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ECONOMICS OF ANTIBIOTIC RESISTANCE

by

Ramanan Laxminarayan

**A dissertation submitted in partial
fulfillment of the requirements for the
degree of**

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Doctoral Dissertation

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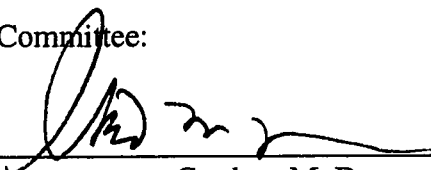
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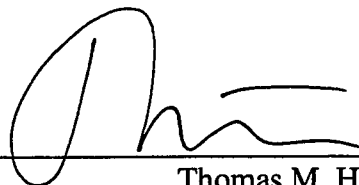
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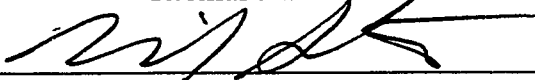


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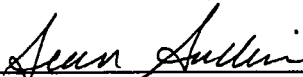
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Abstract

ECONOMICS OF ANTIBIOTIC RESISTANCE

by Ramanan Laxminarayan

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In recent years bacteria have become increasingly resistant to antibiotics, leading to a decline in the effectiveness of antibiotics in treating infectious disease. The first chapter 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 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 of the two antibiotics depends on the difference between the rates at which bacterial resistance to each antibiotic evolves and on the differences in their pharmaceutical costs. The theoretical model is estimated using data from Harborview Medical Center on antibiotic resistance of *Pseudomonas aeruginosa* to a class of antibiotics known as aminoglycosides. In addition to these results, we present a numerical solution to the optimization problem.

The second chapter argues in favor of modifications in patent breadth for antibiotics given the unique role of patents as a policy mechanism to encourage optimal antibiotic use. When the impact of current antibiotic use on future resistance is large, broad patents may be socially optimal when the social

benefit from preserving effectiveness outweighs the deadweight loss associated with a monopolistic market structure. This result is in sharp contrast with common wisdom in the literature on patent breadth that broad patents only serve to increase welfare costs associated with oligopoly and are therefore undesirable. Further, the use of antibiotics as growth promoters in poultry and livestock both increases the overall level of resistance, as well as encourages (intertemporally) inefficient antibiotic use in humans, further exacerbating the resistance problem. Finally, broad patents encourage investment in marginal cost reducing innovations that may be socially beneficial.

The increasing incidence of hospital-acquired infections and the failure of antibiotics to treat these infections is one of the greatest challenges facing modern medicine. Much of the increase in antibiotic resistance has been blamed on widespread antibiotic use in hospitals. Monthly data on both antibiotic resistance and use is becoming more readily available and presents hospital infection committees with an opportunity to estimate the impact of antibiotic use on the resistance of bacterial flora in their hospital. The third and final chapter uses time-series data on antibiotic use and bacterial resistance from Harborview Medical Center, Seattle to jointly estimate (1) the impact of use of aminoglycosides (a class of antibiotics) on the resistance of *Pseudomonas aeruginosa* (PSAR) to aminoglycosides, and (2) the response of physicians' antibiotic prescribing patterns in response to increases in bacterial resistance. The data reveals that a 10% increase in the number of patients treated with gentamicin resulted in only a 0.23% increase in the level of PSAR resistance to gentamicin. Similarly, a 10% increase in resistance to gentamicin resulted in a roughly 0.8% decrease in the number of patients treated with that antibiotic. Finally, using data on antibiotic use to forecast future resistance may produce more accurate estimates than exponential smoothing.

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DEDICATION

To my mother:

Rukmini Laxminarayan

CHAPTER 1: THEORY OF OPTIMAL USE

1. INTRODUCTION

The issue of resistance is a recurring theme in any attempt to curb organisms that are harmful to humans and human enterprise¹. Bacteria develop resistance to antibiotics², 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 one self 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

¹ This chapter first appeared as a co-authored paper with Gardner M. Brown.

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.

*"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 die⁴. 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. One reason for this failure is that the costs of resistance are small in the short run and are difficult to quantify. Moreover, the discount rate reduces the current value we place on antibiotic effectiveness in the future.

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

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. "

that the cost of resistance is equivalent to an increase in the cost of the pesticide (Comins 1977; Comins 1979).

This paper aims to position the problem of optimal use of antibiotic effectiveness within the setting of existing literature in the field of natural resources economics. It uses economic techniques and intuition gained from research about natural resources to describe optimal policy with respect to the use of antibiotics when confronted by the phenomenon of resistance. The model presented in this paper has two physical components. The first component is a version of the Kermack-McKendrick SIS model of disease transmission in which individuals move between susceptible and infected states⁵. 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). 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. This derivation constitutes the second component. The problem posed is one of optimal use of a non-renewable resource. When economic considerations are introduced, conclusions regarding the optimal introduction and use of antibiotics that are close substitutes are distinctly different from those derived from a purely epidemiological model. 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. Finally, we 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. An antibiotic relatively superior from a bio-economics framework should be used

⁵ Hence the name SIS (Susceptible->Infected->Susceptible.)

first, a result consistent with what we know about the optimal use of non-renewable resources of different qualities. However, the result is at variance with conclusions drawn from purely biological models of the same phenomena. 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 transmission⁶, and a derivation of the model of antibiotic resistance. Section 4 describes the optimization problem when antibiotic effectiveness is treated as a non-renewable resource. Section 5 presents the empirical estimation of the model using data on antibiotic use and bacterial resistance to these antibiotics. Simulation results are presented in section 6. Section 7 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

⁶ The interested reader is referred to the standard text on this subject by Anderson and May, 1991.

survive. Therefore, the use of 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 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 1992). 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; computerized monitoring of prescribing behavior, and physician education.

3. MODELING INFECTION AND RESISTANCE

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). Two essential building blocks in this 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. There are two states in this model, Susceptible and Infected. One part of the model used in the paper is a modified version of the Kermack-McKendrick formulation and describes the dynamics of an infectious disease when a fraction of the infected of the infected population is treated. The terms used in the model are defined as follows:

$S =$ Susceptible (healthy) fraction of population,

- $I =$ Infected fraction of population,
- $M =$ Fraction of population that undergoes treatment,
- $r =$ Spontaneous rate of recovery,
- $E =$ Expected increase in rate of recovery (over and above spontaneous recovery) under treatment.

The susceptible population represents those who are currently free from disease but potentially can acquire the disease at any time. The remaining population is deemed infected by the disease. The equation governing the rate of change of infection is

$$\dot{I} = \beta IS - rI - EM$$

Individuals move from being susceptible to a state of infection at a rate βIS , where β represents the force of disease contagion and is referred to as the transmission coefficient. Infected individuals recover at the spontaneous rate of recovery r and reenter the susceptible population⁷. In short, individuals move from being susceptible (S) to being infected (I) and then back to susceptible (S).

⁷ If we denote e as the rate of recovery under treatment, then

$$\dot{I} = \beta I(1 - I) - r(I - M) - eM$$

$$\Rightarrow \dot{I} = \beta I(1 - I) - rI - (e - r)M$$

In other words, $E = e - r$ refers to the contribution of the antibiotic to recovery over and above the spontaneous rate.

Consider a population (normalized to 1) in which fraction I is infected and the remainder $S=1-I$ is susceptible to the infection. M is the fraction of the total population that is treated using the antibiotic. This fraction recovers at a rate E , determined by the prevailing stock of antibiotic effectiveness. E represents the increase in the rate of recovery due to treatment. Since the number treated using antibiotics cannot exceed the number of infected individuals, $I > M$. The infected population I returns to the susceptible state at a natural rate of recovery, r , $r \leq E$, giving rise to Figure 1 and the equation

$$(1) \quad \dot{I} = \beta I(1-I) - rI - EM$$

Without antibiotics, the steady state value of I is given by

$$I = \frac{\beta - r}{\beta}.$$

It is convenient to distinguish between “epidemic” resistance and “acquired” resistance. While primary resistance is caused by infection by a resistant organism, acquired or “*de novo*” resistance develops in individuals infected with a sensitive organism when they are treated using antibiotics⁸.

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

⁸ The spread of resistance due to the latter mechanism is negligible once resistance is established in a small fraction of the infected sub-population. The focus of this paper is on the epidemic transmission of resistant bacteria from person to person and not on the generation of new resistance bacteria.

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, indeed, 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).

Cycling may also be unfeasible for economic reasons. When only one antibiotic is used, and resistance to this antibiotic increases, it becomes optimal to treat using an alternative antibiotic which is now more effective. The optimal policy is, therefore, to instantaneously switch between the two antibiotics. If the fitness cost of resistance is negligible, then bacterial resistance to antibiotics does not decrease even when the use of antibiotics is terminated. In this situation, the problem of optimal antibiotic use can be modeled in much the same way as the optimal extraction of non-renewable ore, as we do below.

Following Bonhoeffer, (Bonhoeffer, Lipsitch et al. 1997).

$$(2) \quad \frac{dS}{dt} = -\beta S(I_w + I_r) + r_w I_w + r_r I_r + f I_w$$

where S is the uninfected (healthy) fraction of the population. Moreover, $\dot{I} = -\dot{S}$, 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. By sensitive we mean that an antibiotic has some level of effectiveness against that strain. Both r_w and r_r refer to the spontaneous (no treatment) rate of recovery of an infected individual. f is the fraction of the infected population treated using the 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 or a resistant organism.⁹ 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. The fitness cost is denoted by $\Delta r = r_r - r_w$ and has a minimum value of zero¹⁰. A static overall absolute size of population is assumed, without loss of generality.

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.

$$(3.1) \quad \frac{dI_w}{dt} = \beta SI_w - r_w I_w - f I_w,$$

$$(3.2) \quad \frac{dI_r}{dt} = \beta SI_r - r_r I_r,$$

⁹ 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.

¹⁰ The notion of fitness cost may be captured by using different transmission rates β_r and β_w for resistant and sensitive organisms (Massad, Lundberg et al. 1993).

and antibiotic effectiveness expressed as a fraction, is given by

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

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. Further,

$$(5.1) \quad \frac{dI}{dt} = \frac{dI_w}{dt} + \frac{dI_r}{dt} = (\beta S - r_r - w(f - \Delta r))I$$

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

The derivation for the case discussed in the next section (involving two antibiotics) is in Appendix 2. Note that w decreases with the use of the antibiotic.

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.¹¹

Two standard assumptions that accompany the basis SIS model are applicable here. We rule out immunity and assume that an individual is

¹¹ $\frac{\partial \dot{w}}{\partial w} = f(2w - 1)$. Therefore, $\text{sign}\left(\frac{\partial \dot{w}}{\partial w}\right) = \text{sign}\left(w - \frac{1}{2}\right)$

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, Lipsitch 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. It is reasonable that the initial resistance of the bacteria to the two antibiotics 1 and 2 is identical, although this assumption is relaxed for the numerical simulation. We denote the initial effectiveness of the antibiotics by w_0 where $w_0 \approx 1$. The model is generally applicable to infections such as tuberculosis, otitis media (ear infections) and gonorrhea in which the organism that causes infection is not normally present in the host¹². Finally, the model makes no provision for individuals to enter or leave the population thereby ignoring new births, migration and deaths in the population.

4. ECONOMICS OF ANTIBIOTIC EFFECTIVENESS AS A DEPLETABLE RESOURCE

Now that the physical components of the story have been introduced, we turn to the more transparent economics considerations. The benefit for each antibiotic used is $xw_i f_i$, where x is the benefit associated with each successful treatment using the antibiotic measured in \$/person, scaled both by the fraction of I treated

¹² 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.

and the effectiveness (w_i) of such treatment. The cost associated with the infection is represented by $c_i I$. The inter-temporal net benefit function is

$$(6) \quad \max \int_0^T \left[xI(t) \left(\sum_i w_i(t) f_i(t) \right) - c_i I(t) - \bar{c} f_2(t) I(t) \right] e^{-\rho t} dt - \gamma(T),$$

where \bar{c} is the unit cost of treatment with antibiotic 2 and the cost of antibiotic 1 is assumed to be 0. A singular feature of this maximand is that stock of infection enters both the benefit and cost function. Although infection is undesirable and is reflected in the term $c_i I$, a higher level of infection also implies a greater number of patients reap the benefits of successful antibiotic treatment for any given $f(t)$. In the interest of clarity, time subscripts are suppressed.

Consider bacteria for which $\Delta r = 0$. This case 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, 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. It is convenient to think of antibiotic effectiveness as an un-extracted stock of oil. Taking the analogy further, one may think of a well of antibiotic effectiveness being depleted by treating a fraction $f(t)$ of the infected population.

We treat potentially with two antibiotics, whose dynamics, set out in (5.2), modified by $\Delta r = 0$, are described by

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

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

Where $k(<1)$ equals a factor introduced to distinguish the resistance profile of antibiotic 1 from antibiotic 2.

The current value Hamiltonian to be maximized, combining (6), (7.1), (7.2) and a rewrite of (5.1), with $S = 1 - I$ and $\Delta r = 0$ that describes the dynamics of infection,

$$\dot{I} = \beta I(1 - I) - rI - I(\sum w_i f_i),$$

is

(8)

$$\begin{aligned} H &= xI \left(\sum_i w_i f_i \right) - c_I I - \bar{c} f_2 I + \varphi \left[\beta I(1 - I) - rI - I \left(\sum_i w_i f_i \right) \right] \\ &\quad + \mu_1 [f_1 k w_1 (w_1 - 1)] + \mu_2 [f_2 w_2 (w_2 - 1)] \\ &= [(x - \varphi)I w_1 + \mu_1 k w_1 (w_1 - 1)] f_1(t) + [(x - \varphi)I w_2 - \bar{c} I + \mu_2 w_2 (w_2 - 1)] f_2(t) \\ &\quad - \varphi (\beta I(1 - I) - rI) - c_I I - \mathcal{H}(T) e^{-\rho T} \end{aligned}$$

where ρ is the social discount rate and costate variables φ , μ_1 and μ_2 are associated with I , w_1 and w_2 respectively. Note that φ is associated with a stock of “bad” capital i.e. infection. In addition,

$$I(t) \leq 1$$

$$0 \leq f_i(t) \leq 1$$

$$\sum_i f_i(t) \leq 1$$

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

$$(8.1) \quad H_{f_1} = (x - \varphi)Iw_1 - \mu_1 kw_1(1 - w_1) \begin{cases} < \\ = \\ > \end{cases} 0 \text{ as } f_1 \begin{cases} = 0 \\ \in [0,1] \\ = 1 \end{cases}$$

$$(8.2) \quad H_{f_2} = (x - \varphi)Iw_2 - \bar{c}I - \mu_2 w_2(1 - w_2) \begin{cases} < \\ = \\ > \end{cases} 0 \text{ as } f_2 \begin{cases} = 0 \\ \in [0,1] \\ = 1 \end{cases}$$

$$(8.3) \quad H_{w_1} = (x - \varphi)If_1 - \mu_1 kf_1(1 - 2w_1) = \rho\mu_1 - \dot{\mu}_1$$

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

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

The transversality conditions are given by Theorem 7.2.1 in (Leonard and Long 1992).

$$(8.6) \quad \lim_{t \rightarrow T} \phi_t = -\gamma$$

$$(8.7) \quad \lim_{t \rightarrow T} e^{-\rho t} \mu_{i,t} w_{i,t} = 0$$

The economic interpretation of (8.1) after rewriting

$$(8.8) \quad xIw_1 - \phi Iw_1 = \mu_1 w_1 (1 - w_1)$$

is that the marginal benefit of changing the fraction of the population treated using antibiotic 1 equals its marginal cost. As such, 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 x to the individual, scaled by the effective fraction successfully treated, (Iw_1) . It also reduces the stock of infection, conferring a benefit of $|\phi Iw_1|$ to society. The user cost or rental rate for a unit of "effectiveness" capital is μ_1 for antibiotic 1. Whereas harvesting a fish *reduces* fish capital by a unit, 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, $\mu_1 \dot{w}_1$.

The interpretation of (8.2) is straightforward. The benefit of changing the fraction of the population treated with antibiotic 2 in each time period 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. In each time period during which a fraction of the infected population is treated using antibiotic 2, the marginal benefit of treatment (represented by the first term) is

equal to the marginal benefit of successful treatment using antibiotics plus the value to society of decreasing the stock of infection, $-\phi I w_2$. The marginal user cost of treatment captures the future opportunity cost of increasing resistance. The same interpretation holds for equation (6.6). If the marginal benefit of antibiotic treatment is less than the user cost of antibiotics, then the use of that antibiotic is discontinued.

ϕ is interpreted as the marginal cost of being infected. It is possible to show that $\phi < 0$ and that $\frac{\dot{\phi}}{\phi} > 0$ when $\beta < \rho + r$ as it is in our case (see Appendix 1). The

shadow cost associated with the resistance function of the two antibiotics is denoted by μ_1 and μ_2 . Since effectiveness represents positive capital, μ_1 and μ_2 are both always positive. Since we rule out the case in which the disease is eradicated we require that $\lim_{t \rightarrow T} \phi(t) e^{-\rho t} = 0$.

From equations (8.1) and (8.2),

$$(9.1) \quad f_1 = 1 \text{ and } f_2 = 0$$

$$f_1 = \frac{1}{1+k} \text{ and } f_2 = \frac{k}{1+k}$$

$$f_1 = 0 \text{ and } f_2 = 1$$

$$\text{as } (x - \phi) I w_1 - \mu_1 k w_1 (1 - w_1) \begin{pmatrix} > \\ = \\ < \end{pmatrix} (x - \phi) I w_2 - \bar{c} - \mu_2 w_2 (1 - w_2)$$

When the equality condition holds,

$$(9.2) \quad \mu_1^* = \frac{(x - \varphi)I}{k(1 - w_1)}$$

$$(9.3) \quad \mu_2^* = \frac{(x - \varphi)I}{(1 - w_2)} - \frac{\bar{c}I}{w_2(1 - w_2)}$$

Assume the second antibiotic has no out of pocket cost, $\bar{c} = 0$, then $\mu_1 > \mu_2$ when the resistance level is the same ($w_1 = w_2$), but a unit's use of drug 1 increases resistance less than for drug 2, $k < 1$ and $w_1 = w_2$. A resource more stable or less vulnerable is more valuable so its rental rate should be less. In this case, a solution that satisfies (8.1)-(8.4) when pharmaceutical costs of the two antibiotics are identical is for the two antibiotics to be use in proportion

$$\frac{f_1}{f_2} = \frac{1}{k}$$

in which case $w_1 = w_2$ and $\mu_2 = \mu_1 k$. Here is where the ore analogy can lead one astray for it is sometimes optimal to use two antibiotics simultaneously, whereas it is not optimal to use ores of different grades simultaneously.

