BACTERIAL RESISTANCE AND THE OPTIMAL USE OF ANTIBIOTICS

Current version: January 2000

First version: January 1998

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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 non-renewable resource. In the model presented, bacterial resistance (the converse of effectiveness) develops as a result of selective pressure on non-resistant strains due to antibiotic use. When two antibiotics differ only in quality, it is optimal to use one antibiotic initially, following which it is optimal to switch to a combination of the two drugs. The optimal proportion and timing of use for the two antibiotics depends precisely on the difference between the rates at which bacterial resistance to each antibiotic evolves and on the differences in their pharmaceutical costs, results that are unique in the literature on antibiotic resistance. We use standard numerical techniques to illustrate cases for which the analytical problem is intractable. JEL Classification Codes: Q3, I1.

[1] Please send comments to ramanan@rff.org. This research was supported by a dissertation fellowship from the Alfred P. Sloan foundation and a grant from the Department of Allergy and Infectious Diseases at the University of Washington. We acknowledge helpful comments from Dave Layton, Dick Startz and two anonymous referees without implicating them in any way. An earlier version of this paper was circulated as a University of Washington Economics Discussion Paper and was presented at the 1998 NBER Summer Institute sessions on Public Policy and Environment, Department of Economics, Ben-Gurion University, Beer Sheva, Israel, University of Gothenburg, Sweden and University of Victoria, Canada. We are grateful to Dr. Lisa Grohskopf, Dr. Mac Hooton and Jackie Scheibert for access to the Harborview data set, and to Sean Sullivan for access to the MediSPAN data.

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[2], malarial parasites to anti-malarial drugs, and pests to pesticides. The problem of resistance represents an externality associated with the use of antibiotics, anti-malarial 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 using 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

> *"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."* [3]

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[4].

[2] We frequently move between referring to bacterial resistance and antibiotic effectiveness where 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.

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

[4] 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. "

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 absence of economic incentives for individuals to take into account the negative impact of their use of antibiotics 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 non-renewable 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, 1979, Comins, 1977).

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[5]. This model describes the dynamics of infection when antibiotic treatment is used (Kermack and McKendrick, 1927). These equations were first used in 1915 by Sir Ronald Ross to describe the epidemic spread of malaria (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 posed is one of optimal use of a non-renewable resource. In a simple non-renewable resource model with variable costs of drugs omitted, the drug with the most effectiveness 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.

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

These results differ in general from those in the only comparable paper written by natural scientists (Bonhoeffer, et al., 1997)[6]. Unlike their epidemiological model that simulates alternative treatment strategies, long-term benefits do depend on the policy of antibiotic use and 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 non-renewable 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, 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. 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[7], and a derivation of the model of antibiotic resistance. It also describes the economic problem of optimal antibiotic use when antibiotic effectiveness is treated as a non-renewable resource. Section 4 presents the results obtained from numerical techniques based on economic and biological parameters. Section 5 concludes the paper.

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, the use of

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

antibiotics gives a selective advantage to the resistant bacteria and over time, the bacterial population is composed entirely of these resistant strains. Treatment of these resistant populations using antibiotics 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 resistance from regions of the world where bacterial resistance has occurred to other regions. A third mechanism by 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 in communities has been attributed to a number of reasons. In hospitals, the use of broad-spectrum antibiotics and the use of antibiotics as prophylaxis, i.e. preventive cure before 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 in the community 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, the failure of patients to complete a full cycle of antibiotic treatment allows a few bacteria in their system to survive with a better ability to deal with 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

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

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 non-renewable natural resource (Carlson, 1972, Hueth and Regev, 1974). 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. For the purpose of this analysis, we shall assume that bacterial resistance evolves through natural selection. For one, the science and mechanisms for natural selection are well understood in the biology literature. Second, 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).

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, et al., 1997, Muder, 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, areas in the hospitals where antibiotic use is more intensive are more likely to be sources of resistant bacteria. Further, the likelihood that patients will be infected with resistant bacteria increases with 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.

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 question of evolutionary disadvantage imposed by resistance is an important one 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, albeit at a rate consistent with high rates of unmitigated infection. This problem is analogous to the one of 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 ground truth as well as 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 and Infected. The infected population is, in turn, characterized by infection either with a sensitive strain or with a resistant strain of bacteria. Individuals who are infected with the sensitive strain are cured faster through antibiotic treatment. Those with a resistant strain also recover, albeit at a slower rate defined as the spontaneous rate of recovery. The equation governing the rate of change of infection is

(1) $$\dot{I} = bI(1-I) - rI - fI$$

Figure 1 illustrates the SIS model where f is the fraction of the infected population treated with a single antibiotic.

Consider the dynamics of infection and resistance to a single antibiotic in a hospital inpatient population. Following Bonhoeffer, (Bonhoeffer, et al., 1997).

(2) $$\frac{dS}{dt} = -bS(I_w + I_r) + r_w I_w + r_r I_r + fI_w$$

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. Both r_w and r_r refer to the spontaneous (no treatment) rate of recovery of an infected individual. 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 or a resistant 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 related to (1) and the definitions above,

(3.1) $$\frac{dI_w}{dt} = bSI_w - r_w I_w - fI_w,$$

(3.2) $$\frac{dI_r}{dt} = bSI_r - r_r I_r,$$

and antibiotic effectiveness expressed as a fraction, is given by

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

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) $$\frac{dI}{dt} = \frac{dI_w}{dt} + \frac{dI_r}{dt} = (bS - r_r - wf)I,$$

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

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 which 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, et al., 1998). The natural rate of recovery of an infected individual from a

[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 b_r and b_w for resistant and sensitive organisms (Massad, et al., 1993).

