_w = r$, then

$$\text{A.1.7} \qquad\qquad\qquad\qquad \dot{w}_1 = f_1 w_1 \left(w_1 - 1 \right) - f_2 \left(w_{12} - w_1 w_2 \right) .$$

By symmetry,

$$\text{A.1.8} \qquad\qquad\qquad\qquad \dot{w}_2 = f_2 w_2 \left(w_2 - 1 \right) - f_1 \left(w_{12} - w_1 w_2 \right) .$$

For low levels of multi-drug resistance and negligible cross-resistance,

$$\text{A.1.9} \qquad\qquad\qquad\qquad\qquad\qquad \dot{w}_1 = f_1 w_1 \left(w_1 - 1 \right)$$

and

$$\text{A.1.10} \qquad\qquad\qquad\qquad\qquad\qquad \dot{w}_2 = f_2 w_2 \left(w_2 - 1 \right) .$$

Appendix 2

When antibiotic 1 is being used along the joint singular path, from equation (8.3) we have

A.2.1
$$\frac{\dot{\mu}_1}{\mu_1} = \rho - kf_1(2w_1 - 1) - \frac{(b-\varphi)If_1}{\mu_1}.$$

Substituting (8.1) into (4.2) yields

A.2.2
$$\frac{\dot{\mu}_1}{\mu_1} = \rho - kf_1 w_1.$$

Differentiating equation (8.1) with respect to time,

A.2.3
$$\dot{\mu}_1 = \frac{(b-\varphi)I\dot{w}_1 + (b-\varphi)\dot{I}w_1 - \dot{\varphi}Iw_1 + \mu_1 kw_1(2w_1 - 1)}{kw_1(1-w_1)}.$$

Substitute for $\dot{\mu}_1$ from equation (A.2.2) and for $\dot{w}_1$, $\dot{I}$, $\dot{\varphi}$ from equations (5.1), (7.1) and (8.5) to get

A.2.4
$$\beta I(b+\varphi) = b(\beta - r - \rho)$$

as long as the disease is not eradicated $(I > 0)$ and $k = 1$. Rewriting this condition as

A.2.5
$$\varphi = \frac{b(\beta(1-I) - r - \rho)}{\beta I}$$

we see that $\varphi < 0$ when $I > \dfrac{\beta - r - \rho}{\beta}$. The steady state condition for infection, when antibiotics are not used, is given by the condition, $I = \dfrac{\beta - r}{\beta}$. Therefore, $\varphi < 0$, as long as the infection lies below $\dfrac{\beta - r}{\beta}$ and above $\dfrac{\beta - r - \rho}{\beta}$, along the singular path.

From equation 8.5,

A.2.6
$$\frac{\dot{\varphi}}{\varphi} = (\rho + r + 2\beta I - \beta) - \frac{(b-\varphi)\sum w_i f_i - c_I - \bar{c}f_1}{\varphi}.$$

From our assumption in foonote 12, which states that $b\sum w_i f_i - c_I - \bar{c}f_2 > 0$, and from the condition $\varphi < 0$, we know that $\dfrac{(b-\varphi)wf - c_I - \bar{c}f_1}{\varphi}$ is negative for all values of w. Therefore,

$\dfrac{\dot{\varphi}}{\varphi} > 0$ when $\left(\rho + r + 2\beta I - \beta\right) \geq 0$. The equivalent condition is that $I > \dfrac{\beta - r - \rho}{2\beta}$, which is true

as long as the condition for $\varphi < 0$, such as $I > \dfrac{\beta - r - \rho}{\beta}$, holds. However, $\dfrac{\dot{\varphi}}{\varphi} < 0$ when

$I < \dfrac{\beta - r - \rho}{2\beta}$.

Appendix 3

In this appendix, we prove that $w_1 = w_2$ when both antibiotics are used, and antibiotics costs are assumed to be zero. Assume $w_1 > w_2$. More specifically, let $w_1 = w_2 + \theta$. Then the necessary condition for both antibiotics to be used simultaneously is given by

A.3
$$z - \mu_1 k(1 - w_1) = z - \mu_2(1 - w_2)$$

where $z = (b - \varphi)I$.

We can write this as

A.3.1
$$\mu_1 k(1 - w_2 - \theta) = \mu_2(1 - w_2).$$

Differentiating with respect to time, we get

A.3.2
$$\frac{\dot{\mu}_1}{\mu_1} - \frac{\dot{w}_2 - \dot{\theta}}{(1 - w_2 - \theta)} = \frac{\dot{\mu}_2}{\mu_2} - \frac{\dot{w}_2}{1 - w_2}.$$

From a solution of equations (8.1)-(8.4), we obtain

A.3.3
$$\frac{\dot{\mu}_1}{\mu_1} = \rho - kf_1 w_1$$

and

A.3.4
$$\frac{\dot{\mu}_2}{\mu_2} = \rho - f_2 w_2$$

which can be combined and rewritten as

A.3.5
$$\frac{\dot{\mu}_1}{\mu_1} + kf_1 w_1 = \frac{\dot{\mu}_2}{\mu_2} + f_2 w_2.$$

From equations A.3.2 and A.3.5 we get

A.3.6
$$-\frac{\dot{w}_2}{1 - w_2} + \frac{\dot{w}_2 + \dot{\theta}}{(1 - w_2 - \theta)} = f_2 w_2 - kf_1 w_1.$$

It is trivial to show that the first term on the left-hand side cancels out the first term on the right if we substitute for $\dot{w}_2$. The other two terms can be written as

A.3.7
$$\dot{w}_2 + \dot{\theta} = -kf_1 w_1(1 - w_2 - \theta).$$

Substituting for $\dot{w}_2$ and w_1 and expanding, we get

A.3.8
$$f_2 w_2^2 - f_2 w_2 + \dot{\theta} = -k f_1 (w_2 + \theta)(1 - w_2 - \theta)$$

and

A.3.9
$$f_2 w_2^2 - f_2 w_2 + \dot{\theta} = w_2^2 (k f_1) + w_2 (k f_1 (2\theta - 1)) + k f_1 (\theta^2 - \theta).$$

Equating coefficients of w_2^2, w_2 and 1 on both sides, we get the following:

A.3.10
$$k f_1 = f_2$$

A.3.11
$$2\theta - 1 = -1 \Rightarrow \theta = 0$$

A.3.12
$$\dot{\theta} = k f_1 (\theta - \theta^2) = 0.$$

Therefore, we have established that if two antibiotics are used simultaneously, then it must be true that $k f_1 = f_2$ and $w_1 = w_2$. From equation (A.3.1) and the condition that $w_1 = w_2$, we also get $k \mu_1 = \mu_2$.

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