From the equations (8.3) and (8.4),

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

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

Substituting for μ_1 and μ_2 from equations (8.1) and (8.2), we get

$$(10.3) \quad \frac{\dot{\mu}_1}{\mu_1} = \rho - kf_1w_1 \text{ and}$$

$$(10.4) \quad \frac{\dot{\mu}_2}{\mu_2} = \rho - f_2(2w_2 - 1) - \frac{(x - \varphi)If_2w_2(1 - w_2)}{(x - \varphi)Iw_2 - \bar{c}I}$$

If only antibiotic 1 is being used, $f_1 = 1$ in (10.3) so that the rental rate on its capital is rising at the discount rate less w_1 (for $k = 1$). Since ρ is small, say 4 percent, $\frac{\dot{\mu}_1}{\mu_1} < 0$ for most of the use of w_1 . Since $w_1 \approx 1$ initially, its rental rate falls for most of the time because of the large stock externality. Use of the antibiotic today reduces w_1 forever after and thus reduces each future annual benefit, xIw_1f_1 .

During the first interval, drug 2 is not being used, $f_2 = 0$ and its rental rate rises at the discount rate (see equation (10.2)). With μ_2 increasing and μ_1 decreasing, the two meet and then both drugs are used. When $\bar{c} > 0$, the case 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 should be. So 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

$$x/w_1 < x/w_2$$

when this loss cannot compensate for the higher marginal cost \bar{c} , it pays to introduce drug2 as well. The second reason the case of using two antibiotics 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.

5. DATA AND ESTIMATION

The case study involves the treatment of *Pseudomonas aeruginosa* (PSAR) using a class of antibiotics known as aminoglycosides. The more general term antibiotics will hereforth replace the more accurate term aminoglycosides. PSAR infections occur most frequently in hospitals where they can cause severe pneumonia in hospitalized patients, especially those in intensive care. The organism is commonly found in moist areas, such as sinks and urine receptacles, and in some instances, in certain antiseptic solutions. The most serious infections from PSAR occur in debilitated people whose immune system is impaired by medications, other treatments, or disease. *Pseudomonas* can infect the blood, skin, bones, ears, eyes, urinary tract, heart valves, and lungs (Craig and Andes 1997). PSAR belong to a class of bacteria called gram-negative rods which are generally more resistant to antibiotics than are gram-positive bacteria (Merck 1950)¹³.

¹³ Gram-negative bacteria have a great facility for exchanging genetic material (DNA) among strains of the same species and even among different species. This means that if a gram-negative bacterium either undergoes a genetic change (mutation) or acquires genetic material that confers resistance to an antibiotic, the bacterium may later share its DNA with another strain of bacteria and the second strain can become resistant as well. Although all bacteria have an inner cell membrane, gram-negative bacteria have a unique outer membrane. This

This study examines data on antibiotic use and PSAR resistance to two commonly used antibiotics, Gentamicin (GENT) and Tobramycin (TOB) at the Harborview Medical Center in Seattle for the 12 year period from January 1, 1985 through December 31, 1996¹⁴. A third antibiotic, amikacin, was used infrequently and was excluded from our analysis.

The case of antibiotic resistance to PSAR fits well with certain stylized assumptions incorporated in our model. For one, PSAR is a hospital-acquired infection and is not usually transmitted in the community. Thus we can treat the hospital as a closed system and ignore the effects of antibiotic use in one hospital on resistance in another hospital. Second, our data reveal that resistance of other bacteria such as *Klebsiella*, *Acinetobacter* and *E. Coli* to antibiotics has been fairly stable in comparison to resistance of PSAR to antibiotics. This indicates that the likelihood that the resistance of these other bacteria to GENT and TOB influenced PSAR resistance to GENT and TOB was fairly small. Finally, the mechanisms by which PSAR develops resistance to the antibiotics under study are different from the methods that PSAR uses against other antibiotics. A Danish study which reported a difference in antibiotic resistance patterns between two hospitals in response to differences in antibiotic use also noted that there was no significant difference in the use of other antibiotics between the two hospitals (Busch-Sorensen, Sonmezoglu et al. 1996).

outer membrane excludes certain drugs and antibiotics from penetrating the cell, partially accounting for why gram-negative bacteria are in general more resistant.

¹⁴ During this period, hospital policy was changed regarding the control of antibiotic agents. Until early 1990, many antibiotics could be used only with permission of the infectious diseases division. Since then this restriction has been removed. However, we found that this change in policy did not affect the prescription of aminoglycosides.

Antibiotic sensitivity testing data on isolates of PSAR were obtained from the Harborview Microbiology Labs. The standard Kirby-Bauer test was used for most of the period to identify isolates as sensitive, intermediate or resistant¹⁵. Since the data contained multiple isolates per patient hospitalization, we selected one isolate per source (blood, urine, wound etc.) per hospitalization for each patient. Hospital admit/discharge dates obtained from pharmacy records were matched to lab records. Approximately twelve percent of our lab records had no corresponding hospital dates and were omitted. For each hospitalization, the last test for each bug/drug/source combination was taken as being indicative of the level of resistance in a patient. This amounted to a little over half of the original number of lab tests that examined the resistance of PSAR to antibiotics. The level of susceptibility in each month was calculated as the fraction of total number of isolates tested that were in the sensitive category. On average, 28 patients were tested each month for resistance to GENT and TOB¹⁶ (see Figure 2). Descriptive summary statistics of PSAR resistance to GENT and TOB are provided in Table 1.

Data on antibiotic use over the 1984-1996 time period were obtained from pharmacy billing records stored in the DatANAL[®] billing system. Monthly fractions of patients treated with GENT and TOB were calculated. Our data confirmed results from earlier studies demonstrating the link between

¹⁵ Starting in mid-1994, all antibiotic sensitivity testing was performed using both the Kirby-Bauer method and the Vitek Automated Microbiological System[®]. Over the next year, the Vitek System was configured in order that the Vitek results were in agreement with the Kirby-Bauer test results. In late 1995, the Kirby-Bauer method was phased out completely and all tests were conducted on the Vitek System.

¹⁶ The Augmented-Dickey Fuller test was used to test for a unit root in the data series on susceptibility of PSAR to GENT and TOB. Based on MacKinnon critical values, we rejected the hypothesis that the data were non-stationary at the 95% confidence level.

patterns of antibiotic usage and PSAR resistance to antibiotics (Busch-Sorensen, Sonmezoglu et al. 1996)¹⁷.

Estimates of k and r , denoted by \hat{k} and \hat{r} respectively are estimated from the following equation, illustrated for gentamicin (GENT).¹⁸

(11.1)

$$\Delta w_{t,GENT} = \hat{k} f_{t,GENT} w_{t,GENT} (w_{t,GENT} - 1) + \hat{r} w_{t,GENT} (w_{t,GENT} - 1) + \hat{\alpha} f_{t,TOB} w_{t,TOB} w_{t,GENT}$$

w_t is the susceptibility of PSAR to the antibiotic and f_t is the fraction of infected patients treated with the antibiotic. This equation is equation (A.2.2) in Appendix 2 amended with a drug interaction term $w_{TOB} w_{GENT}$. An AR(2) specification was used for the GENT model to account for the presence of serial correlation. Our estimate of \hat{k} was positive (and significant at the 90% confidence level), and both \hat{r} and $\hat{\alpha}$ were negative (and significant at the 99% level of confidence). The signs on all three coefficients were as expected. \hat{r} was estimated to be approximately -0.8 for both GENT and TOB (Table 2). The negative sign on $\hat{\alpha}$ indicated a certain degree of cross-resistance between the two antibiotics. In other words, the using TOB has a negative impact on the effectiveness of GENT

¹⁷ The Busch-Sorensen study showed qualitatively that there was a relationship between aminoglycoside use and resistance. However, they did not attempt to estimate a dose-response relationship between use and resistance.

¹⁸ For comparison, let GENT=1 and TOB=2. From equation A.6, for $w_{12} = r_{12} = 0$,

$$\begin{aligned} \dot{w}_1 &= f_1 w_1 (w_1 - 1) + r_2 w_1 (w_1 - 1) + (f_2 + r_1) w_1 w_2 \\ &= (f_1 + r_2) w_1 (w_1 - 1) + (f_2 + r_1) w_1 w_2 \\ &= f_1 w_1 (w_1 - 1) + r_2 w_1 (w_1 - 1) + f_2 w_1 w_2 \end{aligned}$$

on PSAR. PSAR resistance to TOB in response to GENT use was almost twice as great as resistance to GENT in response to TOB use.

The following equation was estimated to obtain the value of $\hat{\beta}$, \hat{h} and \hat{r} ¹⁹,

(11.2)

$$\frac{\Delta I_t}{I_t} = \hat{\beta} - \hat{\beta}I_t - \hat{h}_{t,GENT}w_{t,GENT}f_{t,GENT} - \hat{h}_{t,TOB}w_{t,TOB}f_{t,TOB} + \hat{r}(\hat{h}_{t,GENT}w_{t,GENT} + \hat{h}_{t,TOB}w_{t,TOB})$$

where $\hat{h}_{t,GENT}$ and $\hat{h}_{t,TOB}$ represent the rate of recovery under treatment with GENT and TOB respectively. Our estimate of $\hat{\beta}$ was approximately 0.03 at the 99% confidence level, and was similar to an estimate presented in another study (Kwan-

¹⁹ From equation A.4 in the appendix,

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

Assuming $w_{12} = r_{12} = 0$, the above equation can be rewritten as

$$\frac{\dot{I}}{I} = \beta(1 - I) - w_1(f_1 + r_2) - w_2(f_2 + r_1)$$

If $r_1 = r_2 = r$

$$\frac{\dot{I}}{I} = \beta - \beta I - w_1(f_1 + r) - w_2(f_2 + r)$$

Replace βN with $\hat{\beta}_N$ to obtain the estimated equation.

$$\frac{\dot{I}}{I} = \hat{\beta}_N - \hat{\beta}I - \hat{h}(w_1f_1 + w_2f_2) - \hat{r}\hat{h}(w_1 + w_2)$$

Gett, Nelson et al. 1998). Happily, the estimate of \hat{r} in this regression was similar to the estimates of \hat{r} obtained for both GENT and TOB in the earlier estimation. Our estimates of both $\hat{h}_{i,GENT}$ and $\hat{h}_{i,TOB}$ were significant at the 99% confidence level and represented a mean duration of infection of 11 days for patients infected with PSAR who were treated with GENT. Serial correlation was ruled out using the Breusch-Godfrey large sample test for auto correlated disturbances (Breusch 1978; Godfrey 1978). Unlike the standard Durbin-Watson estimator, this test is appropriate for lagged dependent variable models.

According to the MediSPAN[®] database, 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.

8. SIMULATION

A numerical simulation was used to determine optimal extraction paths for the two antibiotics GENT and TOB. The simulation used parameters estimated from the Harborview data (Table 4). Since the simulation described the treatment of antibiotic effectiveness as a depletable resource, Δr was assumed to be equal to zero.

The following equations describe the discrete time version of the model. h is the rate of recovery from a susceptible infection under antibiotic treatment.

$$(11.1) \quad I_{t+1} = I_t [1 + \beta - r - w_{1,t} f_{1,t} h - w_{2,t} f_{2,t} h] - \beta I_t^2$$

$$(11.2) \quad w_{2,t+1} = w_{2,t} [1 + f_{2,t} h w_{1,t} - f_{2,t} h]$$

$$(11.3) \quad \begin{aligned} \varphi_{t+1} = \varphi_t [1 + \rho - \beta + r + 2\beta I_t + h(w_{1,t} f_{1,t} + w_{2,t} f_{2,t})] \\ - x(w_{1,t} f_{1,t} + w_{2,t} f_{2,t}) - c_1 f_{1,t} - c_2 f_{2,t} - c_t \end{aligned}$$

$$(11.4) \quad \mu_{1,t+1} = \mu_{1,t} [1 + \rho - f_{1,t} k h (2w_{1,t} - 1)] - [x - \varphi_t h] I_t f_{1,t}$$

$$(11.5) \quad \mu_{2,t+1} = \mu_{2,t} [1 + \rho - f_{2,t} h (2w_{2,t} - 1)] - [x - \varphi_t h] I_t f_{2,t}$$

In the simplest 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, μ_1 increases at the discount rate (Figure 4). $\mu_1 = \mu_2$ 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 simulation 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 antibiotic 1 to that of antibiotic 2 is roughly ten to one. The movement of the costate variables over time is plotted in Figure 6.

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. x is assumed to be \$200²⁰. 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 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 Bonhoeffer's conclusion 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

²⁰ We used this figure ($x=\$200$) as a lower end estimate in order to compare the optimal path for this case with the optimal path when $x=\$2,000$. 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.

(lower cost antibiotic) is used. 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 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 x is assumed to be \$200. On the other hand, if x 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. The shadow value of antibiotic 2 (of lower variable costs) decreases, and the shadow value of antibiotic 1 increases until both antibiotics are used (Figure 9). Hereon, both μ_1 and μ_2 decline. When antibiotic costs, c_1 and c_2 are relatively small compared to the benefit of successful therapy, x (see Figure 10), the role of variable costs in selecting the less expensive antibiotic over the more expensive one is somewhat diminished.

9. CONCLUSIONS 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 make the leap of understanding that the effect of declining antibiotic effectiveness on the social benefit function is parallel to the effect of declining ore quality on the value of ore extraction, 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 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.

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 resistance²¹. 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.

²¹ Although Bonhoeffer *et. al* introduce the notion of fitness cost in their model, fitness cost is set equal to zero throughout.

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. The transparent 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 use of antibiotics in cattle and poultry feed continues to be a contentious issue that is unlikely to be resolved any time soon.

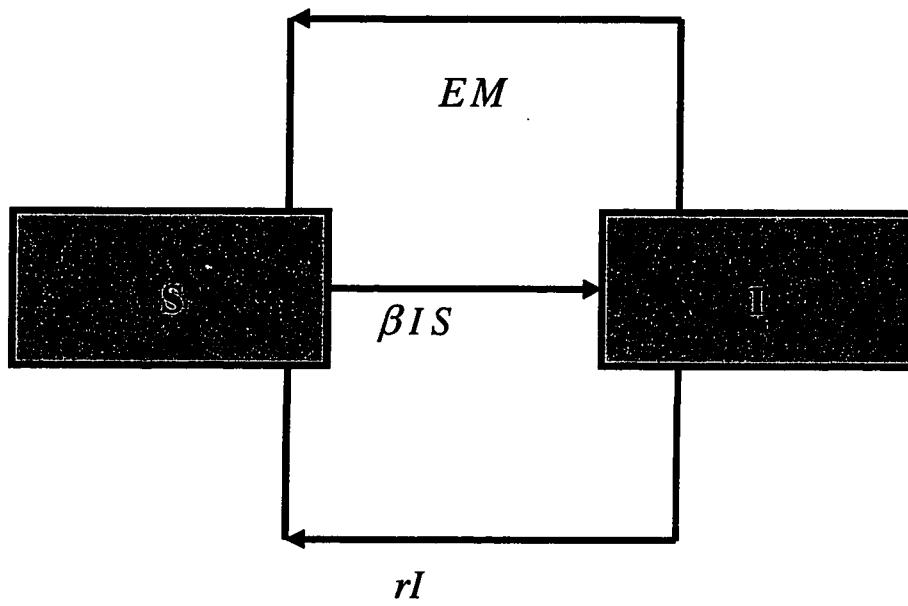


Figure 1: The SIS Model of Infection

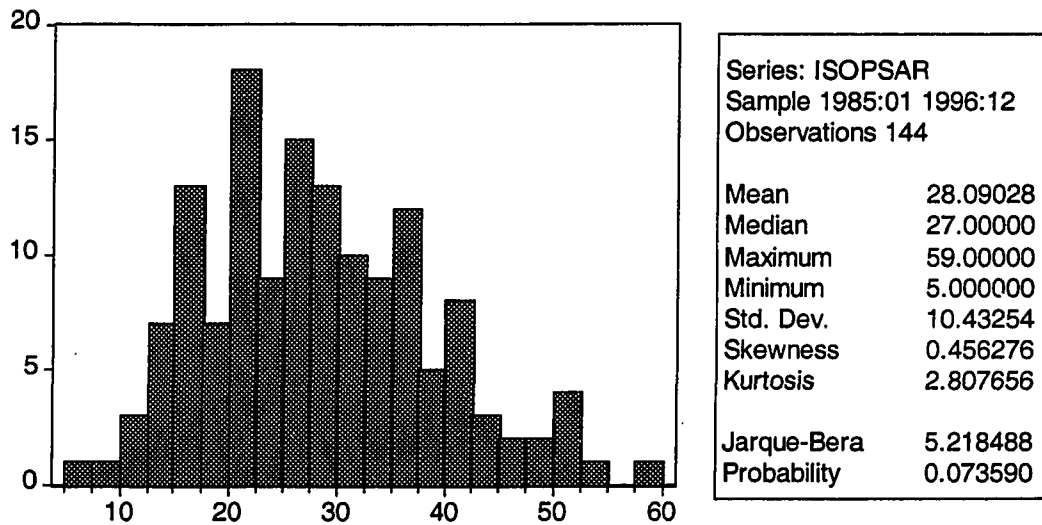


Figure 2: Histogram of PSAR isolates tested for resistance to GENT and TOB

Table 1: Summary statistics of PSAR resistance to GENT and TOB at Harborview Medical Center, Seattle. 1985-1996.

	PSAR Susceptibility to GENT (%)	PSAR Susceptibility to TOB (%)
<i>Mean</i>	76.08	93.75
<i>Median</i>	81.25	96.15
<i>Maximum</i>	100.00	100.00
<i>Minimum</i>	21.43	68.97
<i>S.D.</i>	17.56	7.10

Table 2: Parameter estimates for the evolution of resistance to GENT and TOB*
(t-stats in parantheses)

	<i>GENT</i>	<i>TOB</i>
\hat{k}	0.703 (1.80)	0.604 (1.32)
\hat{f}	-0.786 (-2.11)	-0.833 (-7.23)
$\hat{\alpha}$	-0.322 (-2.69)	-0.066 (-6.06)
R^2	0.34	0.33

* Coefficients of AR(1) and AR(2) terms in the GENT estimation equation were -0.58 (-6.6) and -0.29 (-3.3) respectively.

Table 3: Parameter estimates for the evolution of infection.