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 the antibiotic use. The decrease in w is analogous to the case of declining ore quality in the case of 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. This feature of the extraction in our model has the visual equivalence of an hour-glass shaped well of antibiotic effectiveness. We see that $\partial \dot{w}/\partial w$ is positive until $w = 0.5$ and is negative thereafter.[10]

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 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 a reasonable one to make for a small, infected population (Bonhoeffer, et al., 1997). We further assume that resistance has already been introduced into the infected population and that a small sub-population of infectives 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].

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

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

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. The cost associated with the infection is represented by $c_I I(t)$. The inter-temporal net benefit function is

$$\max \int_0^\infty \left[b\left(\sum_i w_i(t) f_i(t) I(t) \right) - \bar{c} f_2(t) I(t) - c_I I(t) \right] e^{-rt} dt, \tag{6}$$

where $\bar{c}$ is the unit cost of treatment with antibiotic 2 and the cost of antibiotic 1 is assumed to be 0[12]. 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 assumption that $\Delta r = 0$ are described by

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

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

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)[13] is

$$H = bI\left(\sum_i w_i f_i \right) - c_I I - \bar{c} f_2 I + j\left[bI(1-I) - rI - I\left(\sum_i w_i f_i \right) \right] + m_1[f_1 k w_1 (w_1 - 1)] + m_2[f_2 w_2 (w_2 - 1)] \tag{8}$$

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[12] 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.

[13] 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 .

1 and $0 \leq f_i \leq 1$

where r is the social discount rate and costate variables m_1, m_2 and j are associated with w_1, w_2 and I respectively. We further assume that no patient is treated with both antibiotics simultaneously. Therefore, $f_i \leq 1$ and $\Sigma f_i \leq 1$ are constraints harmlessly omitted from (8) as will become clear in the ensuing discussion. Relevant necessary conditions for a maximization of (8) are as follows,

(8.1) $$f_1 \begin{pmatrix} =0 \\ \in [0,1] \\ =1 \end{pmatrix} as \ (b-j)I - m_1 k(1-w_1) \begin{pmatrix} < \\ = \\ > \end{pmatrix} 0 \quad \text{for } w_1 \neq 0 \ ,$$

(8.2) $$f_2 \begin{pmatrix} =0 \\ \in [0,1] \\ =1 \end{pmatrix} as \ (b-j)I - \frac{\bar{c}I}{w_2} - m_2(1-w_2) \begin{pmatrix} < \\ = \\ > \end{pmatrix} 0 \qquad \text{for } w_2 \neq 0 \ ,$$

(8.3) $$(b-j)If_1 - m_1 k f_1(1-2w_1) = rm_1 - \dot{m}_1$$

(8.4) $$(b-j)If_2 - m_2 f_2(1-2w_2) = rm_2 - \dot{m}_2$$

(8.5) $$b\left(\sum_i w_i f_i\right) - c_I - \bar{c}f_2 + j\left[b - 2bI - r - \sum_i w_i f_i\right] = rj - j$$

plus the transversality conditions

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

(9.2) $$\lim_{t\to\infty} j_t I_t e^{-rt} = 0$$

The economic interpretation of (8.1) after rewriting as

(10) $$bIw_1 - jIw_1 = m_1 w_1(1-w_1)$$

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

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, conferring 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 $|jIw_1|$ to society. The user cost or rental rate for a unit of "effectiveness" capital is m_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, $m_1\dot{w}_1$. 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, $(b-j)Iw_i$ 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) $$w_1(0) = w_2(T) = \frac{1}{1+ce^{kT}} \text{ where } c = \frac{1-w_2(0)}{w_2(0)}$$

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, m_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) $$\frac{\dot{w}}{w-1} = f_1 k = f_2$$

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 $f_1 + f_2 \le 1$ where the equality holds because the Hamiltonian is linear in f_i and therefore, use should be the maximum permissible. Using the ore analogy to understand antibiotics breaks down here. While it is sometimes optimal to use two antibiotics simultaneously, it is not optimal to use ores of different grades simultaneously.

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) $$\frac{\dot{m}_1}{m_1} = r - kf_1 w_1 = \frac{\dot{m}_2}{m_2} = r - f_2 w_2$$

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

Figure 2 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 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 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,

intertemporal 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.

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 i.e. 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, for cases that are more complex than the ones considered so far. 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 1 (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. 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) $$w_{1,t+1} = w_{1,t}\left[1 + f_{1,t} khw_{1,t} - f_{1,t} kh\right]$$

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

(15.4) $$\begin{aligned} j_{t+1} = j_t\Big[1 + r - b + r + 2bI_t + h\left(w_{1,t} f_{1,t} + w_{2,t} f_{2,t}\right)\Big] \\ - b\left(w_{1,t} f_{1,t} + w_{2,t} f_{2,t}\right) - c_1 f_{1,t} - c_2 f_{2,t} - c_I \end{aligned}$$

(15.5) $$m_{1,t+1} = m_{1,t}\left[1 + r - f_{1,t} kh\left(2w_{1,t} - 1\right)\right] - \left[b - j_t h\right] I_t f_{1,t}$$

(15.6) $m_{2,t+1} = m_{2,t}\left[1 + r - f_{2,t}h\left(2w_{2,t} - 1\right)\right] - \left[b - j_t h\right]I_t f_{2,t}$

In the benchmark experiment, we considered two antibiotics with $k = 1$ and identical costs. The initial effectiveness of antibiotic 1 (GENT) was 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 was to use only antibiotic 2, until the level of resistance to the two antibiotics was identical (Figure 3). After this point, both antibiotics were used simultaneously. The level of infection drops in response to the introduction of antibiotics, but swings upwards as resistance increases. Initially, m_1 increases at the discount rate (Figure 4). $m_1 = m_2$ at the point in time when antibiotic 1 is brought into use,. After this, both m_1 and m_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 5). 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 antibiotic1 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 6.

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 j, increases in response to the decrease in infection level[14]. 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

[14] Note that j is non-positive.

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 7 - 10). 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[15]. The marginal benefit of each successful treatment, b, is assumed to be $200[16]. In order to focus on the role of costs, we assume the initial effectiveness of the two antibiotics to be identical. Figure 7 illustrates the optimal extraction path when the cost of the two antibiotics is identical and set equal to zero, and is provided for comparison. Here, the optimal policy is to use 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*, 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), there is an initial period of time (nine months in this case), during which only antibiotic 1 (lower cost antibiotic) is used[17]. 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

[15] In 1997, 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.

[16] 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 infectious disease related illnesses.

[17] 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).

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. The shadow value of antibiotic 2 (lower variable costs) decreases, and, as previously, the shadow value of antibiotic 1 increases until both antibiotics are used (Figure 9). Hereafter, both m_1 and m_2 decline. When antibiotic costs, c_1 and c_2 are relatively small compared to the benefit of successful therapy, b (see Figure 10), the role of variable costs in selecting the less expensive antibiotic over the more expensive one is somewhat diminished.

6. CONCLUSION AND EXTENSIONS

The problem of declining antibiotic effectiveness presents a classic case of resource extraction. Antibiotic effectiveness can be treated as renewable or non-renewable depending on biological and bio-chemical attributes of the bacteria and antibiotic under consideration. When we apply the economic objectives of inter-temporal 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 conclusions 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. If the rate at which bacteria acquire resistance to one antibiotic exceeds the rate it acquires resistance with respect to another antibiotic, then it is optimal to use a smaller fraction of the first such that the effectiveness of the two antibiotics is identical at all times. The marginal cost of an antibiotic includes the direct cost of the antibiotic, the cost of administering the antibiotic, and the cost associated with side effects. If two antibiotics have the same initial effectiveness and the marginal cost of using one antibiotic exceeds another then the less expensive antibiotic is used first. This continues until the net marginal benefits of the two antibiotics are identical. From this point on, both antibiotics are used simultaneously. These results are distinct

from those found in the population biology and epidemiological literature in which economic considerations play no role[18].

It is perhaps prudent to remind the reader that these results are conditional upon two caveats. First, we have assumed that there is no fitness cost associated with resistance[19]. 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 the recommendation of 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 and to treat 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 another paper. Finally, the

[18] The potential for divergence between economic results and results from purely epidemiological models has been noted by other researchers in this field (Philipson, 1999).

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

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
$$\dot{I}_w = bSI_w - r_w I_w - (f_1 + f_2) I_w$$
$$\dot{I}_1 = bSI_1 - r_1 I_1 - f_2 I_1$$
$$\dot{I}_2 = bSI_2 - r_2 I_2 - f_1 I_2$$
$$\dot{I}_{12} = bSI_{12} - r_{12} I_{12}$$

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,

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

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 $$\frac{\dot{I}}{I} = bS - w_1 f_1 - w_2 f_2 - r_1(w_2 - w_{12}) - r_2(w_1 - w_{12}) - r_w w_{12} - r_{12}(1 - w_1 - w_2 + w_{12})$$

A.1.4 $$\frac{\dot{I}}{I} = bS - w_1(f_1 + r_2 - r_{12}) - w_2(f_2 + r_1 - r_{12}) + w_{12}(r_1 + r_2 - r_{12} - r_w) - r_{12}$$

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

A.1.5 $$\frac{\dot{I}}{I} = bS - w_1 f_1 - w_2 f_2 - r$$

The rate at which effectiveness declines over time is given by

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

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

A.1.6 $$= [bS - r_w - (f_1 + f_2)]w_{12} + [bS - r_2 - f_1][w_1 - w_{12}]$$
$$- w_1[\beta S - w_1 f_1 - w_2 f_2 - r_1(w_2 - w_{12}) - r_2(w_1 - w_{12}) - r_w w_{12} - r_{12}(1 - w_1 - w_2 + w_{12})]$$

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

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

By symmetry,

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

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

A.1.9 $$\dot{w}_1 = f_1 w_1(w_1 - 1)$$
A.1.10 $$\dot{w}_2 = f_2 w_2(w_2 - 1)$$

APPENDIX 2

When antibiotic 1 is being used, from equation (8.3), we have

A.2.1 $\frac{\dot{m}_1}{m_1} = r - kf_1(2w_1 - 1) - \frac{(b - j)If_1}{m_1}$

Substituting (8.1) into (4.2) yields

A.2.2 $\frac{\dot{m}_1}{m_1} = r - kf_1 w_1$

Differentiating equation (8.1) with respect to time,

A.2.3 $\dot{m}_1 = \frac{(b - j)I\dot{w}_1 + (b - j)\dot{I}w_1 - \dot{j}Iw_1 + m_1 kw_1(2w_1 - 1)}{kw_1(1 - w_1)}$

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

A.2.4 $bI(b + j) = b(b - r - r)$

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

A.2.5 $j = \frac{b(b(1 - I) - r - r)}{bI}$

we see that $j < 0$ when $I > \frac{b - r - r}{b}$. That this condition holds is fairly intuitive from a biological standpoint. The basic necessary condition for the disease to not be naturally eradicated when there is no antibiotic treatment is for $\dot{I} \geq 0$, or equivalently, $I \geq \frac{b - r}{b}$ in the natural world. Therefore, for a positive discount rate r, $I > \frac{b - r - r}{b}$ must hold.