Parameter estimates	
$\hat{\beta}$	0.01 (3.64)
\hat{h}_{GENT}	2.55 (4.13)
\hat{h}_{TOB}	1.05 (2.03)
\hat{f}	0.96 (7.00)
R^2	0.37

Table 4: Parameters used in simulation

<i>Coefficient of disease transmission, β</i>	0.01
<i>Social discount rate, ρ</i>	0.05
<i>Rate of recovery from antibiotic treatment, h</i>	2.55
<i>Initial effectiveness of GENT, $w_{GENT}(0)$</i>	0.81
<i>Initial effectiveness of TOB, $w_{TOB}(0)$</i>	0.96
<i>Marginal benefit of successful antibiotic treatment, χ</i>	\$200 (Low) \$2,000 (High)
<i>Marginal cost of GENT, c_{GENT}</i>	\$0.96
<i>Marginal cost of TOB, c_{TOB}</i>	\$43

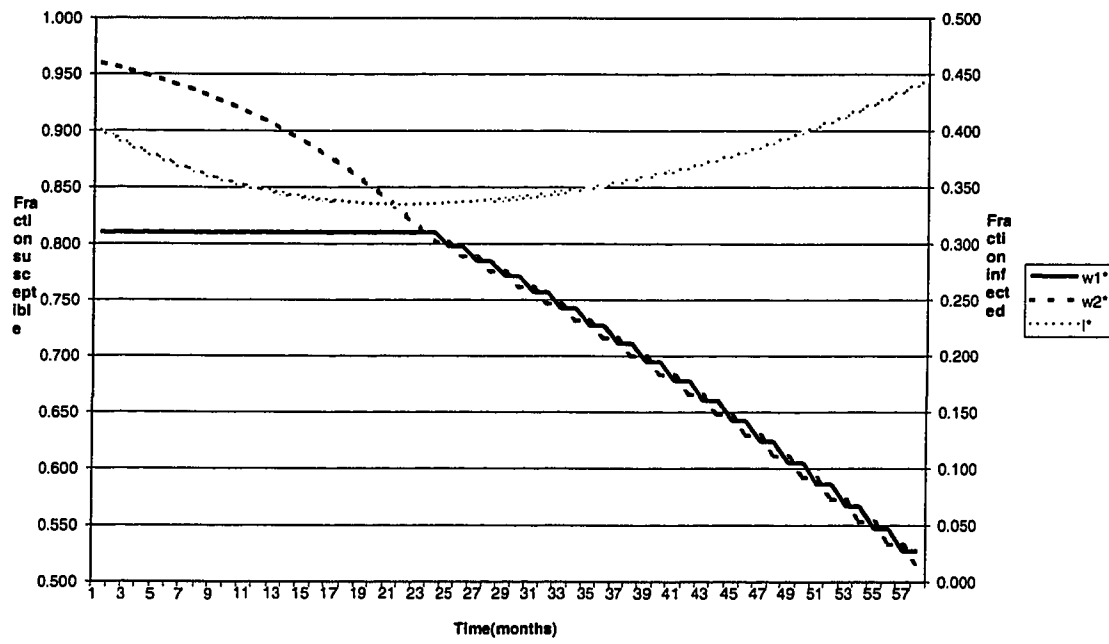


Figure 3: Time path of antibiotic effectiveness and infection ($k=1$, no costs)

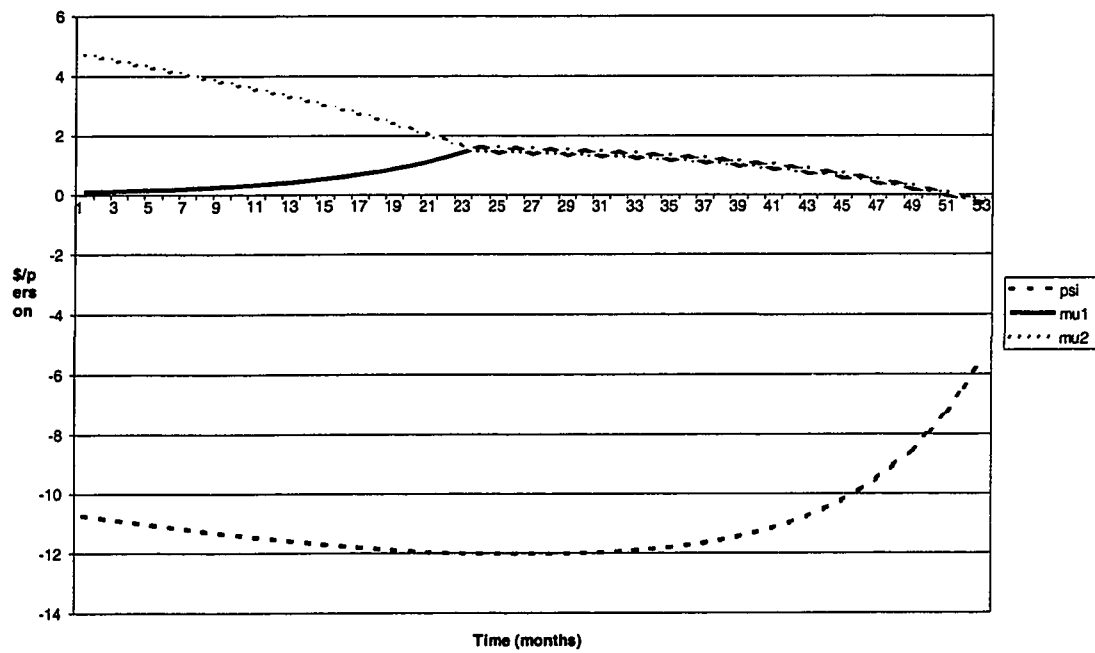


Figure 4: Plot of costate variables ($k=1$, no costs)

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

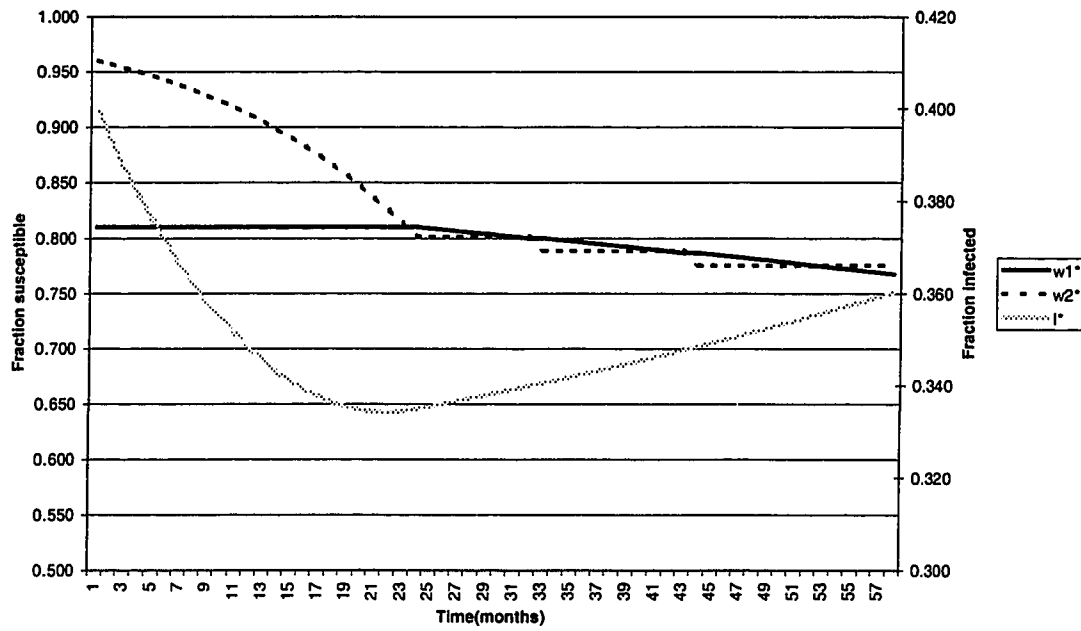


Figure 5: Time paths of antibiotic effectiveness and infection ($k=0.1$.no costs)

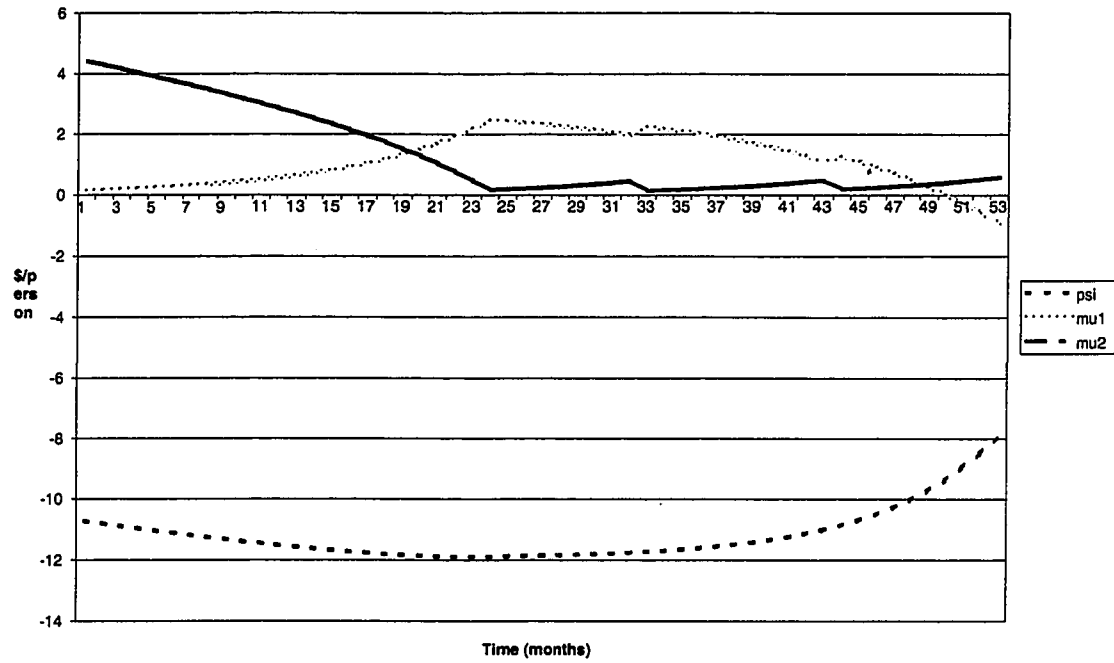


Figure 6: Costate variables ($k=0.1$, no costs)

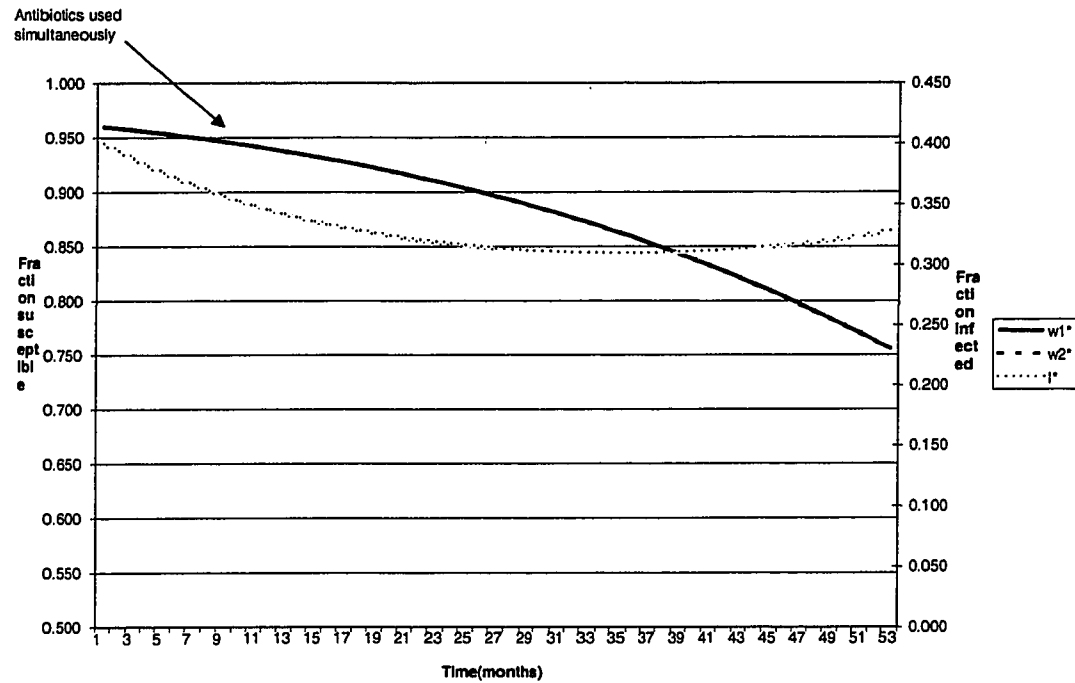


Figure 7: Time paths of antibiotic effectiveness and infection when initial effectiveness is identical ($k=1$, no costs, $x=200$)

Initial period
during which
antibiotic 2 is
not used.

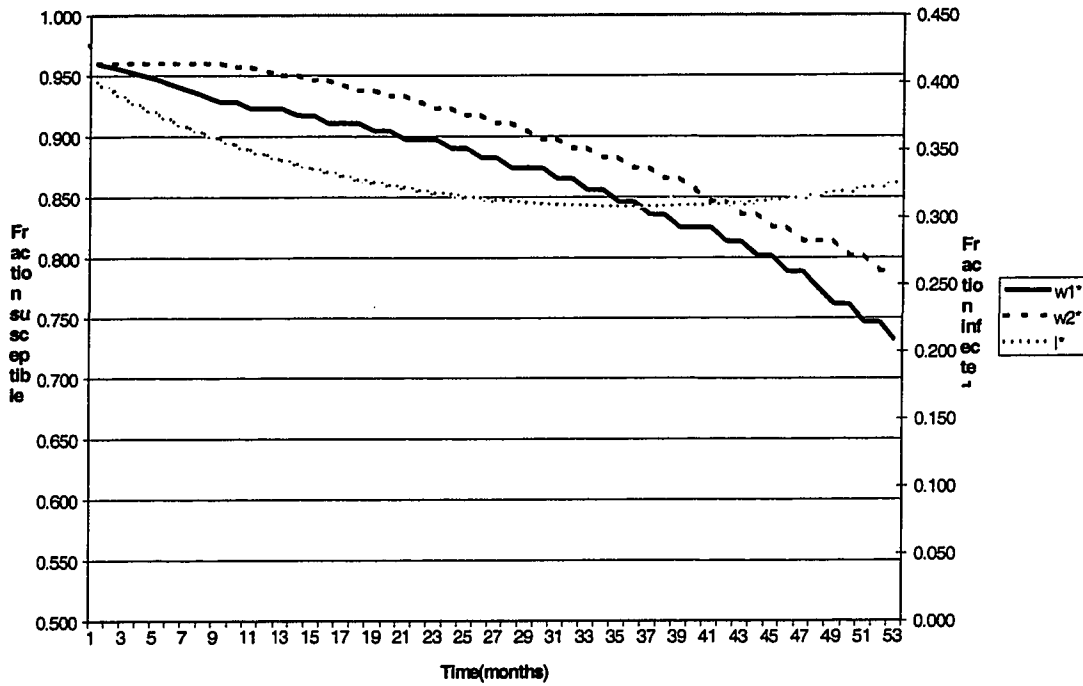


Figure 8: Time paths of antibiotic effectiveness and infection with identical initial effectiveness ($k=1$, with costs, $x=200$)

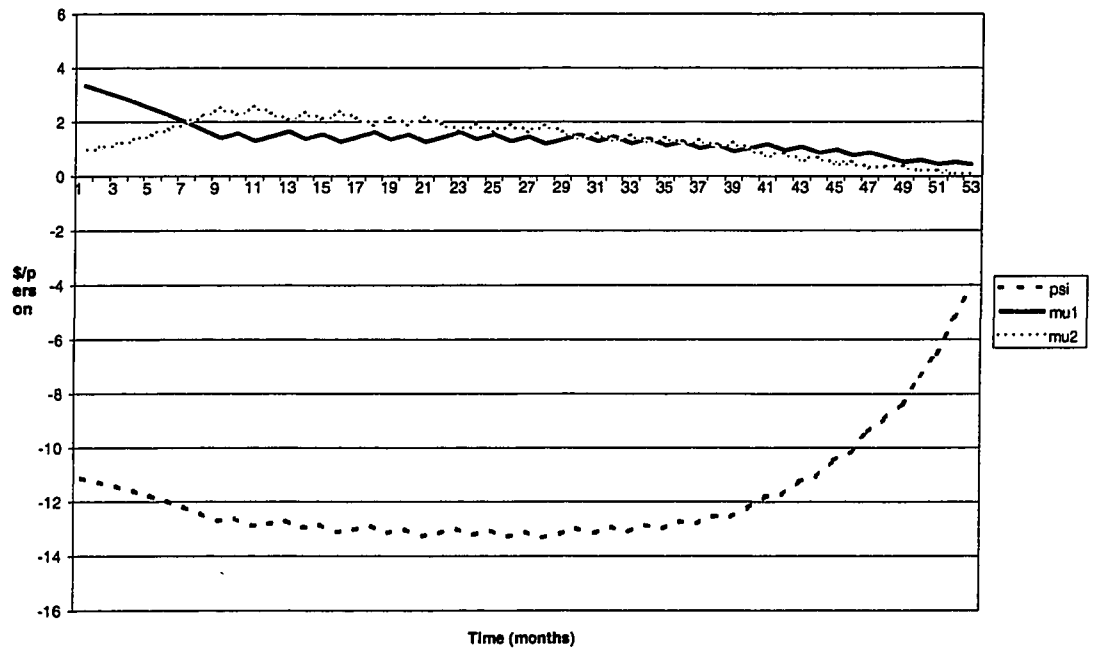


Figure 9: Costate variables ($k=1$, with costs, $x=200$)

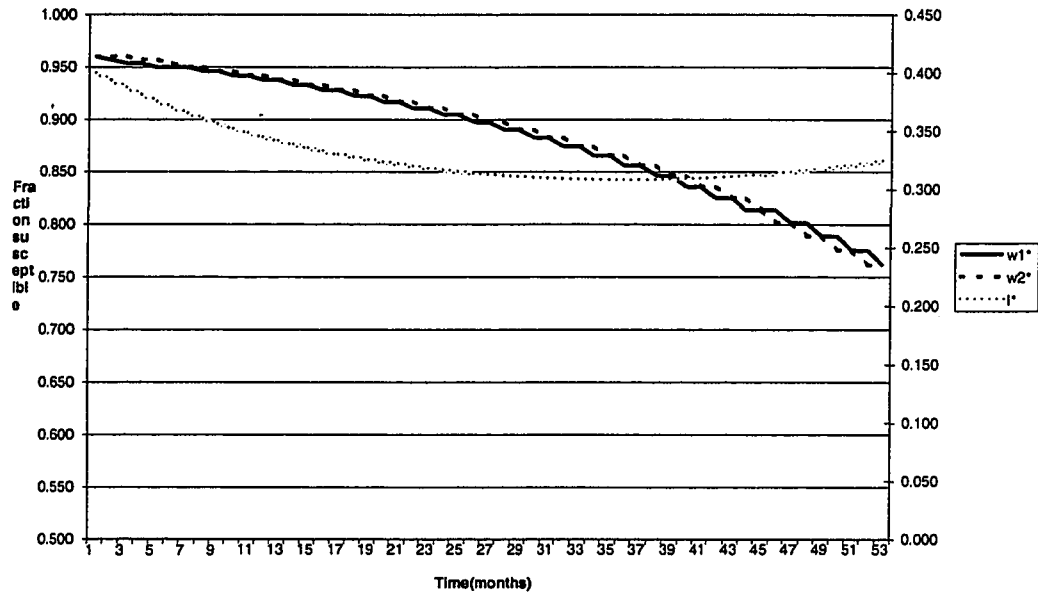


Figure 10: Time paths of antibiotic effectiveness and infection ($k=1$, with costs, $x=2000$)

CHAPTER 2: OPTIMAL PATENT BREADTH FOR ANTIBIOTICS

1. INTRODUCTION

Science has contributed in no small way to our efforts to control biological agents ranging from disease causing viruses and bacteria to destructive pests and vectors. Control agents ranging from antibiotics and anti-malarials to herbicides and pesticides have reduced the burden of infectious diseases and helped protect agriculture from the vagaries of pest infestation. However, the advances made by science have been diminished by the ability of these biological agents to adapt, evade and survive in the presence of control agents that are commonly used in medicine and agriculture. For instance, the increasing resistance of bacteria to antibiotics in recent years represents a significant threat to human health and our ability to treat common infections. The phenomenon by which natural selection and other evolutionary mechanisms enable biological agents to adapt in ways that make our efforts at controlling them futile is commonly referred to as “resistance.” It is widely recognized that the rapidly increasing use of control agents such as antibiotics is the single most important reason for the emergence and spread of resistance.