From equation 8.5,

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

Since $j < 0$, $\frac{(b - j)wf + c_I + \bar{c}f_1}{j}$ is negative for all values of w. Therefore, $\frac{\dot{j}}{j} > 0$ when $(r + r + 2bI - b) \geq 0$. The equivalent condition is that $I > \frac{b - r - r}{2b}$. However, $\frac{\dot{j}}{j} < 0$ when $I < \frac{b - r - r}{2b}$.

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 $w_1 = w_2 + q$. Then the necessary condition for both antibiotics to be used simultaneously is given by

A.3 $\quad z - m_1 k(1 - w_1) = z - m_2(1 - w_2)$

where $z = (b - j)I$

We can write this as

A.3.1 $\quad m_1 k(1 - w_2 - q) = m_2(1 - w_2)$

Differentiating with respect to time, we get

A.3.2 $\quad \dfrac{\dot{m}_1}{m_1} - \dfrac{\dot{w}_2 - \dot{q}}{(1 - w_2 - q)} = \dfrac{\dot{m}_2}{m_2} - \dfrac{\dot{w}_2}{1 - w_2}$

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

A.3.3 $\quad \dfrac{\dot{m}_1}{m_1} = r - kf_1 w_1$,

A.3.4 $\quad \dfrac{\dot{m}_2}{m_2} = r - f_2 w_2$,

which can combined and rewritten as

A.3.5 $\quad \dfrac{\dot{m}_1}{m_1} + kf_1 w_1 = \dfrac{\dot{m}_2}{m_2} + f_2 w_2$

From equations A.3.2 and A.3.5 we get

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

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 $\quad \dot{w}_2 + \dot{q} = -kf_1 w_1(1 - w_2 - q)$

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

A.3.8 $\quad f_2 w_2^2 - f_2 w_2 + \dot{q} = -kf_1(w_2 + q)(1 - w_2 - q)$

A.3.9 $\quad f_2 w_2^2 - f_2 w_2 + \dot{q} = w_2^2(kf_1) + w_2(kf_1(2q - 1)) + kf_1(q^2 - q)$

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

A.3.10 $\quad kf_1 = f_2$

A.3.11 $\quad 2q - 1 = -1 \Rightarrow q = 0$

A.3.12 $\quad \dot{q} = kf_1(q - q^2) = 0$

Therefore, we have established that if two antibiotics are used simultaneously, then it must be true that $kf_1 = f_2$ and $w_1 = w_2$. From equation (A.3.1) and the condition that $w_1 = w_2$, we also get $km_1 = m_2$.

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Figure 1: The SIS Model of Infection

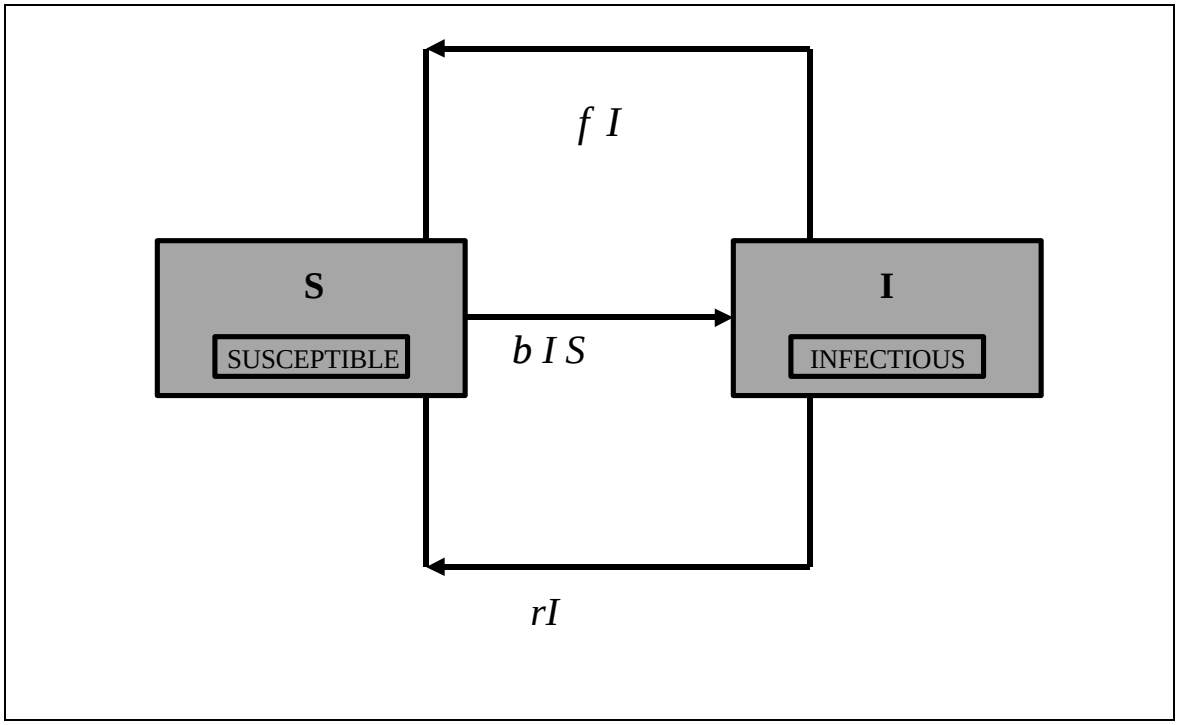


Figure 2: Optimal Paths of Effectiveness

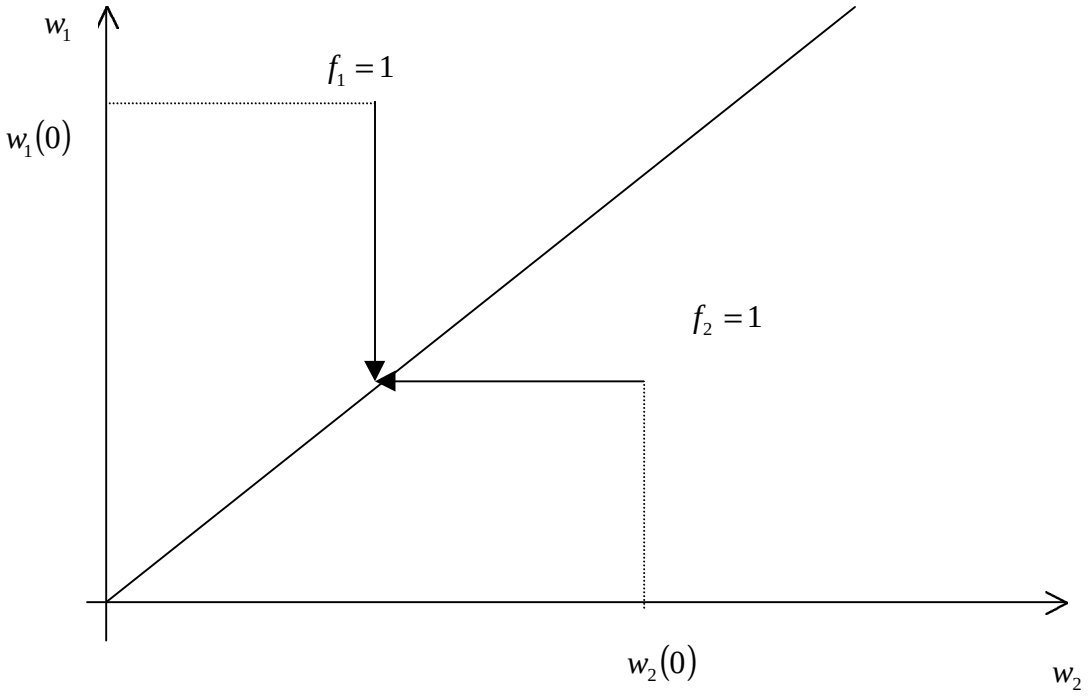


Table 1: Parameters used in numerical computations

Coefficient of disease transmission, b	0.01
Social discount rate[20]*,* r	0.004
Rate of recovery from antibiotic treatment[21]*,* 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

[20] We used a annual social discount rate of 5% that corresponds to the monthly rate expressed in the table.
[21] 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 3: Infection and antibiotic effectiveness (k=1, no costs)

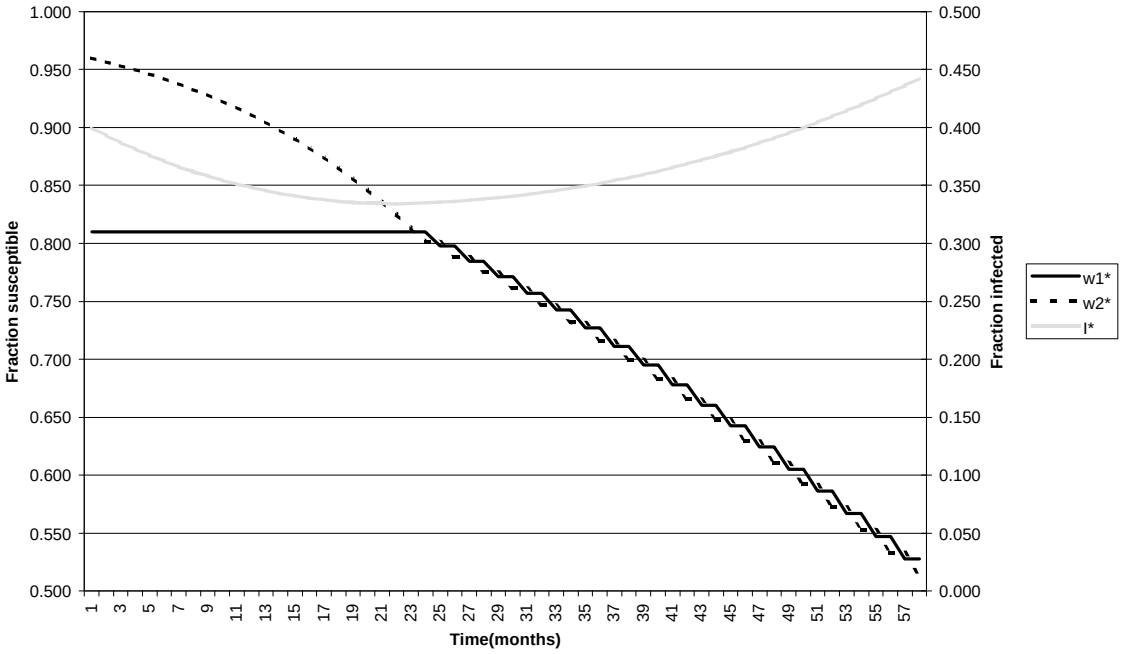


Figure 4: Costate variables (k=1, no costs)