At the present time, the literature on the economics of antibiotic resistance is restricted to discussions of the social externality imposed by antibiotic use, and policies for optimal antibiotic use in hospitals (Brown and Layton 1996; Laxminarayan and Brown 1998). However, critical economic questions that deal with broad social policies that encourage optimal antibiotic use remain unanswered. For instance, under what circumstances, if at all, should the livestock industry be allowed to continue sub-therapeutic use of antibiotics that are also used to treat infectious diseases in humans? Since antibiotic effectiveness

is a common pool resource, resistance to an antibiotic increases regardless of the manufacturer or user of the antibiotic. Therefore, current antibiotic use, both in humans and in animals, imposes an externality on future users. In a competitive market for the supply of antibiotics, no single firm has an incentive to independently take into consideration the effect of their sales of antibiotics on overall level of future antibiotic effectiveness. In the past, drug firms dealt with the problem of decreased effectiveness by constantly innovating to discover new antibiotics. However, it appears that the pool of antibiotics is relatively fixed and that the cost of finding new antibiotics is increasing.

From a policy perspective, mechanisms to regulate antibiotic use (and resistance) are scarce. Short of direct intervention in medical practice, and encouraging more responsible antibiotic use, there are few other methods by which the externality issue associated with antibiotic use may be corrected²². In general, the rate at which antibiotic effectiveness is exhausted is determined, in part, by the rate at which antibiotics are used, one over which one has control. This, in turn, is determined, in part, by pricing decisions made by the patent holding monopolist.

Antibiotic patents may be a useful instrument to influence the price setting behavior of an innovator who holds a patent to a control agent. The logic underlying such thinking is that patent policy could be designed to limit the number of firms that compete for the same common pool of antibiotic effectiveness. The drug firm that is provided with a broad patent has a greater incentive to internalize the costs associated with resistance than does a drug firm

²² New legislation (HB 1139) introduced in the Colorado State Legislature would provide measures to admonish and even revoke licenses of medical professionals who repeatedly prescribe antibiotics without clinical justification. Backers of the bill say that the Colorado Board of Medical Examiners could be given the task of dealing with potential violations (Schrader 1997). Predictably, this measure faces serious opposition and criticism from the medical community, including the American Medical Association (AMA).

with a narrow patent. (The notion of patent breadth is elucidated in the next section.) Therefore, broad patents encourage lower antibiotic sales than do narrow patents. In fact, the optimal patent breadth is one that ensures that the benefit of enhanced future effectiveness associated with decreased antibiotic use exceeds the welfare cost associated with higher antibiotic prices. A 1995 Office of Technology Assessment report to the U.S. Congress that warned of the growing costs of antibiotic resistance suggested that changes in the patent laws governing antibiotics might be an effective method of increasing the stake of pharmaceutical manufacturers in resistance (Office of Technology Assessment 1995).

How applicable is the current literature on patents to the case of antibiotics? A patent for an antibiotic whose effectiveness (or quality) declines with use is essentially different from a patent from a “non-deteriorating” commodity. For one, the patentee’s profit maximization problem is dynamic or inter-temporal in the case of antibiotics whereas it is static in the case of the “non-deteriorating” commodity²³. Consequently, the shape of the net return function from an antibiotic patent is endogenously determined. Since the existing patenting literature primarily addresses the role of patents as incentive structures for innovation, it may be inapplicable to the case of antibiotics.

This paper captures the key notion that optimal patents in the case of antibiotics (and other such resistance inducing control agents) may be quite different from those for other products, due to the unique nature of these products. Since the effectiveness of antibiotics is directly related to the quantity of antibiotics used, it may be desirable to design broader patents for antibiotics, than would be optimal in the absence of resistance. This paper demonstrates that the general result that

²³ Although the phenomenon of “resistance” is similar to technological obsolescence, it is different in that resistance is a function of use (endogenous) while obsolescence is a function of time (exogenous).

narrow patents of infinite length are optimal, as is the case with most other products breaks down when the economic costs of resistance are considered (Gilbert and Shapiro, 1990). In general, a broad patent may be more socially optimal for products that induce resistance. The discussion on banning the use of antibiotics as growth promoters in cattle and poultry feed, a critical policy issue, is an apt metaphor for the concept of broader patent breadth. While the impact of such use on resistance in humans has been recognized, a secondary impact that encourages a greater degree of antibiotic use in humans is less obvious (National Research Council 1999). Finally, we examine the role of broader patents in encouraging investment that reduces the future marginal cost of producing antibiotics.

The paper is organized as follows. Section 2 provides a survey of the literature on antibiotic resistance and on optimal patent breadth. Section 3 describes a general two-period model of firm behavior that offers some basic understanding of the problem at hand. Section 4 compares the social welfare implications of the different scenarios considered in Section 3. Section 5 concludes the paper.

2. BACKGROUND AND LITERATURE REVIEW

The fundamental purpose of the patent system is to reward innovation. However, doing so necessitates some welfare loss associated with monopoly power imparted to the patentee. A large section of the patent literature focuses on the determination of optimal patent length based on the tradeoff between the dynamic benefits of the innovation and the static costs of the patent holder's monopoly power (Frank and Salkever 1992). The seminal contribution to this debate by Nordhaus provides the crux of the argument that the optimal patent policy is one that ensures that patent lengths are long enough that they encourage innovation,

and yet not so long as to prolong unnecessary monopoly distortions (Nordhaus 1969). A subset of that patent literature addresses the issue of socially optimal patent breadth and length (Gilbert and Shapiro 1990; Gallini 1992; Denicolo 1996; Klemperer 1998). Increasing patent breadth increases the patent holder's monopoly power and thereby increases the deadweight loss associated with the patent. A longer patent, on the other hand, increases the reward to the patentee. Gilbert and Shapiro find that the optimal patent is one that is broad enough to sufficiently compensate the innovator for the cost of undertaking the innovation, but infinitely long (Gilbert and Shapiro 1990).

2.1 Interpretations of Patent Breadth

While there are many definitions of patent breadth, all of them embody the notion that a broader patent, by reducing the number of effective substitutes, increases the ability of the patentee to earn a higher rate of profit during the life of the patent²⁴. A number of possible interpretations of the idea of patent breadth have been used in the literature in this area and a summary of these interpretations is contained in Denicolo (Denicolo 1996).

²⁴ The patenting process works as follows. The innovator applies to the patent office for a patent on her innovation. The patent office then requires the innovator to set the scope of the patent, by describing all the potential uses of the innovation. The patent office will typically require that the innovator describe the processes associated with all these different uses in detail that is sufficient to enable any knowledgeable agent to actually use the innovation in that manner. This is described as the "enabling rule" in legal parlance. A broad patent is described as one that would allow the innovator to "claim" more uses on her patent application than would a narrow patent. In the case of antibiotics, the inventor of a new antibiotic would be allowed to claim related chemical entities and their uses both as antibiotics in humans, as growth promoters in cattle and also for agricultural uses.

This paper follows two interpretations of the patent breadth concept for reasons that will become clear later in the next section on policy implications. According to the first interpretation, which is followed in Matutes *et. al.*, patent breadth “determines the number of applications of an innovation in independent markets which are reserved for the patentee.” (Matutes, Regibeau et al. 1996) In the case of antibiotics, a broader patent on a new antibiotic would reserve the use of the chemical entity that underlies the antibiotic not just for use in humans, but also in the markets for disease prevention and treatment in both agriculture and in aquaculture.

The second interpretation followed in this paper is in the same vein as in (Gilbert and Shapiro 1990; Gallini 1992; Klemperer 1998), where increasing patent breadth implies decreasing competition in the product market. Although some of these papers measure patent breadth in terms of post-innovation profits of the innovating firm, we use a more explicit definition of patent breadth that is measured by the number of entrants that use the patented chemical entity, thereby depleting the common-property resource, antibiotic effectiveness. This latter approach is similar to that followed in Denicolo (Denicolo 1996).

Regardless of the specific interpretation of patent breadth that one may choose to think in terms of, in general, increasing patent breadth grants greater monopoly power to the patentee. In doing so, it reduces the rate at which antibiotic resistance develops, by raising the price of the patented product²⁵. In the case of

²⁵ We assume that a single product represents the innovation, as is the case in Gilbert and Shapiro (Gilbert and Shapiro 1990). Klemperer takes a different approach in which the patentee offers a wide variety of products within the scope of the patent, to cater to every customer’s tastes. In this case, a broader patent discourages substitution away from the patented good (as is the case in Gilbert and Shapiro) and encourages customers to buy a patented good (with desirable characteristics) in place of unpatented goods (with inferior characteristics.) Patent breadth, in this case, is not necessarily a bad thing and

products such as antibiotics, where the common-access nature of the product's attributes may encourage a rate of depletion that is greater than is socially optimal, increasing patent breadth may serve a useful social purpose. Patent breadth delays the development of antibiotic resistance, by providing innovators with an incentive to internalize, at least in part, the costs of resistance. However, as explained earlier, increasing patent breadth increases the social welfare costs associated with diminished competition. This paper examines the tradeoff between the benefit from increased patent breadth and the welfare cost of monopoly distortions introduced by increasing patent breadth. It characterizes demand conditions under which increasing patent breadth is beneficial to society, a result that is counter-intuitive from the standpoint of existing literature which asserts that narrow patents are preferable to broad ones (Gilbert and Shapiro 1990; Gallini 1992).

Determining optimal patent length of antibiotics is more complex and involves careful consideration of issues such as brand loyalty, off-patent behavior of pharmaceutical firms and effective patent length, (that is dependent on the length of the FDA approval process) and lies outside the scope of this paper (Hellerstein 1994).

2.2 Policy Implications

I now turn to the task of describing the applicability of the two interpretations of patent breadth to the policy debate surrounding antibiotic resistance. The first example conforms to the Matutes interpretation of patent breadth (Matutes, Regibeau et al. 1996). Consider the example of an incumbent firm that holds a patent to an antibiotic approved for use in humans. Narrow antibiotic patents have two consequences. An entrant may observe an incumbent's patent and

for sufficiently low demand elasticity, an optimal patent has very wide scope but fairly short duration (Klemperer 1998).

choose to innovate around the patent and introduce an antibiotic for use in an entirely different market (say as growth promoters for cattle and poultry). In this situation, the incumbent and the entrant compete for the common pool of antibiotic effectiveness, but do not face each other in the product market.

An alternate scenario, and one that conforms to the second interpretation of patent breadth, is when the entrant decides to introduce a variant of the incumbent's compound for use in humans and therefore competes on both supply and demand sides.

The former scenario is of particularly significant policy relevance. The issue of bacterial resistance that occurs as a result of antibiotic use in farm animal feed and agriculture is a contentious one that is currently under debate. Antibiotics are used for improving feed efficiency and rate of weight gain (sub-therapeutic use), and for disease prevention (therapeutic use) (Levy 1992). Because these uses promote the development of drug resistant bacteria in animals, and routes for the movement of these resistant bacteria to humans are available, drug resistance in bacteria associated with food animals can affect the proportion of drug resistant bacteria that cause human diseases²⁶. Therefore, the potential exists for compromise of drug therapy in animals and in humans.

In fact, recognizing the impact of antibiotic use in non-human, sub-therapeutic use on the overall level of bacterial resistance in the environment, many countries in Europe have either banned or restricted the use of antibiotics for these

²⁶ A number of studies have documented the impact of sub-therapeutic use of antibiotics on resistance in humans (Bates, Jordens et al. 1994; Gordts, Landuyt et al. 1995; National Research Council 1999; Wegener, Aarestrup et al. 1999). A recent study found that the occurrence of VRE (Vancomycin resistant enterococci) in poultry was strongly associated with the use of Avoparcin as a growth promoter (Wegener, Aarestrup et al. 1999). In fact, VRE has not been detected in countries where Avoparcin has not been used sub-therapeutically.

purposes. However, antibiotics continue to be used in farm feed and agriculture in the United States. In fact, almost half the 50 million pounds of U.S.-produced antibiotics is used in farm animals (of which 80 percent is used to help animals grow faster and the rest is used treat disease), and 40,000 pounds are sprayed on fruit trees (Office of Technology Assessment 1995). Table 5 provides a list of antibiotics used in cattle, which are also commonly used to treat infections in humans.

Recently the Centers for Disease Control and Prevention (CDC), in Atlanta urged the Environmental Protection Agency to refuse a Mexican company's request to treat blighted fruit trees with Gentamicin, an antibiotic that is widely used in humans²⁷. While the cattle and poultry industries claim that there is no impact on resistance or human health of using antibiotics as growth promoters, many in the medical community disagree. In 1997, the World Health Organization called for a complete ban on the sub-therapeutic use of antibiotics in cattle and poultry feed as growth promoters (W.H.O. 1997).

The second scenario discussed earlier addresses the broader question of whether firms should be allowed to patent an entire class of antibiotics drawing on the "same" stock of effectiveness, in return for restrictions on the number of uses that the patented antibiotic would receive approval for. In fact, a similar proposal put forth by the Office of Technology Assessment in a report to the U.S. Congress and is under consideration by policy makers (Office of Technology Assessment 1995).

²⁷ The fruits were for export to the United States.

3. MODEL

For the purpose of illustrating optimal patent breadth, we use a two-period model of firm behavior. A two-period model is preferred over a dynamic multi-period model because it allows us to focus attention on the two key aspects of antibiotic resistance, namely rate of depletion and social welfare implications, with minimal analytical complexity²⁸.

Our analysis covers three cases that correspond respectively to the benchmark and the two interpretations of patent breadth discussed earlier. In the base case (1), the patentee, firm A, holds a “broad” patent of finite length such that he faces no competition in either the supply of antibiotic effectiveness or in the demand for antibiotics.

In case 2, which conforms to the Matutes *et. al* interpretation of patent breadth, we relax the assumption that there is no competition for the supply of antibiotic effectiveness, without changing any assumptions on the demand side. One can imagine a situation in which a firm patents a new antibiotic for use in humans. However, the patent is not broad enough to prevent another firm (B) from introducing a similar compound that is intended for use in poultry as a growth promoter. While firm B does not compete with firm A on the demand side, the sale of the growth promoter by firm B impinges on the stock of effectiveness that firm A’s product draws upon to treat infections, and thereby affects firm A’s intertemporal production decision.

In case 3, we analyze the situation in which firm B introduces a new antibiotic that is structurally related to firm A’s antibiotic for use in humans. Case 3

²⁸ Solving for sub-game perfect Cournot-Nash equilibria in differential game problems is known to be an analytical challenge in all but the simplest examples. Two-period models enable us to focus on the issue of patent breadth with some measure of analytical ease.

involves a further degree of complexity from case 2 in that firm B competes with firm A both for the common stock of antibiotic effectiveness, as well as for the market represented by the illnesses treated using these antibiotics.

The quantity of antibiotic demanded in each period is an increasing function of the antibiotic's effectiveness and a decreasing function of price. We can specify the inverse demand function for antibiotics modified for the introduction of antibiotic effectiveness as a quality attribute as

$$(1) \quad p = aw - bQ^d$$

where p is the per-unit price of Q units of antibiotics (measured in defined daily doses), w is antibiotic effectiveness, and a, b and d are positive parameters. An almost identical demand specification (without antibiotic effectiveness) is used in earlier patent breadth literature (Gallini 1992; Wright 1999). The key feature of this specification is that decreased antibiotic quality (effectiveness) cannot be overcome by increased quantity of use. In other words, if a certain infection is resistant to penicillin, then it does not help to double the dose of penicillin administered²⁹. The demand specification is convex, linear or concave depending on whether $d < 1, = 1, > 1$. As mentioned earlier, in Case 1, the patentee is a monopolist on both supply and demand sides.

²⁹ For this reason, the quality of the antibiotic is not interacted with quantity. If we were to do so, the resulting specification would represent quality adjusted prices, a notion that is unsuited to this paper. To this end, the reader is invited to verify that point elasticity of the demand function is invariant to changes in antibiotic effectiveness. If we were to use quality adjusted prices, then demand becomes more elastic as antibiotic effectiveness decreases. While this is true for most goods where quantity is a substitute for quality, it is fundamentally untrue in the case of antibiotics. In any case, all the results presented in this paper have been found to be invariant to using quality adjusted prices instead of the specification followed here.

In case 2, the incumbent patentee is a monopolist while $n-1$ entrants produce non-patent infringing chemical entities that are sold in $n-1$ different markets (in addition to the incumbent's market.) In this case, the patentee retains his monopoly power in the market in which his product is sold. However, he is affected by the entry of the other $n-1$ firms because they draw on the same common pool of effectiveness that he is dependent upon.

In Case 3, the $n-1$ entrants produce chemical entities that are sold in the same market as the incumbent's product. In this case, the entrants compete with the incumbent both for the common pool of effectiveness (supply side) as well as on the demand side. Initially, we assume that all n firms (including the incumbent) face identical demand functions if they operate in n different markets in set B. This assumption is relaxed in a later section of the paper.

The analysis in this paper is presented at two levels. The first level, which uses general functional forms, sketches out the three cases analyzed in this paper and demonstrates that broader patents discourage faster depletion of antibiotic effectiveness. The purpose of this analysis is to demonstrate that this result holds regardless of the specification of the dose-response relationship between antibiotic use in the first period and antibiotic effectiveness in the second period.

At the second level, we use specific functional forms for both demand and the dose-response relationship to analyze the impact of broader patents on social welfare and their role in encouraging R&D spending on marginal cost reducing innovations.

The profit function in each period is given by

$$(2) \quad \Pi(q, w, c) = D(q, w)q - cq ,$$

where $D(q, w)$ is as described earlier in this section. Gross profits are represented by $\pi(q, w) = D(q, w)q$ ³⁰. Profits are greater for higher levels of antibiotic, $\frac{\partial \pi}{\partial w} > 0$. Moreover, greater antibiotic effectiveness increases the marginal revenue associated with antibiotic sales, $\frac{\partial^2 \pi}{\partial w \partial q} > 0$. c represents a fixed marginal cost of production (set equal to zero for the analysis in this section.) Let π_{1A} and π_{2A} represent the firm A's profit functions in the first and second periods. Superscripts represent the specific case under discussion. q_{mA}^* , q_{mA}^{**} and q_{mA}^{***} represent optimal quantities produced by the incumbent firm for cases 1, 2 and 3 in period m , where $m = 1, 2$.

Case 1: "Broad" patents (no competition on supply or demand sides)

In Case 1, there is no competition for either the supply of antibiotic effectiveness or in the market for antibiotics, and therefore the patentee exercises his monopoly in both periods.

The patentee (firm A) chooses q_{1A} , q_{2A} to intertemporally maximize the net present value of his profits denoted by

$$(3) \quad \pi_A^1 = \pi_{1A}^1(w_1, q_{1A}) + \delta \pi_{2A}^1(w_2, q_{2A})$$

where profits in period 1 are a function of w_1 , the initial endowment of effectiveness, and q_1 , the quantity of antibiotic produced. In the second period,

³⁰ The parameter d is omitted from the representation for the sake of clarity (it is not assumed to be zero).

effectiveness is diminished by the extent of antibiotic use in period 1. The dose response relationship between antibiotic use and effectiveness in the subsequent period is given by,

$$(4) \quad w_2 = g(w_1, q_{1A})$$

such that $\frac{\partial g(w_1, q_{1A})}{\partial w_1} > 0$ and $\frac{\partial g(w_1, q_{1A})}{\partial q_{1A}} < 0$. These conditions represent the

commonly observed phenomena that effectiveness in the second period is a positive correlate of initial effectiveness, and is negatively impacted upon by antibiotic use in period 1. Profits in period 2 are discounted to the present by a discount factor $\delta = \frac{1}{1+r}$ where r is the social discount rate. Throughout this paper, we assume that the patentee's private discount rate is equal to the social discount rate, r .

The optimal level of production in period 2, q_{2A}^* , is determined by setting

$$(5.1) \quad \frac{\partial \pi^1}{\partial q_{2A}} = \frac{\partial \pi_{2A}^1}{\partial q_{2A}} = 0.$$

The firm then assumes the optimal level of production in period 2, q_{2A}^* to determine the optimal quantity to produce in period 1, q_{1A}^* , by setting

$$(5.2) \quad \frac{\partial \pi^1}{\partial q_{1A}} = \frac{\partial \pi_{1A}^1}{\partial q_{1A}} - \delta \frac{\partial g(w_1, q_{1A})}{\partial q_{1A}} \frac{\partial \pi_{2A}^1(w_2, q_{2A}^*)}{\partial w_2} = 0$$

Since $\frac{\partial \pi_{2A}^1(w_2, q_{2A}^*)}{\partial w_2} > 0$, it must hold that $\frac{\partial \pi_{1A}^1}{\partial q_{1A}} > 0$. Therefore, the quantity

produced in the first period is less than what firm A would produce if he were to

set $\frac{\partial \pi_{1A}^1}{\partial q_{1A}} = 0$. Further, the degree to which the patentee slows down production in period 1 is positively influenced both by the discount factor, δ , and $\frac{\partial g(w_1, q_{1A})}{\partial q_{1A}}$. A larger (absolute) value of $\frac{\partial g(w_1, q_{1A})}{\partial q_{1A}}$ reflects a stronger impact of current use on future resistance and consequently q_1^* is smaller. A larger discount factor (or smaller discount rate) implies a greater weight placed on profits in period 2, and causes the price of antibiotics to be higher in period 1. In all cases discussed, a smaller discount factor reduces the economic impact of resistance since future effectiveness is less valued when discounted to a greater degree.

Case 2: “Narrow” antibiotics patents (competition for the common stock of effectiveness)

Assume that the patentee (firm A) is given a “narrow” patent for the antibiotic he innovates, which allows entry by a competitor who patents a compound that belongs to the same class of antibiotics as firm A’s innovation. Further assume that the competitor (firm B) chooses to market his product for use in animals as growth promoters. The sale of growth promoters by firm B increases the level of resistance to both firm A’s and firm B’s products. In this case, firm B competes with firm A only for the common stock of effectiveness and not for the market. Firm A’s intertemporal profit function is given by

$$(6.1) \quad \pi_A^2 = \pi_{1A}^2(w_1, q_{1A}) + \delta \pi_{2A}^2(g(w_1, q_{1A}, q_{1B}), q_{2A})$$

where q_{1B} is the quantity of antibiotics made by firm B in period 1. Similarly, firm B chooses the optimal quantity to produce in periods 1 and 2 based on

$$(6.2) \quad \pi_B^{21} = \pi_{1B}^2(w_1, q_{1B}) + \delta \pi_{2B}^2(g(w_1, q_{1A}, q_{1B}), q_{2B})$$

Assuming that firm A maximizes π , the optimal quantity of antibiotics in period 2 q_{1A}^{**} is given by

$$(6.3) \quad \frac{\partial \pi_A^2}{\partial q_{1A}} = \frac{\partial \pi_{1A}^2}{\partial q_{1A}} - \delta \frac{\partial g(w_1, q_{1A}, q_{1B})}{\partial q_{1A}} \frac{\partial \pi_{2A}^2(w_2(q_{1A}, q_{1B}), q_{2A}^{**})}{\partial w_2} = 0$$

Similarly, in the case of firm B, the optimal first period production q_{1B}^{**} is given by setting

$$(6.4) \quad \frac{\partial \pi_B^2}{\partial q_{1B}} = \frac{\partial \pi_{1B}^2}{\partial q_{1B}} - \delta \frac{\partial g(w_1, q_{1A}, q_{1B})}{\partial q_{1B}} \frac{\partial \pi_{2B}^2(w_2(q_{1B}, q_{1A}), q_{2B}^{**})}{\partial w_2} = 0$$

Case 3: “Very narrow” patents (Competition on both supply and demand sides)

In this case, firm B competes with firm A for the common pool of effectiveness as well as for the antibiotics market for humans. The intertemporal objective function for the incumbent is given by

$$(7.1) \quad \pi_A^3 = \pi_{1A}^3(w_1, q_{1A}, q_{1B}) + \delta \pi_{2A}^3(g(w_1, q_{1A}, q_{1B}), q_{2A}, q_{2B})$$

Assuming that the optimal second period quantities are chosen, the optimal first period production quantities q_{1A}^* and q_{1B}^* are given by setting

$$(7.2) \quad \frac{\partial \pi_A^3}{\partial q_{1A}} = \frac{\partial \pi_{1A}^3}{\partial q_{1A}} - \delta \frac{\partial g(w_1, q_{1A}, q_{1B})}{\partial q_{1A}} \frac{\partial \pi_{2A}^3(w_2(q_{1A}, q_{1B}), q_{2A}^{***}, q_{2B}^{***})}{\partial w_2} = 0,$$

and

$$(7.3) \quad \frac{\partial \pi_B^3}{\partial q_{1B}} = \frac{\partial \pi_{1B}^3}{\partial q_{1B}} - \delta \frac{\partial g(w_1, q_{1A}, q_{1B})}{\partial q_{1A}} \frac{\partial \pi_{2B}^3(w_2(q_{1B}, q_{1A}), q_{2B}^{***}, q_{2A}^{***})}{\partial w_2} = 0$$

3.1 Rate of Depletion

Proposition 1: Decreasing patent breadth encourages earlier depletion of antibiotic effectiveness by the incumbent firm.

Proofs of this and other propositions are provided in Appendix 1.

We begin with a discussion of the importance of resistance in this analysis. In the base case, we recognized that the incumbent firm produces the optimal first period quantity keeping in mind the impact of period 1's production on period 2's effectiveness. In the absence of the resistance problem, the incumbent would produce more antibiotics in period 1 than he does in the base case with resistance. What is the impact of patent breadth on this reduction? Introducing a separate market (and competition for the common stock of effectiveness) simply lowers the value of preserving effectiveness for the future from the incumbent's point of view. Therefore, the incumbent reacts by increasing period 1's production to the extent that the cost of cutting back in period 1 is compensated by the benefit associated with the (now diminished savings) effectiveness in period 2. The problem of resistance is akin to the typical tragedy of the common property problem where individual agents fail to consider the full impact of their current consumption on future stocks, and therefore consume more they would if they were the sole owners of the property.

The specific functional form of the dose response function plays an important role in determining the economic implications of the common property nature of effectiveness. If the dose-response function is linear in the quantity of antibiotics consumed, then production in period 1 by firm B only reduces the total stock of effectiveness. However, if the dose-response function is quadratic, then

production in period 1 by firm B has two effects. Not only does it reduce overall effectiveness, but it also increases the marginal impact on the incumbent's production on lowering antibiotic effectiveness. In economic terms, the social cost associated with antibiotic use is greater in the case of a quadratic dose-response specification than for the linear specification.

3.2 Investment

Next consider the situation where firm A has the option of investing an amount I in the first period at a cost denoted by $c(I)$ ($c'(I) > 0$) in order to reduce the marginal cost of production in the second period, c_2 . Then we can prove the following.

Proposition 2: Extending patent breadth encourages investment in marginal cost reducing innovations by the incumbent.

Proof is provided in Appendix 1.

The intuition underlying this proposition is similar to that discussed in the case of proposition 1. The entry by a competitor for the supply of antibiotic effectiveness reduces the present value of profits obtained in the second period. The optimal level of investment is one at which the marginal cost of incurring R & D spending in period 1 is offset by the discounted marginal benefit of lower production costs in period 1. Since entry reduces effectiveness and by extension, the incumbent's profitability in the second period, it discourages cost reducing research investment in the first period. This result holds even if the benefit from the reduction in marginal costs accrues only to the incumbent.

4. SOCIAL OPTIMA

Although results in the earlier section show that increasing patent breadth discourages earlier depletion of antibiotic effectiveness, and encourages greater initial investment in marginal cost reducing innovations, these results, *per se*, do not support policies that would extend patent breadth. In order to arrive at such a conclusion, we must first examine the social welfare consequences of increasing patent breadth.

On the positive side, increases in patent breadth could increase social welfare by decreasing antibiotic use. This would correct the problem of intertemporally inefficient increases in resistance associated with multi-firm extraction from the common pool of antibiotic effectiveness. Moreover, increasing patent breadth encourages marginal cost reducing innovations that have a salutary effect on social welfare. On the negative side, increasing patent breadth would give greater monopoly power to the patentee and society would have to bear the negative welfare consequences associated with such monopoly power. As one might predict, the optimal patent breadth would be such that the marginal costs of increasing patent length in terms of welfare losses are equal to the welfare gains associated with enhanced effectiveness and lower marginal costs of production.

In order to compare the social welfare consequences of adjusting patent breadth, we consider four cases (4.1-4.3) where the cases are analogous to Cases 1, 2 and 3 discussed using the more general model. In the base case (4.1), patents are broad enough to preserve the incumbent's control over the stock of effectiveness and to endow him with a monopoly in the market for antibiotics. This case is used as the benchmark for comparing the other cases discussed in this section.

In Case 4.2, we consider n firms with identical demand functions. These n firms do not interact on the demand side, but compete for the same stock of effectiveness. As will be demonstrated later in this section, consumer surplus in

this case is always increasing with the number of firms, n . This is a reasonable conclusion since the n different (but identical) firms cater to n identical markets, and the welfare losses associated with the closure of any one market always outweigh the welfare gains associated with more efficient depletion of effectiveness³¹.

Case 4.2' is a special case of Case 4.2 in which there are only two firms ($n=2$). The assumption that the two firms are identical is relaxed and they are allowed to have different intercept and slope coefficients. Here, social surplus is always lower than if only one firm was allowed to make the antibiotic (through broader patents.) Specifically, we should only permit the firm with a smaller slope coefficient to manufacture the antibiotic since the social surplus obtained from production by this firm, exceeds social surplus obtained from the other firm's product.

Case 4.2" is also a special case of Case 4.2 in which the incumbent has a monopoly in his market, but the $n-1$ entrants operate in a different market and are perfectly competitive. In this case, broader patents are always preferred to narrow patents since the marginal increase in social welfare associated with selling the antibiotic in an additional competitive market is always less than the social cost of reducing effectiveness in the future.

In Case 4.3, we turn to the issue of competition in both input and product markets (similar to Case 3 in the previous section). Once again, consider n identical firms. Increasing the number of firms decreases social surplus because the welfare loss associated with sub-optimal depletion of effectiveness is greater than the welfare gains from greater competition and fewer oligopoly related distortions.

³¹ As will be shown in the rest of this section, the net welfare change associated with reducing the number of firms (through a broader patent) is zero only at the limit when both the discount factor and the parameter α are very large.

Demand for the antibiotic is represented by equation (1). Antibiotic effectiveness is denoted by w and is depleted by antibiotic use according to the equation

$$(8) \quad w_2 = g(w_1, q_1) = w_1 - \alpha q_1$$

where α is a positive parameter and q_1 is the quantity of antibiotics (measured in daily defined doses) used in the earlier period³². The assumption that the dose-response relationship is linear is relaxed during in the numerical computation and a quadratic functional form is assumed. Marginal costs of production are assumed to be zero for the remainder of this section.

Since analytical solutions are not forthcoming when either the demand function or the dose response function (or both) are non-linear, we use numerical computations to analyze these cases. This analysis is contained in the following section.

CASE 4.1

This case is identical to Case 1 discussed in the previous section. The innovator is given a patent that is so broad that the innovator faces no competition on either the demand or the supply side. The social surplus obtained

³² We portray the dose-response relationship as being linear only to sharply focus on the impact of antibiotic use on future resistance. The precise functional form is not critical or essential in proving any of the results contained in this section. Although some population geneticists believe that the dose-response relationship may be logistic; i.e. antibiotic resistance goes up slowly, followed by a sharp increase after resistance has crossed a certain threshold, there are no data in this literature that actually demonstrates that such a relationship exists for bacterial resistance to antibiotics that are commonly used in outpatient settings. A linear function captures the essential dose-response notion and is therefore ideally suited to our purpose both in this section and the next.

in this base case is used a benchmark against which the social surplus obtained in the other cases is evaluated. The quantities produced in periods 1 and 2 are given by

$$(9.1) \quad q_1 = aw_1 \left(\frac{2b - a\alpha\delta}{4b^2 - a^2\alpha^2\delta} \right) \text{ and}$$

$$(9.2) \quad q_2 = aw_1 \left(\frac{2b - a\alpha}{4b^2 - a^2\alpha^2\delta} \right) \text{ respectively.}$$

Consumer surplus is given by

CASE 4.2

Consider n identical firms (whose products have identical demand functions) that compete for antibiotic effectiveness. However, they do not compete in product markets. The optimal quantity manufactured in periods 1 and 2 are given in Table 6. As before, these equilibrium quantities were computed in a three-step process. In the first step, we calculate the optimal quantity to produce in period 2 by setting $\frac{\partial \pi}{\partial q_{2i}} = 0$, ($i = 1$ to n).

Second, we solve for the sub-game perfect Cournot-Nash equilibrium in the second period as a function of q_{1i} . Finally, we substitute these optimal second period quantities back into the profit function to solve for the sub-game perfect Cournot-Nash equilibrium in the first period denoted by (q_{1i}^*) , ($i = 1$ to n). Social surplus, V , the sum of consumer and producer surplus, is calculated as the area under the demand curve, and for the two period model with linear demand, we can write this as

(10)

$$V = n \left(\left(aw_1 - \frac{bq_1^*(w_1, n)}{2} \right) q_1^* + \delta \left(aw_2(w_1, q_1^*, n) - \frac{bq_2^*(w_1, n)}{2} \right) q_2^* \right),$$

where n denotes both the number of entrants and the number of new product markets. Figure 11 graphs the social surplus against n , for different values of α .

We find that *increasing* the number of firms (*decreasing* patent breadth) is always welfare enhancing, a result that is consistent with the existing patent literature. However, as the measure of the resistance effect, α increases, the increase in social surplus accompanying an increase in the number of firms becomes smaller because having more firms exacerbates the rate of extraction from the common-access resource and therefore increases the second-period costs associated with increasing resistance. In the limiting case, when α is very high, the benefit associated with the product being sold in different markets as a result of a narrower patent is completely offset by the social cost of sub-optimal depletion of antibiotic effectiveness.

Although the results obtained in this case indicate that narrow patents are socially beneficial, one must keep in mind that we are working under three fairly restrictive assumptions. First, we assume that the n different firms patent n variations of the same chemical entity, and sell these entities in n different markets, where the elasticity of demand in each of these markets is identical. Second, in each of n markets, the firm occupying the market is assumed to be a monopolist because it holds a patent to a variation of the innovation. Our third assumption is that antibiotic use in these different markets has the same marginal impact on overall resistance.

However, Case 2 represents an extreme situation and is useful only as an aid to thinking. In reality, one or more of these n firms may operate in competitive

markets (where close substitutes for the patented chemical entity are available) and in such instances, it may be optimal to increase patent breadth. Further, even if the n firms were monopolists in each of their markets, they may not face identical demand functions. This situation is considered explicitly in case 4.2 below and can be illustrated by the following example. Consider a situation in which there exists a small market for a new antibiotic in hobby fish tanks and this use of the antibiotic had a disproportionately large impact on antibiotic resistance in humans. In this instance, awarding a broader patent to the incumbent patentee (who sells antibiotics for human consumption) may enhance society's welfare.

CASE 4.2'

I consider a special instance of Case 4.1 where $n = 2$, and allow both intercept and the slope coefficient for the demand functions to be different ($a_1 \neq a_2, b_1 \neq b_2$). Note that the slope coefficient referred to in this paper represents the slope of the *inverse* demand function and *not* the slope of the demand function. Social surplus is measured in the same manner as in Case 4.1. Optimal quantities and social surplus measures are in Table 7. Figure 12 plots the total social welfare function with a_2 and b_2 , the intercept and slope coefficients for firm B. Social welfare is maximized for the case when the slope coefficients for the two product markets are identical (as in Case 4.1) and equal to 1 in our numerical demonstration. For all other values of b_2 , social welfare is lower and is even lower than the social welfare when only one firm is in the market. This indicates that decreasing patent breadth decreases social surplus when $b_1 \neq b_2$.

CASE 4.2''

This is perhaps the easiest case to analyze. Here, the entrants do not patent their respective variations of the innovation and therefore, face perfect

competition in the market in which they sell their product, where the demand function is identical to that in the incumbent's market. Being price takers, they equate price to marginal cost (which is held to be zero). The results on table 6 details the optimal quantities produced by the incumbent in first and second periods. Social welfare in this case is always less than if the entrants were excluded from the second market.