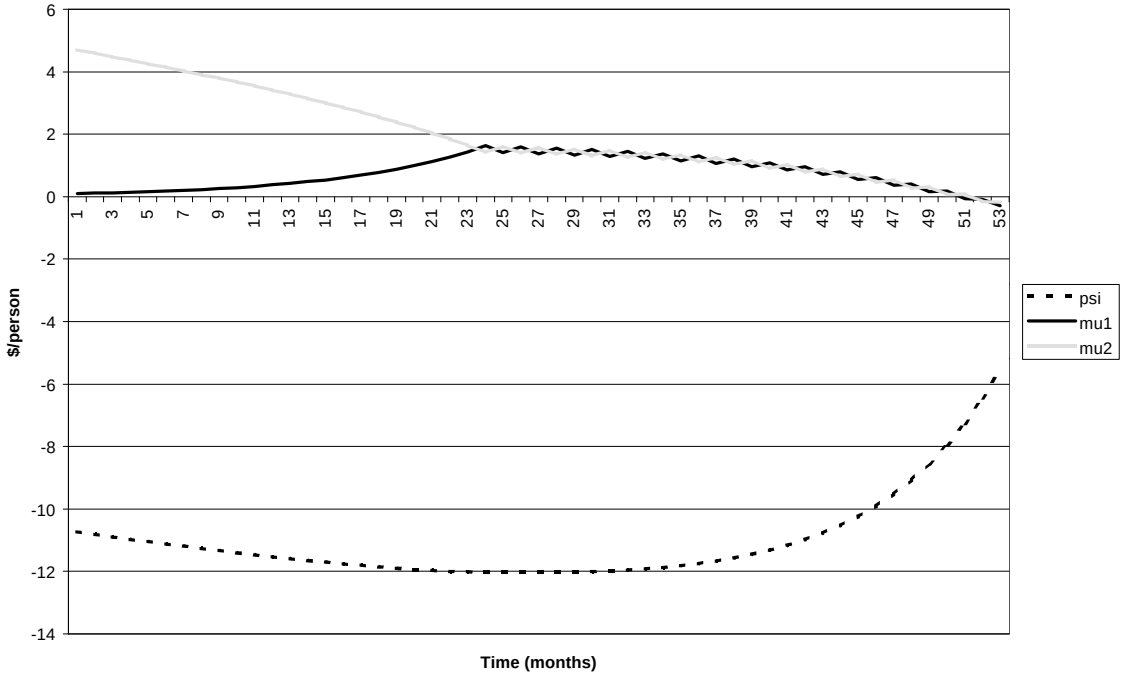


Figure 5: Infection and antibiotic effectiveness (k=0.1, no costs)

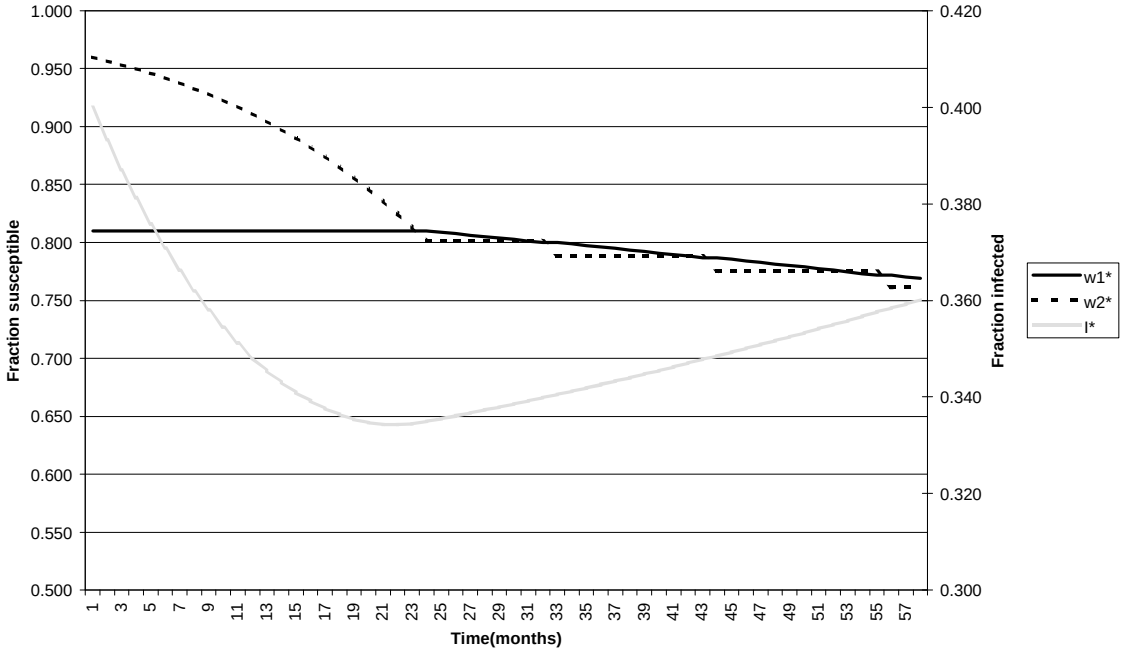


Figure 6: Costate variables (k=0.1, no costs)