CASE 4.3

We turn our attention to the case of n identical firms, all of which compete, on both the product and input (effectiveness) markets. Optimal quantities produced by each firm in periods 1 and 2 are in Table 6. Social surplus from the market for antibiotics is given by

$$(11) \quad V = \left(\left(aw_1 - \frac{nbq_1^*}{2} \right) q_1^* + \delta \left(aw_2 - \frac{nbq_2^*}{2} \right) q_2^* \right)$$

where $w_2 = w_1 - anq_1^*$.

Before we proceed with the n firm case, we compare the two extremes represented by Case 1 (monopoly on both supply and demand sides) and perfect competition on both supply and demand sides. The social surplus for the perfect monopoly case is obtained from Case 1. When there is perfect competition (in a single product market), the quantity of antibiotics produced in each period is given by

$$(12.1) \quad Q_1^* = \frac{aw_1}{b} \text{ in period 1, and}$$

$$(12.2) \quad Q_2^* = \frac{a(w_1 - \alpha Q_1^*)}{b} \text{ in period 2.}$$

Correspondingly, the level of consumer surplus in period 2 is given by,

$$(12.3) \quad V = \left(\left(aw_1 - \frac{bQ_1^*}{2} \right) Q_1^* + \delta \left(aw_2 - \frac{bQ_2^*}{2} \right) Q_2^* \right)$$

Substituting for Q_1^* and Q_2^* , we get,

$$(12.4) \quad V = \left(\left(\frac{a^2 w_1^2}{2b} \right) + \delta \left(\frac{a^2 \left(w_1 - \alpha \frac{aw_1}{b} \right)^2}{2b} \right) \right)$$

Comparing equations () and (12.4), we get

Figure 13 charts the social surplus associated with varying patent breadths (captured by the extent of market concentration). A larger value of n implies a narrower patent for the new antibiotic. We find that the social welfare drops off fairly rapidly with decreasing patent breadth (increasing n). Furthermore, the rate of decline is greater for larger values of α . In other words, when the impact of resistance is greater, social surplus declines more rapidly with narrowing patent breadth.

5. NUMERICAL SOLUTIONS

Analytical solutions are not forthcoming when the demand function is assumed to be concave or convex, or when the linearity assumption for the dose-response function is relaxed. Therefore, we use numerical methods to compute optimal production quantities and the social surplus associated with the base case (1) and Case 2 in which there is competition only on the supply side and not on the demand side. Further, we compare the production in each period by the incumbent and the resulting social surplus with the corresponding values in the benchmark case (1).

Tables 7 and 8 contain the results from these analyses for the linear dose-response function, when both d and α are varied. Table 9 presents the corresponding results for a quadratic dose response function. While the purpose of the numerical analysis is to demonstrate the robustness of the paper's conclusions to functional forms, it also permits us to examine the sensitivity of first and second period production decisions and social surplus to changes in specification.

Tables 7 and 8 show that $q_{1A}^* < q_{1A}^{**}$ regardless of whether the demand function is convex linear or concave (corresponding to $d < 1, = 1, > 1$). However, the increase in first period depletion by the incumbent is greater for convex rather than concave demand functions. A more concave demand function implies lower demand elasticity and a greater degree of monopoly power. An incumbent with more monopoly power on the demand side makes fewer alterations to his production decisions to take into account the impact of the resistance problem. Conversely, both Tables 7 and 8 show that the incumbent's second period production is smaller for Case 2 under all values of α and d . However, the decrease in q_{2A} is larger for convex than for concave functions. Here too, the greater degree of monopoly implied by the lower elasticity of concave functions

ensures that the impact of entry on the incumbent's production decision is smaller. Finally, we observe that the increase in social surplus from allowing entry is least for a concave (relative to linear and convex) demand function. The policy implications of this observation are clear. The greater the degree of convexity of demand, the more elastic the demand function. Therefore, the welfare losses associated with monopoly power are smaller. In the case 4.2", we see from Table 8 that social welfare is enhanced by increasing patent breadth, a result that runs counter to conventional thinking in the field of patents.

Table 9 presents results of a numerical computation of optimal quantities and social surplus when the dose-response relationship between antibiotic use and effectiveness is quadratic. Here too, $q_{1A}^* < q_{1A}^{**}$ while $q_{2A}^* > q_{2A}^{**}$. Further, the result shown earlier that greater the degree of convexity, the greater the welfare gain associated with increasing patent breadth holds.

6. CONCLUSIONS

This paper examines the issue of optimal patent breadth in the case of control agents, such as antibiotics, that induce resistance. The effectiveness of the antibiotic may be considered a non-renewable resource since the use of the resource in any period depletes its effectiveness in future periods. Our first result derived from a simple two-period model is that broader patents discourage earlier depletion of antibiotic effectiveness. The economic intuition underlying this result is that broader patents give the patentee a greater incentive to conserve effectiveness for the future.

Second, we find that very narrow patents are optimal in the case of antibiotics only under two special conditions. First, the two firms must compete only on the supply side, and second, the demand functions in the markets in which they operate are identical (a degenerate case). For all other cases, broad patents are

optimal. While this appears to be fairly intuitive, it is quite different from the general result in the literature on patent breadth that asserts that patents should only be broad enough so that the monopoly rents accruing to the patentee from patent breadth are sufficient to compensate him for his efforts. However, the case of antibiotics is unique in that patents serve as an additional purpose to protect against sub-optimal use of antibiotic effectiveness due to the open access nature of the resource.

Finally, we examine the effect of patent breadth on investment decisions that affect the marginal cost of production in the future. We know that narrower patents reduce the benefits from future antibiotic effectiveness. The marginal benefit associated with each dose of antibiotic sold in the future is also diminished and consequently, incentives to innovate for marginal cost reductions in the future are also smaller.

These results are timely additions to the antibiotic use debate and are of policy relevance. Often antibiotics that are patented for use in humans are also available for use in agriculture as growth promoters in cattle and poultry feed. While such use has the obvious effect of increasing the overall level of resistance and thereby rendering antibiotics less effective for use in humans, it has a secondary, indirect impact. Use in animals reduces incentives for firms selling antibiotics for human use to preserve effectiveness for future periods, thereby expediting antibiotic use. When the cost of sub-optimal use of effectiveness outweighs the deadweight loss associated with monopolies, it becomes optimal to assign broad patents to antibiotics that prevent different firms from competing for the same pool of antibiotic effectiveness.

Given the paucity of tools at the policy maker's disposal, the use of optimal patent breadth to influence antibiotic use has both direct and valuable practical applicability in achieving optimal and judicious antibiotic use. When resistance is

significant, it may be optimal to assign broad patents to antibiotics that cover an entire class of antibiotics. These patents may prevent many firms from competing (inefficiently) for the same pool of effectiveness. Although state legislatures have the power to regulate antibiotic prescribing by physicians, they are unlikely to do so to avoid accusations of interference with the practice of medicine (Fidler 1998). The U.S. Congress could formally regulate antibiotic use, but this is likely to face serious opposition from both the medical community and the pharmaceutical industry. Ultimately, price incentives are likely to be the most successful in regulating antibiotic use, especially given the price sensitivity of managed care organizations in the modern era of health care, and their power to curb antibiotic misuse.

Table 5: Antibiotics Approved Use both for Dairy Cattle and for Humans

Compound	Cows (with Rx^a)	Cows (OTC^b)	Humans (with Rx)	Indications for use in humans
Amoxicillin	Yes	No	Yes	Polymicrobial infections
Cephapirin	No	Yes	Yes	Gram positive cocci, aerobic gram negative cocci, <i>E. coli</i> , <i>P. mirabilis</i> .
Cloxacillin	Yes	No	Yes	<i>Strep. pneumoniae</i> , Strep. Group A, B, C, G.
Erythromycin	No	Yes	Yes	<i>N. gonorrhoea</i> , <i>M. catarrhalis</i> , <i>Chlamydia</i> , <i>Staph. aureus</i>
Novobiocin	Yes	Yes	Yes	Methicillin resistant <i>Staph aureus</i>
Oxytetracycline	No	Yes	Yes	<i>M. tuberculosis</i> , <i>P. aeruginosa</i>
Penicillin	No	Yes	Yes	Polymicrobial infections
Penicillin/Novobiocin	No	Yes	Yes	Polymicrobial infections
Penicillin/Streptomycin	Yes	Yes	Yes	<i>M. tuberculosis</i>

^a Rx = available by prescription^b OTC= Available over the counter

Source: Adapted from FDA Approved Animal Drug List (Green Book), 1998a, Feed Additive Compendium, 1997 and The Sanford Guide to Antimicrobial Therapy, 1997.

Table 6: Optimal quantities produced in each period for Cases 4.1-4.3*

Cases	q_1^*	q_2^*
4.1	$aw_1 \left(\frac{2b - a\alpha\delta}{4b^2 - a^2\alpha^2\delta} \right)$	$aw_1 \left(\frac{2b - a\alpha}{4b^2 - a^2\alpha^2\delta} \right)$
4.2	$aw_1 \left(\frac{2b - a\alpha\delta}{4b^2 - na^2\alpha^2\delta} \right)$	$aw_1 \left(\frac{2b - na\alpha}{4b^2 - na^2\alpha^2\delta} \right)$
4.2' ^a	$aw_1 \left(\frac{a\alpha\delta b_2(2b_2 - a\alpha) + b_1(a^2\alpha^2\delta - 4b_2^2)}{2a^2\alpha^2\delta b_2^2 + 2b_1^2(a^2\alpha^2\delta - 4b_2^2)} \right)$	$aw_1 \left(\frac{a\alpha\delta b_2 - b_1b_2(2b_2 - a\alpha)}{a^2\alpha^2\delta b_2^2 + b_1^2(a^2\alpha^2\delta - 4b_2^2)} \right)$
4.2''	$-\frac{-2ab^2w_1 + a^2b\alpha\delta w_1 - a^3\alpha^2\delta w_1}{b(4b^2 - a^2\alpha^2\delta)}$	$-\frac{a \left((-b + a\alpha) w_1 - \frac{\alpha(-2ab^2w_1 + a^2b\alpha\delta w_1 - a^3\alpha^2\delta w_1)}{4b^2 - a^2\alpha^2\delta} \right)}{2b^2}$
4.3	$aw_1 \left(\frac{2a\alpha\delta - b(n+1)^2}{2a^2n\alpha^2\delta - b^2(n+1)^3} \right)$	$aw_1 \left(\frac{(n+1)(a\alpha - b(n+1))}{2a^2n\alpha^2\delta - b^2(n+1)^3} \right)$

* Both dose-response and demand functions are assumed to be linear. Marginal costs of production are assumed to be zero. Corresponding social welfare functions are plotted in Figures 11, 12 and 13.

^aQuantities are for firm A. For firm B, substitute b_2 in place of b_1 and vice versa.

Table 7: Comparison of optimal first and second period quantities and social surplus for convex, linear and concave models for linear dose-response relationship $\alpha = 0.1$ *

<i>d</i>	<i>Case</i>	<i>Optimal quantity in period 1</i>	<i>Optimal quantity in period 2</i>	<i>Social surplus</i>	<i>Social Surplus/Base Case S. Surplus</i>
0.5	Case 4.1	0.4124	0.4086	0.4317	1
0.5	Case 4.2	0.4151	0.3737	0.8162	1.89
1	Case 4.1	0.4786	0.4761	0.6700	1
1	Case 4.2	0.4797	0.4520	1.281	1.91
1	Case 4.2"	0.4808	0.4259	0.649	0.97
2	Case 4.1	0.5626	0.5609	0.9267	1
2	Case 4.2	0.5630	0.5438	1.7792	1.92

* Parameter values used in computations are $a = 1, b = 1, \delta = 0.9, n = 2, w_1 = 1$.

Table 8: Comparison of optimal first and second period quantities and social surplus for convex, linear and concave models for a linear dose-response relationship $\alpha = 1^*$

<i>d</i>	<i>Case</i>	<i>Optimal quantity in period 1</i>	<i>Optimal quantity in period 2</i>	<i>Social surplus</i>	<i>Social Surplus/Base Case S. Surplus</i>
0.5	Case 4.1	0.2787	0.2312	0.264	1
0.5	Case 4.2	0.4392	0.0065	0.492	1.86
1	Case 4.1	0.3548	0.3225	0.432	1
1	Case 4.2	0.5	0	0.750	1.74
2	Case 4.1	0.4530	0.4270	0.6088	
2	Case 4.2	-	-	-	

* Parameter values used in computations are $a = 1, b = 1, \delta = 0.9, n = 2, w_1 = 1$. Only complex solutions were obtained for the last case.

Table 9: Comparison of optimal first and second period quantities and social surplus for convex, linear and concave models for a quadratic dose-response relationship. $\alpha = 0.1$ *

<i>d</i>	<i>Case</i>	<i>Optimal quantity in period 1</i>	<i>Optimal quantity in period 2</i>	<i>Social surplus</i>	<i>Social Surplus/Base Case S. Surplus</i>
1	Case 4.1	0.4789	0.4885	0.6817	1
1	Case 4.2	0.4620	0.4614	1.2786	1.88
2	Case 4.1	0.5605	0.5682	0.9421	1
2	Case 4.2	0.5458	0.5419	1.747	1.85

* Parameter values used in computations are $a = 1, b = 1, \delta = 0.9, n = 2, w_1 = 1$.

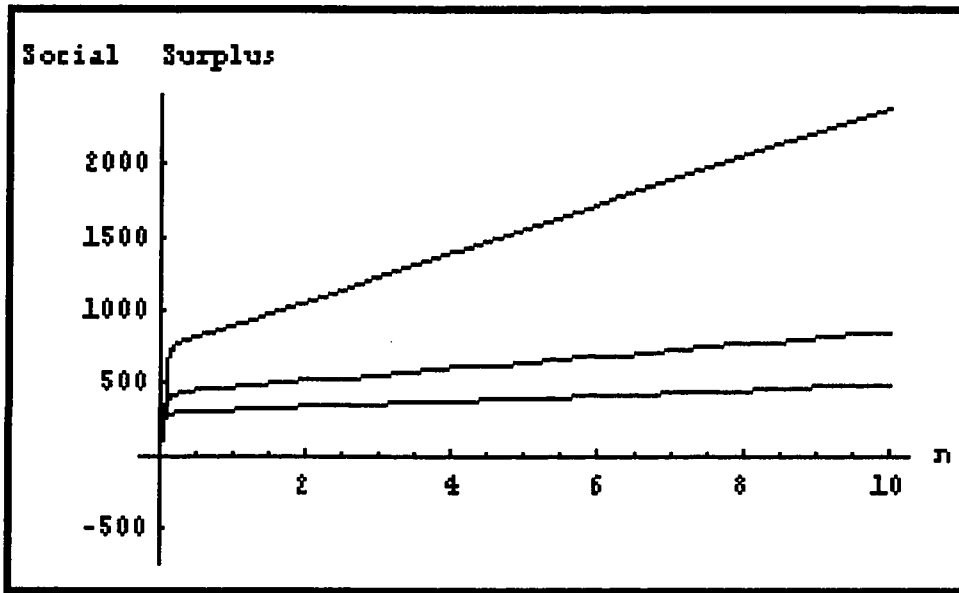


Figure 11: Variation of social surplus with number of firms in Case 4.1³³

(Note: As alpha increases, the plots move closer to the x-axis) *Parameter values used:*
 $a = 1, b = 0.0001, \delta = 0.9, w_1 = 1$

³³ Figures generated using Mathematica 3.0. Source programs are available from author.

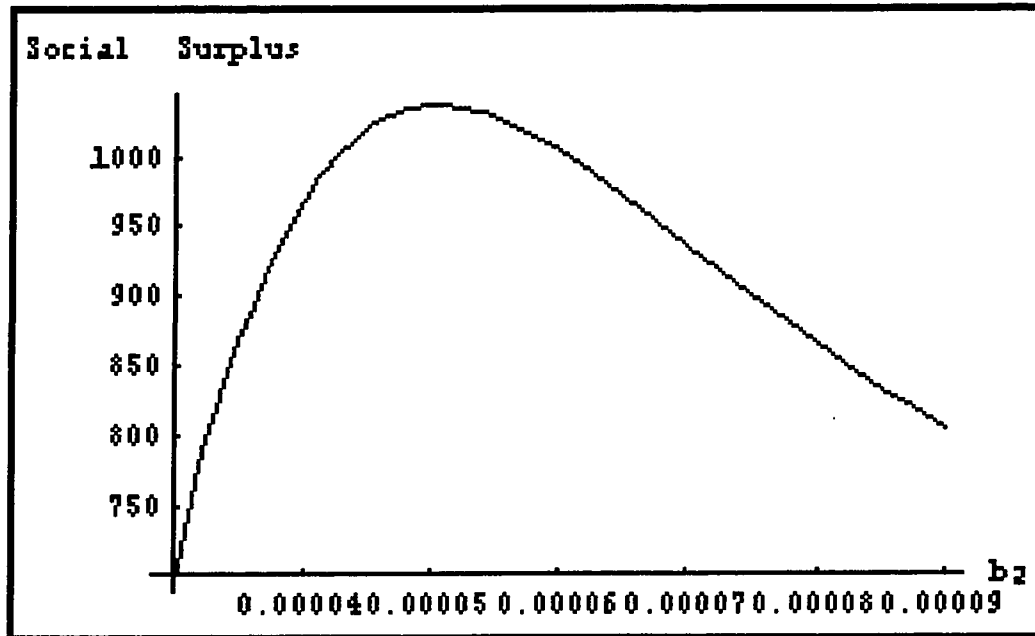


Figure 12: Variation of social surplus with slope coefficient b_2 of firm B in Case 4.2. Parameter values used: $a = 1$, $b_1 = 0.0005$, $\delta = 0.9$, $w_1 = 1$

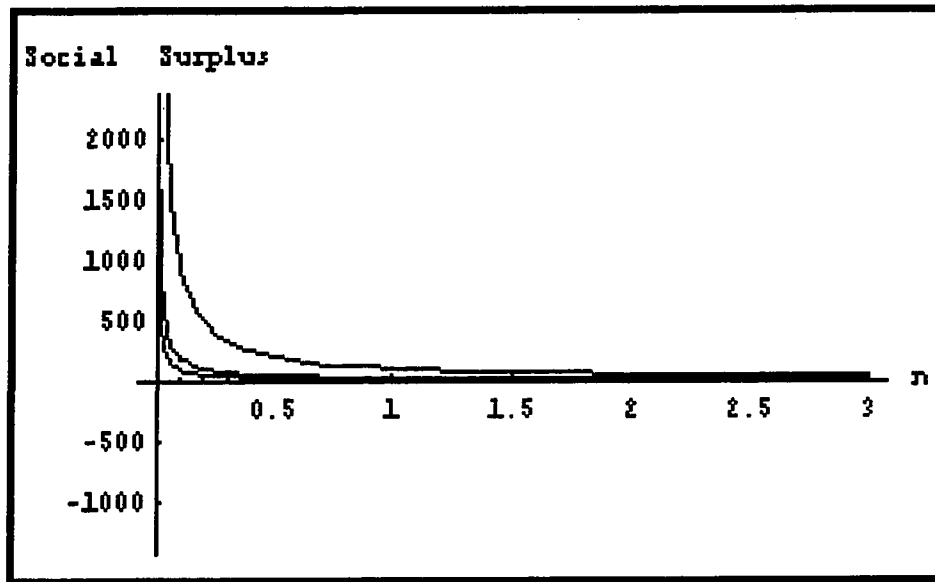


Figure 13: Variation of social surplus with number of firms in Case 4.3 (As α increases, the plots move closer to the origin.) Parameter values used: $a = 1$, $b = 0.0001$, $\delta = 0.9$, $w_1 = 1$.

CHAPTER 3: FORECASTING RESISTANCE

1. INTRODUCTION

In recent years, surveillance programs that monitor the incidence of hospital acquired infections have reported the emergence and rapid proliferation of infections that are partly or entirely resistant to antibiotics (McGowan 1983). This increase has been noted in all types of hospitals, but particularly in large teaching institutions. The increase in antibiotic resistance associated with nosocomial (hospital-acquired) infections has resulted in increased morbidity and mortality, longer hospital stays and more frequent hospital and ICU readmission (Office of Technology Assessment 1995). Consequently, the cost of treating a drug resistant bacterial infection has been reported to be much greater than the cost of treating a susceptible infection (Harrison and Lederberg 1992; Levy 1992).

Although there are a number of reasons for the increase in antibiotic resistance in hospitals, the widespread use of antibiotics in general and broad-spectrum antibiotics in particular, are believed to be significant contributing factors³⁴. While the transmission of resistant infections within the hospital is one mechanism by which levels of resistance increase, some antibiotics are able to induce the development of resistance in initially susceptible bacteria. This

³⁴ For example, *Clostridium difficile* proliferates in the bowel when other normal inhabitants are killed, allowing for the development of an infectious colitis which requires other antibiotics for treatment. Broad antibiotic coverage also eliminates many species of bacteria that normally colonize the skin and mucous membranes, thus selecting for the proliferation of yeasts (which can cause oral thrush, vaginal infections, and in hospitalized patients with catheters, severe bloodstream infections).

phenomenon has been recorded in the case of beta-lactam antibiotics, a large and commonly used group of agents that are structurally similar to penicillin. Certain antibiotics within this family, particularly third-generation cephalosporins, are known to induce the production of a beta-lactamase, an enzyme that destroys the antibiotic, by various species of bacteria such as those of the genus *Enterobacter* (which are significant agents of nosocomial infection)³⁵. The expanding application of medical technologies in hospitals is also to blame for increasing levels of nosocomial infection and bacterial resistance³⁶. Finally, procedures such as organ transplantation and bone marrow transplantation require that the immune system of the patient be suppressed, thus leaving the patient vulnerable to serious (and possibly fatal) infection with common bacterial pathogens (Cohen and Tartasky 1997).

Meanwhile, hospitals face a greater incentive than ever before to reduce the incidence of nosocomial infections particularly and resistant nosocomial infections. Resistant infections vastly increase the duration of hospitalization and the cost of treatment (Coast, Smith et al. 1996; Rubin, Harrington et al. 1999). Under the per-case prospective payment plan for Medicare patients, hospitals are reimbursed a lump sum amount that is determined on the basis of diagnosis-related groups (DRGs). Hospitals, therefore, bear the entire burden of increased treatment costs in the event that their patients acquire drug resistant infections (McGowan 1983).

³⁵ Personal communication, Dr. Lisa Grohskopf, Infectious Diseases Fellow, Harborview Medical Center, September 1997.

³⁶ Hospitals care for much sicker patients now than was the case fifteen or more years ago and these patients are taken care of for longer periods of time. Many of the procedures commonly performed on the seriously ill today, such as central venous catheterization and mechanical ventilation, predispose to colonization of the patient with hospital associated bacteria and an enhanced susceptibility to invasive infection with these agents.

Earlier studies have applied nosocomial surveillance data to the problem of forecasting outbreaks of resistant infections by using one of the following methodologies³⁷. The first is to set a baseline rate for nosocomial infections based on past data, and to specify a threshold value based on the baseline rate above which an epidemic is predicted (Birnbaum 1984; Parkhurst, Blaser et al. 1985; Schifman and Palmer 1985; Morrison, Kaiser et al. 1987; Klem and Dasta 1996). This threshold is then periodically updated based on a running average over a progressively longer time series. An alternative and arguably better method is to use exponential smoothing in which a greater weight is placed on more recent observations relative to older observations (Ngo, Tager et al. 1996).

The main drawback of these approaches is that they assume that future resistance is entirely predicted by past resistance. The main reason for making this assumption is that time series data on both antibiotic use and bacterial resistance has not been readily available in the past. Further, the complexity of statistical analysis to forecast resistance has precluded their broad acceptance and application by hospital infection control teams. Consequently, earlier studies implicitly ignore both the impact of antibiotic use on resistance patterns and the effect of increasing resistance on physicians' prescribing practices. Although the causal link between increases (or decreases) in antibiotic resistance and increases (or decreases) in antibiotic use has been firmly established, time-series data on antibiotic use has not been used to forecast the prevalence of resistance (McGowan 1983; Cohen 1992; Raz, Hefter et al. 1993). Since increased antibiotic use has the effect of increasing the level of bacterial resistance in a hospital, it is important to incorporate data on past antibiotic use to determine the threshold above which an outbreak is indicated.

³⁷ An outbreak is defined as an increase in bacterial resistance above some predetermined baseline.

This paper aims to empirically estimate both the effect of antibiotic use on resistance, as well as the response of physicians to increasing resistance. Furthermore, this paper demonstrates the application of seemingly unrelated regressions and a forecasting procedure that uses as its inputs, data on past levels of prevalence of resistance, and on past antibiotic use. The analysis used 12 years of microbiology data on antibiotic resistance, and pharmacy data on antibiotic use from Harborview Medical Center, Seattle to illustrate this forecasting method.

2. METHODS

The model describes the treatment of *Pseudomonas aeruginosa* (PSAR) using a class of antibiotics known as aminoglycosides, and the evolution of aminoglycoside resistance in PSAR. The two aminoglycosides considered here are Gentamicin (GENT) and Tobramycin (TOB). PSAR infections occur most frequently in hospitals where they can cause severe pneumonia in hospitalized patients, especially those in intensive care. The organism is commonly found in moist areas, such as sinks and urine receptacles, and in some instances, in certain antiseptic solutions. The most serious infections from PSAR occur in debilitated people whose immune system is impaired by medications, other treatments, or disease. PSAR can infect the blood, skin, bones, ears, eyes, urinary tract, heart valves, and lungs (Craig and Andes 1997). PSAR belong to a class of bacteria called gram-negative rods which are generally more resistant to antibiotics than are gram-positive bacteria (Merck 1950)³⁸.

³⁸ Gram-negative bacteria have a great facility for exchanging genetic material (DNA) among strains of the same species and even among different species. This means that if a gram-negative bacterium either undergoes a genetic change (mutation) or acquires genetic material that confers resistance to an antibiotic, the bacterium may later share its DNA with another strain of bacteria and the

There were two compelling reasons to focus our attention on the evolution of resistance in PSAR. First, PSAR is a hospital-acquired infection and is not usually transmitted in the community. Thus we can treat the hospital as a closed system and ignore the effects of antibiotic use outside Harborview on our resistance data. Second, our data reveal that resistance of other bacteria such as *Klebsiella*, *Acinetobacter* and *E. coli* to antibiotics has been fairly stable in comparison to resistance of PSAR to antibiotics. This indicated that the likelihood that the resistance of these other bacteria to GENT and TOB influenced PSAR resistance to GENT and TOB was fairly small³⁹.

In general, the effectiveness (the converse of resistance) of PSAR to antibiotic i , denoted by w_i , evolves in response to the number of patients treated with that antibiotic in previous periods, denoted by $TREAT_{ik,t-k}$. The two models estimated in the paper examine the case for including lagged treatment values as an explanatory variable for predicting future bacterial resistance. Model A, represented by equation (1) used only lagged values of effectiveness as explanatory variables.

$$(1) \quad w_{it} = \alpha_{i0} + \alpha_{i1}w_{i,t-1} + \alpha_{i2}w_{i,t-2} + \xi_{i,t}$$

Model B, represented by equation (2), used both lagged values of effectiveness and lagged values of treatment as explanatory variables.

second strain can become resistant as well. Although all bacteria have an inner cell membrane, gram-negative bacteria have a unique outer membrane. This outer membrane excludes certain drugs and antibiotics from penetrating the cell, partially accounting for why gram-negative bacteria are in general more resistant.

³⁹ For a detailed discussion of the evolution of resistance and its dynamics, see Laxminarayan and Brown (Laxminarayan and Brown 1998) and Bonhoeffer *et al.* (Bonhoeffer, Lipsitch et al. 1997)

$$(2) \quad w_{it} = \alpha_{i0} + \alpha_{i1}w_{i,t-1} + \alpha_{i2}w_{i,t-2} + \beta_{i1}TREAT_{i,t-1} + \beta_{i2}TREAT_{i,t-2} + \xi_{i,t}$$

A simple F-test was used to demonstrate that model B performed better than model A. These test results are discussed in the next section.

Having established that the inclusion of treatment improves our ability to estimate future antibiotic effectiveness we turn to the task of specifying a model that in addition to the regressors used in equation (2) also incorporates treatment using other antibiotics, and PSAR resistance to these antibiotics. Model C, represented by equation (3), was used to estimate the dependence of effectiveness and antibiotic use on past values of these two variables. Treatment using a related antibiotic j also affects the effectiveness of antibiotic i , as represented in the following equation.

$$(3) \quad w_{it} = \alpha_{i0} + \alpha_{i1}w_{i,t-1} + \alpha_{i2}w_{i,t-2} + \beta_{i1}TREAT_{i,t-1} + \beta_{i2}TREAT_{i,t-2} + \gamma_{j1}w_{j,t-1}TREAT_{j,t-1} + \xi_{i,t}$$

Next, we turn to the specification of an equation that describes changes in antibiotic prescriptions in hospitals. Physicians are known to respond to increases in resistance to antibiotic i by cutting back on its use. They acquire information on the prevailing level of resistance in two ways. Each year, physicians practicing at Harborview are given a summary of the previous year's resistance levels broken down by combinations of bacteria and antibiotic. The summary chart is fairly comprehensive and covers approximately 20 bacterial species and 30 commonly prescribed antibiotics. Physicians can also gauge the extent of prevailing resistance based on treatment failures encountered in their patients due to lack of response to the antibiotic.

We account for the former effect using the annual resistance data in reports made available to physicians (denoted by the variable CHART). Since

physicians are more likely to use information from the charts in the quarters immediately following their distribution, we estimated the interaction of the CHART instrument with quarter dummy variables, QTR. The resistance levels included in the charts were essentially drawn from the same data set as the one used in this study, the only difference being that duplicate isolates drawn from the same patient were not excluded for the purpose of determining annual resistance.

(3)

$$\begin{aligned} TREAT_{it} = & \delta_{i0} + \delta_{i1}w_{it-1}TREAT_{i,t-1} + \delta_{i2}TREAT_{i,t-1} + \delta_{i3}w_{i,t-1} \\ & + \delta_{i4}CHART_{i,t-1}QTR_{i,1} + \delta_{i5}CHART_{i,t-1}QTR_{i,2} + \delta_{i6}CHART_{i,t-1}QTR_{i,3} + \varepsilon_{i,t} \end{aligned}$$

The following exponential smoothing model was estimated to compare the results of this forecasting procedure with the one presented in this paper. There is fundamental difference between the exponential smoothing model and the regression model presented earlier. While antibiotic effectiveness is predicted on the basis of past value of effectiveness alone, in the exponential smoothing model, effectiveness is predicted on the basis of both past antibiotic use, and past antibiotic effectiveness in the regression model.

$$(3) \quad \hat{w}_{t+1} = S_t = \alpha w_t + (1 - \alpha)S_{t+1}$$

where S_t and S_{t+1} represent the forecast antibiotic effectiveness in periods t and $t+1$. α ($0 \leq \alpha \leq 1$) is the weight placed on the most recently observed level of effectiveness in predicting effectiveness for the next period. Therefore, the smoothing equation is based on the averaged (smoothing) past values of a series in a decreasing (exponential) manner. Past observations are weighted with more weight being placed on more recent observations. For instance, the most recent observation (at time t) carries a weight α , the observation at time $t-1$ carries a

weight $\alpha(1-\alpha)$, the observation at time $t-2$ carries a weight $\alpha(1-\alpha)^2$ and so forth. Therefore, we can rewrite equation (3) in the following manner,

$$(4) \quad S_{t+1} = \beta_0 w_t + \beta_1 w_{t-1} + \beta_2 w_{t-2} + \dots,$$

where S_{t+1} represents forecast antibiotic effectiveness at time $t+1$, w_1, w_2, \dots, w_t represent observed effectiveness for months $1, 2, \dots, t$ and $\beta_i = \alpha(1-\alpha)^i$ is a geometric series that sums to unity.

Finally, we also estimated a Holt-Winters exponential smoothing model to examine trends in our effectiveness data. The method computes recursive estimates of two damping parameters, one for the intercept or permanent component, and the other for the trend coefficient by finding values that minimize the sum of squared forecasting errors.

3. DATA

This study examines data on aminoglycoside use and *Pseudomonas aeruginosa* (PSAR) resistance to Gentamicin (GENT) and Tobramycin (TOB) at Harborview Medical Center in Seattle over a 12-year period from January 1, 1985 through December 31, 1996⁴⁰. Harborview Medical Center is a 351-bed county hospital

⁴⁰ Our data spans a period during which many of the most recently developed antibiotics, such as advanced third-generation cephalosporins and beta-lactam/beta-lactamase inhibitor combinations were introduced to the hospital formularies. Also during this period, hospital policy was changed regarding the control of antibiotic agents. Until early 1990, many antibiotics could be used only with permission of the infectious diseases division. Since then this restriction has been removed.

into which, on average, 13,788 patients are admitted annually⁴¹. Average percentage occupancy was roughly 80% while average patient length of stay was 7.5 days during the 1995-98 period. Antibiotic sensitivity testing data on isolates of PSAR has been stored electronically by Harborview Microbiology Labs since 1985 and was made available for this study. The Kirby-Bauer test was used to identify isolates as sensitive, intermediate or resistant. Starting in mid-1994, all antibiotic sensitivity testing was performed using both the Kirby-Bauer method and the Vitek Automated Microbiological System[®]. Over the next year, the Vitek System was configured in order that the Vitek results were in agreement with the Kirby-Bauer test results. In late 1995, the Kirby-Bauer method was phased out completely and all tests were conducted on the Vitek System.

Since the data contain multiple isolates per patient hospitalization, we selected one isolate per source (blood, urine, wound etc.) per hospitalization for each patient. Hospital admit/discharge dates obtained from pharmacy records were matched to lab records. Lab records that had no corresponding hospital dates were omitted. For each hospitalization, the last test for each bug/drug/source combination was taken as being indicative of the level of resistance in a patient. This amounted to a little over half of the original number of lab tests that examined the resistance of PSAR to aminoglycosides. The level of susceptibility (or effectiveness) in each month was calculated as the fraction of total number of isolates tested which were in the sensitive category.

On average, 28 patients were tested each month for resistance to GENT and TOB over the 12-year period from January 1, 1985 through December 31, 1996. (see Figure 2). The Augmented-Dickey Fuller test was used to test for a unit root in the data series on susceptibility of PSAR to GENT and TOB. Based on MacKinnon critical values, we rejected the hypothesis that the data were non-

⁴¹ Based on average for 1995-96 to 1997-98 period.

stationary at the 95% confidence level. The monthly average level of PSAR susceptibility to GENT ranged between 21.43% (February 1986) and 100% (August, October 1988 and April 1994). PSAR susceptibility to TOB ranged from 68.97% (September 1995) and 100% (multiple months). Descriptive summary statistics of PSAR resistance to GENT and TOB are provided in Table 1.

Data on antibiotic use over the 1985-1996 time period were obtained from pharmacy billing records stored using the DatANAL[®] billing system. On average 172 patients were treated using GENT each month. In comparison, only 32 patients were treated using TOB on average each month (see Table 2).

4. ESTIMATION AND RESULTS

We estimated the basic equations discussed earlier in Section 2. Both equation-by-equation weighted least square regressions and seemingly unrelated regressions (SURs) were used to estimate the impact of past antibiotic use and past GENT effectiveness ($w_{GENT,t-1}$) on current GENT effectiveness ($w_{GENT,t}$) and TREATG (number of patients treated with GENT). Since the disturbance in the effectiveness equation ($\xi_{i,t}$) is likely to be correlated with the disturbance in the antibiotic use equation ($\varepsilon_{i,t}$), SURs were deemed appropriate. VARs were not used because the exogenous and lagged endogenous variables in our model were not identical for the two estimated equations. In order to control for heteroskedasticity arising from variations in the number of isolates tested each month, we used a weighted least squares estimation. Weights were proportional to the square root of the number of isolates from which the effectiveness data was derived, and were therefore, inversely proportional to the standard deviation of the disturbances. Serial correlation was ruled out using the Breusch-Godfrey large sample test for autocorrelated disturbances. The F-statistic generated failed

to reject the null hypothesis that the coefficient of all the lagged residuals was zero in both GENT and TOB regressions⁴². Unlike the standard Durbin-Watson estimator, this test is appropriate for lagged dependent variable models.

Regression output is presented in Tables 3 and 4. Antibiotic effectiveness data provided to physicians in the form of summary charts (CHARTG) was interacted with QTR and included in one set of regressions. Table 3 presents the results from estimations based on equations (1) and (2) that represent models A and B respectively. Both of these models were estimated independently using weighted least squares and jointly with equation (4) using SURs. An F-test confirmed that past treatment using antibiotics was preferred to the one without past antibiotic treatment at a 95% degree of confidence⁴³.

We estimated Model C (using equations 3 and 4) in the same manner (both independently using weighted least squares and jointly using SURs). Estimates of equations (3) and (4) using SUR regressions indicate that the elasticity of GENT effectiveness with respect to use in the previous month was 0.023 (Table 5). In other words, treating an additional 10% of patients using GENT had the effect of reducing GENT effectiveness (by a little more than 0.2%). Conversely, a 10% increase in the level of GENT effectiveness increases the number of patients that are treated using GENT. Also, a 10% increase in the number of patients treated with TOB reduced GENT effectiveness by 0.4%. In other words, TOB use had a slightly greater impact on GENT effectiveness for the following month than did GENT use.