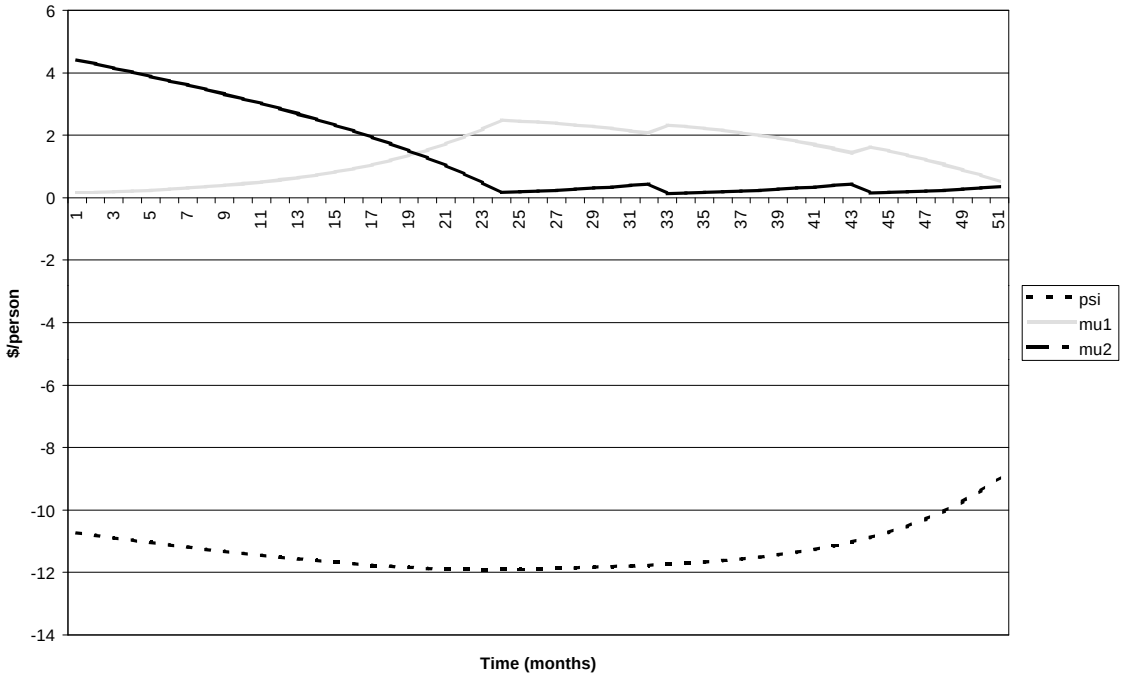
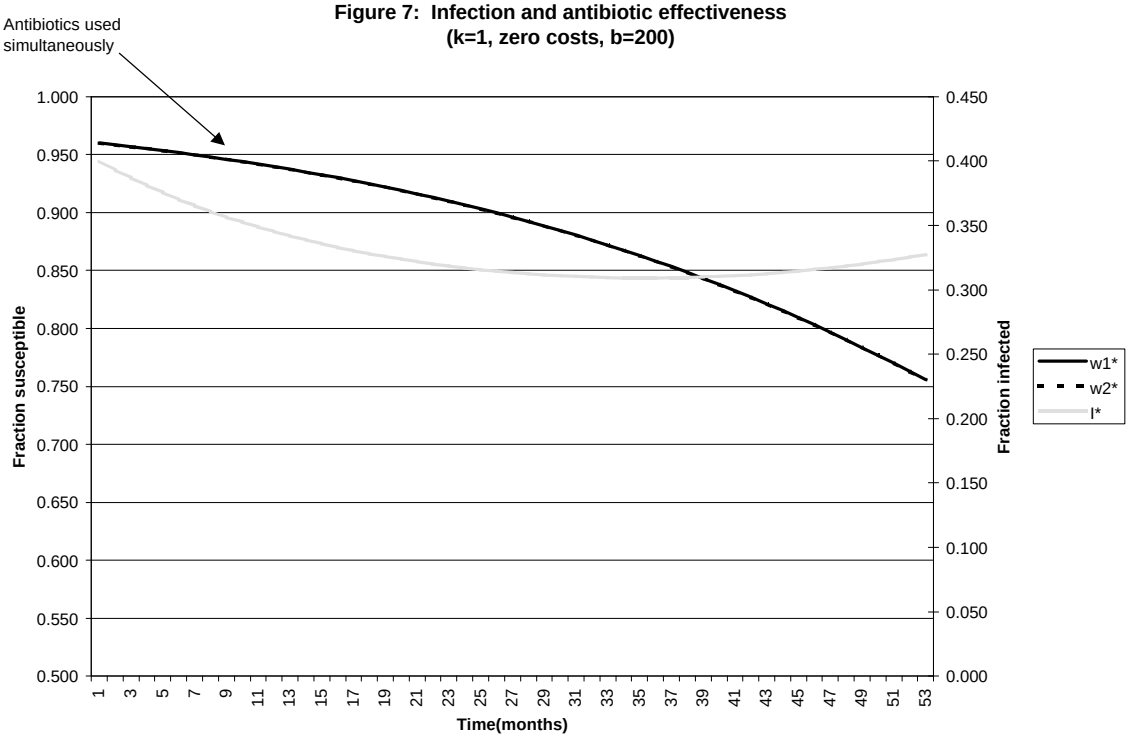


Figure 7: Infection and antibiotic effectiveness (k=1, zero costs, b=200)



Initial period during which antibiotic 2 is not used.

Figure 8: Infection and antibiotic effectiveness (k=1, with costs, b=200)

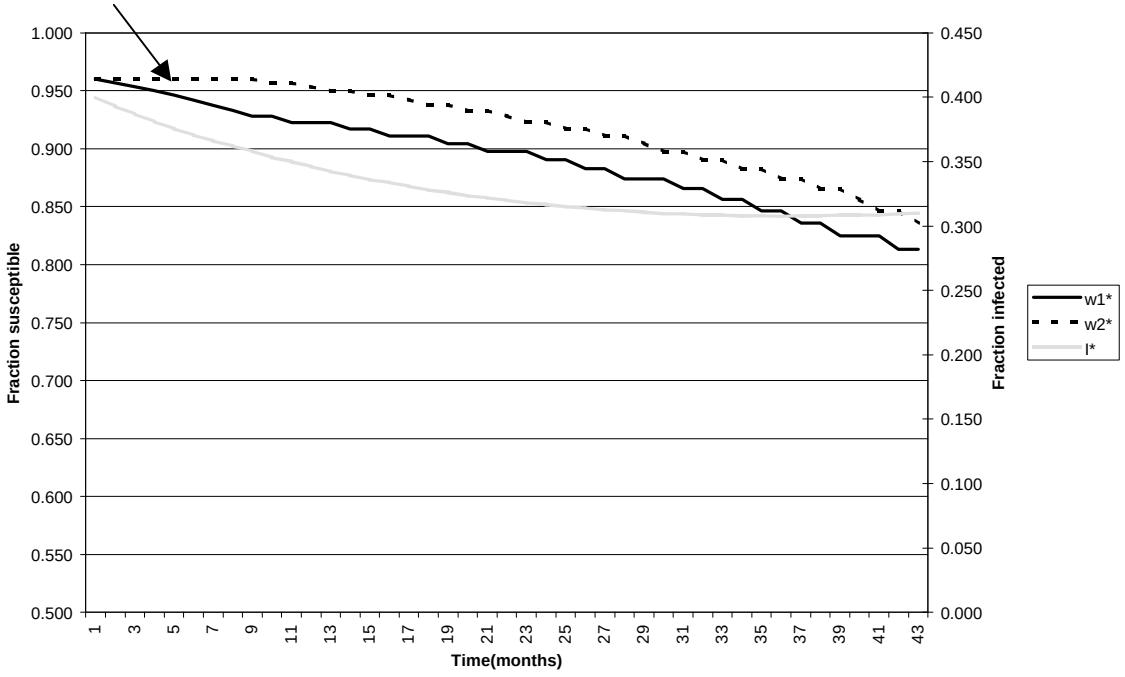


Figure 9: Costate variables (k=1, with costs, b=200)

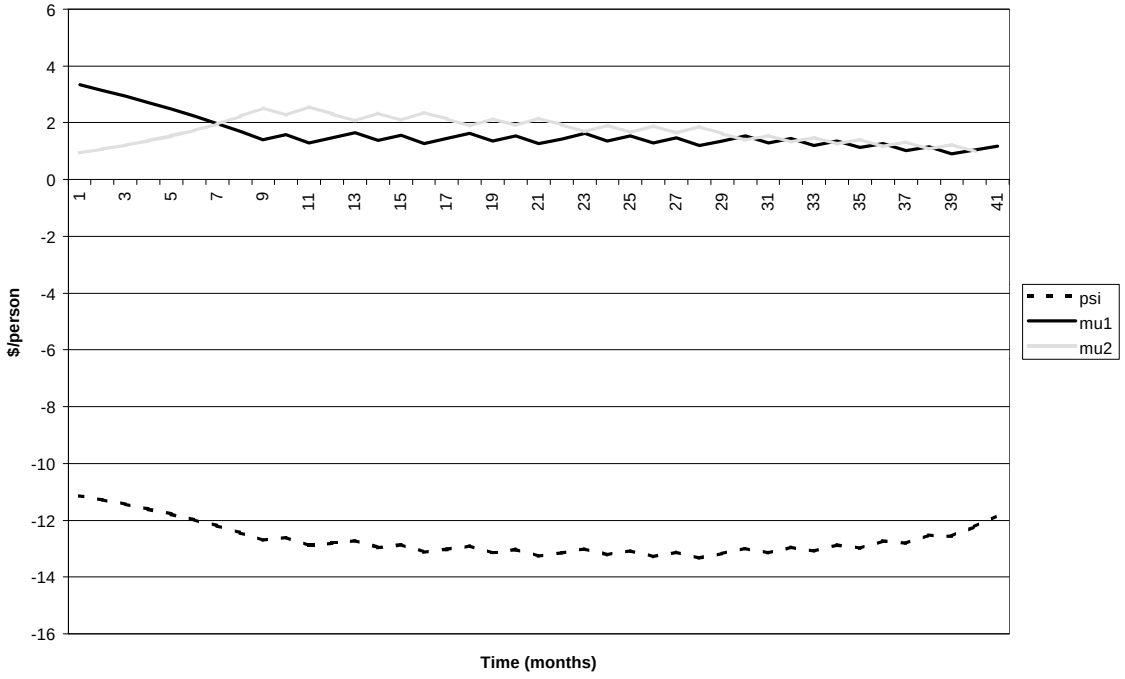


Figure 10: Infection and antibiotic effectiveness (k=1, with costs, b=2000)