⁴² The F-statistic was 2.515 for GENT and 1.16 for TOB, and failed to reject the null hypothesis that there is no serial correlation at the 95% level of confidence.

⁴³ The F-statistic is calculated as $F_{r,n-k} = \frac{(SSE_R - SSE_U)/r}{SSE_U/(n-K)} = 9.45$ where R represents the restricted regression A, U represents the unrestricted regression B, r is the number of restrictions, and K is the number of regressors.

In the case of TOB, a 10% increase in TOB use was associated with a 0.35% decrease in TOB effectiveness the following month. A similar increase in GENT use had a 0.4% negative effect on TOB effectiveness. Physicians responded to increases in TOB effectiveness with a 0.99% increase in TOB use for every 10% increase in w_{TOB} . The CHART variables were not statistically significant in the TOB regression.

Impulse response functions were plotted to examine the effect of a spontaneous one standard deviation increase in $w_{GENT,t}$ on both GENT effectiveness as well as the number of patients treated with GENT in following time periods ($t+1, t+2...$) (Figures 14 and 15). The coefficients used to plot the response functions were based on Model C. All variables other than the effectiveness of GENT and TREATG, such as the effectiveness of TOB and the number of patients treated with TOB were held at their long run average values. The response plots indicate that a 17% (equal to one standard deviation) exogenous increase in GENT effectiveness persists for about 15 months before dying out. Moreover, this increase in effectiveness is followed by a temporary increase in the number of patients treated using GENT. In fact, the increase in GENT use is greatest two months after the increase in effectiveness is recorded. Thereafter, GENT use returns to its long run average level within the course of the following year.

The effect of a one standard deviation one-time increase in the number of patients treated with GENT was also examined. Figure 16 indicates that treating an additional 70 patients using GENT in any one month is likely to be followed by a roughly 5% decline in antibiotic effectiveness during the following month. However, this decrease is not permanent and antibiotic effectiveness returns to its long run average by the end of a 15-month period. According to Figure 17, a

spontaneous increase in GENT use was found to persist for about 5 months before dying out.

5. COMPARISON OF FORECASTS

Monthly aggregate data from January 1, 1985 to December 31, 1994 were used as the baseline from which the forecast for period January 1, 1995 to December 31, 1996 was developed. These forecasts were compared with actual data over this period to compare the accuracy of the different forecasting methods.

Both static and dynamic forecasts were obtained using the estimated SURs as well as exponential smoothing and the Holt-Winters forecasting method. The essential difference between the static and the dynamic forecast is this. Consider a forecasting period extending from periods $t+1$ to $t+n$. A dynamic forecast predicts the value of the desired variable for the entire forecasting period at time t . However, a static forecast can forecast only one period ahead, at a time. In other words, at time t , the static forecast will predict the value of the desired variable at time $t+1$. The observed value at $t+1$ is then used to predict the value for $t+2$ and so forth. The strength of the dynamic forecast is that it allows for long range planning. Specifically, it allows us to predict the value of the variable n periods into the future without observing the actual value of the variable for the previous $n-1$ periods. Therefore, the forecast for the n^{th} period is based solely on the predicted value of the value in the previous $n-1$ periods.

On the other hand, a static forecast does not permit long range planning since at any given time, we only know the predicted value for the next period and no further. Generally, a static forecast is more accurate than a dynamic forecast

because it has the benefit of periodic updating with observed values of the variable unlike the dynamic forecast. Availability of both static and dynamic forecasts is essential to enable effective short and long term planning by infection control specialists.

Figure 18 shows the relation between α , the smoothing constant for the forecast model, and the sum of squared errors around the estimate of the “one month ahead” forecast cumulative incidence. The value of α that minimizes the sum of squared errors was determined to be 0.36. A larger α places greater value on the most recently observed level of resistance and hence limits our ability to forecast resistance well in advance. For instance, an earlier study that looked at the application of exponential smoothing to forecast resistance of PSAR to GENT determined the smoothing parameter in their data to be only 0.16 (Ngo, Tager et al. 1996). In general, the variability of α in different data sets may limit the widespread application of exponential smoothing as a consistently reliable forecasting tool. The Holt-Winters forecast indicated that the smoothing coefficient for the permanent component was 0.36 while the trend coefficient was zero.

In order to compare the forecasts using the SUR and exponential smoothing methods, we computed the sum of square errors (SSE) for both static and dynamic forecasts using the two sets of methods (Table 6). The dynamic forecast model required no updating and provided a two year forecast (for the 1995-1996) period based solely on data from 1984-94. The static forecast model, on the other hand, required monthly updating with actual data during the forecast period (1995-96).

5.1 *DYNAMIC FORECASTS*

Dynamic forecasts were obtained from the SUR model estimated using Model C, as well as from the exponential smoothing and Holt-Winters models. These forecasts were made for a two-year period starting January 1995 (immediately following the January 1985-December 1994 period over which the forecast parameters were estimated.) Other variables, such as the effectiveness of the other antibiotic that is used as regressors were held at their long run mean until the beginning of the forecast period.

Since these forecasts did not require monthly updating, they attempted to predict monthly incidence of antibiotic effectiveness, as seen in Figure 19. Note that the exponential smoothing and Holt-Winters methods produced forecasts that were fairly similar. The sum-of-squared-errors (SSE) for the SUR dynamic forecast that predicted the level of effectiveness over the entire two year forecast period was 0.491. In comparison, the SSE associated with the exponential smoothing and Holt-Winters forecasts were 0.695 and 0.741 respectively.

5.2 *STATIC FORECASTS*

SUR and exponential smoothing estimates were used to produce a static forecast of monthly incidence of antibiotic effectiveness. In order to produce the static forecasts, the model was updated with data on both number of patients treated with antibiotics and the level of antibiotic effectiveness in each month in order to produce the next month's forecast. Other variables such as the effectiveness of the other antibiotic that are used as regressors was based on their most recently reported value.

Forecasts are plotted in Figure 20. As expected, the static forecasts were more accurate than the dynamic forecasts, by virtue of their monthly updating.

The SUR static forecast provided the lowest SSE of 0.46. The static forecast using exponential smoothing did not perform as well and had a SSE of 0.56. Figure 20 also illustrates our conclusion that the most accurate month ahead forecast was provided by the SUR static forecast.

6. CONCLUSIONS

Recent advances in database management have encouraged record keeping on both antibiotic use and bacterial resistance in hospitals. Using this data to determine the impact of antibiotic use on resistance has two major benefits. First, hospitals acquire information on the expected impact of changes in antibiotic prescribing policy on resistance. The precise nature of this dose-response relationship is mediated by factors unique to each hospital such as degree of emphasis placed on infection control, degree of nursing staff sequestration and patient demographics. Second, this information can be used to forecast resistance in the future, so that expected changes in resistance due to changes in antibiotic use are distinct from “outbreaks” of resistance in the hospital.

Using both equation-by-equation OLS and SUR models, we estimated the impact of GENT use on PSAR resistance to resistance, as well the impact of increasing resistance levels to GENT on the willingness of physicians to prescribe this antibiotic. We found the elasticity of resistance to GENT use was -0.044 while the converse (elasticity of GENT use to changes in resistance) was 0.076 . In the case of TOB, a 10% increase in TOB use was accompanied by a 0.35% increase in PSAR resistance to TOB. Conversely, a 10% increase in TOB effectiveness was associated with a roughly 1% increase in TOB use.

The low elasticity of antibiotic resistance to antibiotic use leads one to conclude that the fitness cost associated with antibiotic resistance is fairly high. The fitness cost is evolutionary disadvantage placed on resistant organisms in that they are more likely to die out in the absence of antibiotics (Anderson 1982). In a hospital setting, it is possible that when selective pressure imposed by antibiotic use is reduced, or when infection control measures are applied, a relatively high fitness cost will lower the incidence of resistant bacteria. Therefore, in a data series aggregated by month, it may appear that antibiotic use does not have a marked effect on resistance. Another piece of evidence supporting the hypothesis of high fitness cost is provided by the long-run response to an increase in antibiotic use (as seen in the impulse response plots). The fact that a spontaneous increase in use has practically no long-term effect on resistance may show that in the absence of continued selective pressure (caused by antibiotic use), fitness cost will ensure that resistance returns to a natural equilibrium dictated by the long-run mean level of antibiotic use.

The current state-of-the-art method in using resistance data for nosocomial infection surveillance is based on exponential smoothing. This method involves a month-by-month updating of the forecast and is therefore static. Therefore, long-run forecasts are not possible using exponential smoothing. Further, in the absence of any exogenous predictor of resistance such as past antibiotic use, monthly variations in resistance may appear to follow a random walk, and forecasting may be limited to updating the threshold based on the most recently observed level of resistance.

Using regression analysis on data on both antibiotic use and resistance has three advantages and one disadvantage. First, it permits long run dynamic forecasts in a manner similar to that permitted by a vector-autoregression (VAR) process. Second, the method is not critically dependent on the ability of past levels of resistance to forecast future levels as is the case with exponential

smoothing. Finally, the analysis offers the added advantage of quantifying the dose-response relationship between antibiotic use and resistance in a hospital. This enables a hospital to precisely know the impact of its current antibiotic prescribing policies on the expected level of bacterial resistance in coming months. However, as a practical matter, the complexity of this analysis may limit its widespread acceptance and implementation by hospital infection control committees.

Table 10: Coefficient estimates for Gentamicin (GENT) from OLS and Seemingly Unrelated Regressions (SURs). Dependent variables are Gentamicin effectiveness (GP), and number of patients treated using GENT, (TREATG)*.

MODELS	A			B			C		
	Weighted Coefft.	LS t-ratio	SUR Coefft.	Weighted Coefft.	LS t-ratio	SUR Coefft.	Weighted Coefft.	LS t-ratio	SUR Coefft.
<i>C</i>	0.234	4.118	0.236	0.235	3.650	0.244	0.341	4.125	0.356
<i>GP(-1)</i>	0.385	4.911	0.387	0.419	5.271	0.413	0.367	4.424	0.357
<i>GP(-2)</i>	0.306	3.914	0.302	0.300	3.798	0.299	0.255	3.126	0.251
<i>TREATG(-1)</i>				-0.001	-2.166	-0.001	-0.001	-2.035	0.000
<i>TREATG(-2)</i>				0.000	1.741	0.000	0.000	1.471	0.000
<i>TREATT(-1)*TP(-1)</i>							-0.001	-2.036	-0.001
<i>R-square</i>	0.64		0.64	0.66		0.66	0.67		0.67
<i>C</i>	159.388	9.233	159.280			159.087			158.977
<i>GP(-1)</i>	-94.337	-3.421	-98.718			-93.345			-93.329
<i>TREATG(-1)*GP(-1)</i>	0.647	7.838	0.669			0.643			0.643
<i>CHARTG(-1)*QTR1</i>	-7.783	-0.563	-10.609			-10.787			-10.658
<i>CHARTG(-1)*QTR2</i>	6.964	0.502	8.374			7.531			7.281
<i>CHARTG(-1)*QTR3</i>	19.252	1.475	22.463			21.597			22.416
<i>R-square</i>	0.63		0.63	0.63					1.811

* GP denotes GENT effectiveness and TREATG is the number of patients treated with GENT. CHARTG denotes GENT effectiveness in previous year and QTR is a quarter dummy. A total of 120 observations were used for each estimation corresponding to data over the period 1985-1994.

Table 11: Coefficient estimates for Tobramycin (TOB) from weighted least squares and Seemingly Unrelated Regressions (SURs). Dependent variables are Tobramycin effectiveness (TOB), and number of patients treated using TOB, (TREAT)*.

MODELS	A			B			C		
	Weighted LS Coefft.	SUR t-ratio	SUR Coefft	Weighted LS Coefft.	SUR t-ratio	SUR Coefft.	Weighted LS Coefft.	SUR t-ratio	SUR Coefft.
C	0.516	5.653	0.515	5.707	5.474	0.498	5.457	0.495	5.561
TP(-1)	0.357	4.292	0.357	4.334	4.483	0.371	4.486	0.372	4.598
TP(-2)	0.091	1.078	0.092	1.101	1.029	0.071	0.833	0.072	0.867
TREAT(-1)					-1.357	-0.001	-0.464	-0.001	-0.256
TREAT(-2)					2.730	0.000	2.345	0.000	2.463
TREATG(-1)*GP(-1)					-0.001	-0.924	-0.001	-1.393	
R-square	0.88		0.88		0.88	0.89			
C	6.636	0.241	6.694	0.248	6.827	0.253	6.828	0.253	
TP(-1)	1.344	0.045	1.289	0.044	1.119	0.038	1.236	0.042	
TREAT(-1)*TP(-1)	1.045	10.681	1.045	10.916	1.045	10.924	1.040	10.883	
CHART(-1)*QTR1	2.330	0.379	2.380	0.396	2.551	0.424	2.702	0.451	
CHART(-1)*QTR2	-1.315	-0.220	-1.327	-0.227	-1.258	-0.215	-1.216	-0.208	
CHART(-1)*QTR3	2.333	0.412	2.272	0.410	2.192	0.396	2.053	0.372	
R-square	0.49		0.49		0.48		0.49		

* TP denotes TOB effectiveness and TREAT is the number of patients treated with TOB. CHART denotes TOB effectiveness in previous year and QTR is a quarter dummy. A total of 120 observations were used for each estimation corresponding to data over the period 1985-1994.

Table 12: Elasticity estimates for GENT.

	$w_{GENT,t-1}$	$w_{TOB,t-1}$	$TREATG_{t-1}$	$TREATT_{t-1}$
w_{GENT}			-0.023	-0.044
w_{TOB}			-0.041	-0.035
$TREATG$	0.076		0.488	
$TREATT$		0.099		0.97

Table 13: Sum of squared errors for range of forecasts.

	SUR	Exp. Smooth	Holt-Winter
<i>Dynamic forecast</i>	0.491	0.695	0.741
<i>Static forecast</i>	0.463	0.555	

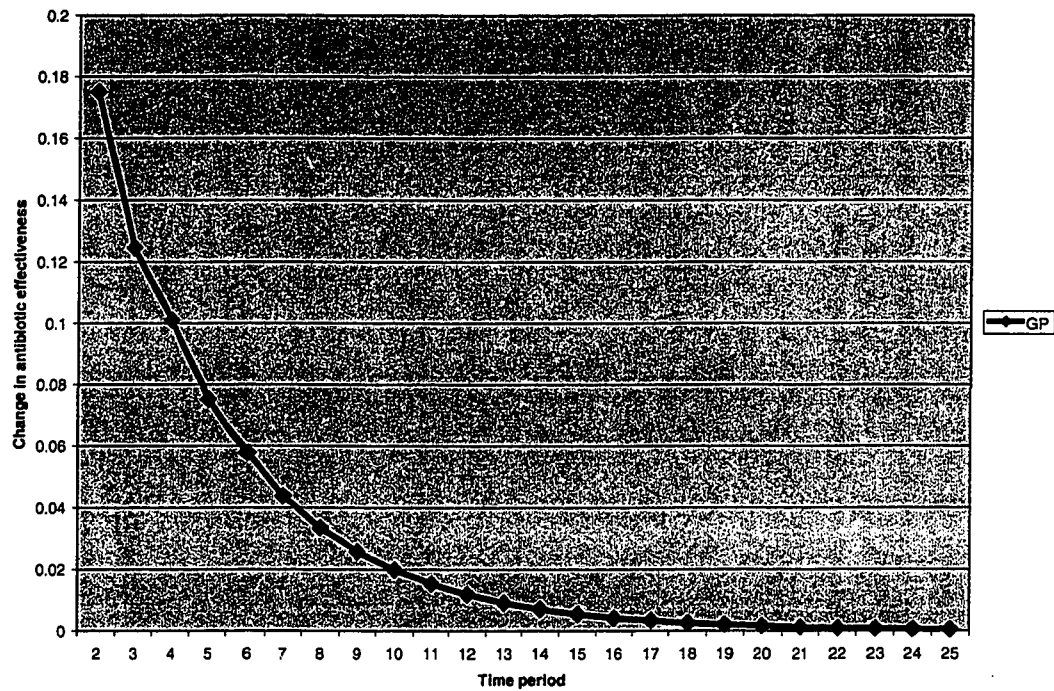


Figure 14: Response of GENT effectiveness to a one standard deviation spontaneous increase in GENT effectiveness.

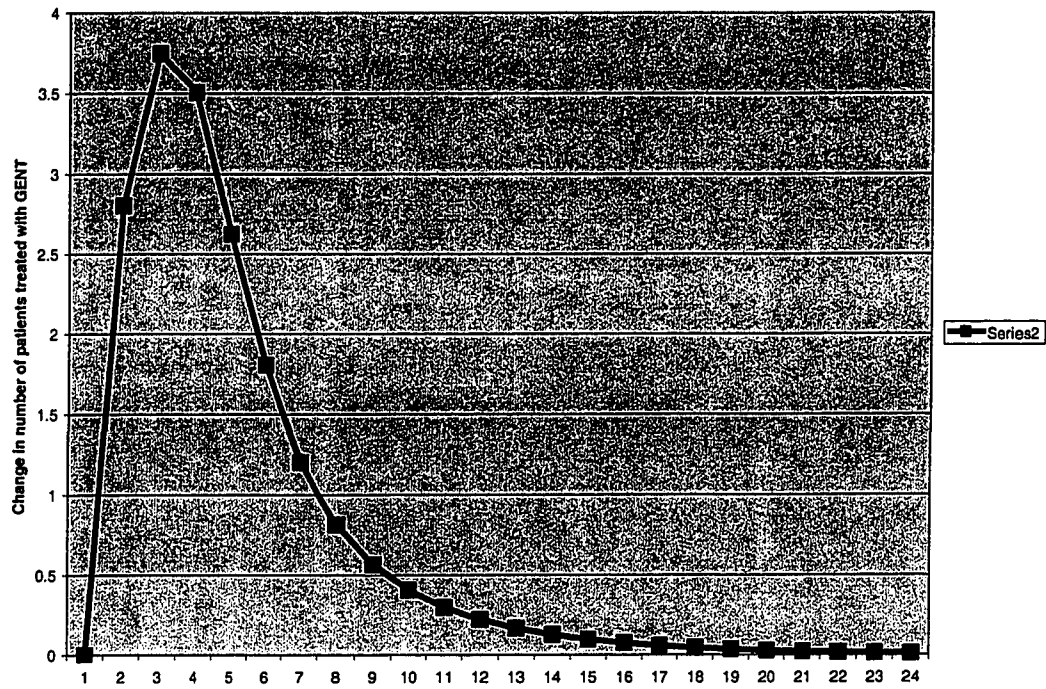


Figure 15: Response of TREATG to a one standard deviation spontaneous increase in GENT effectiveness.

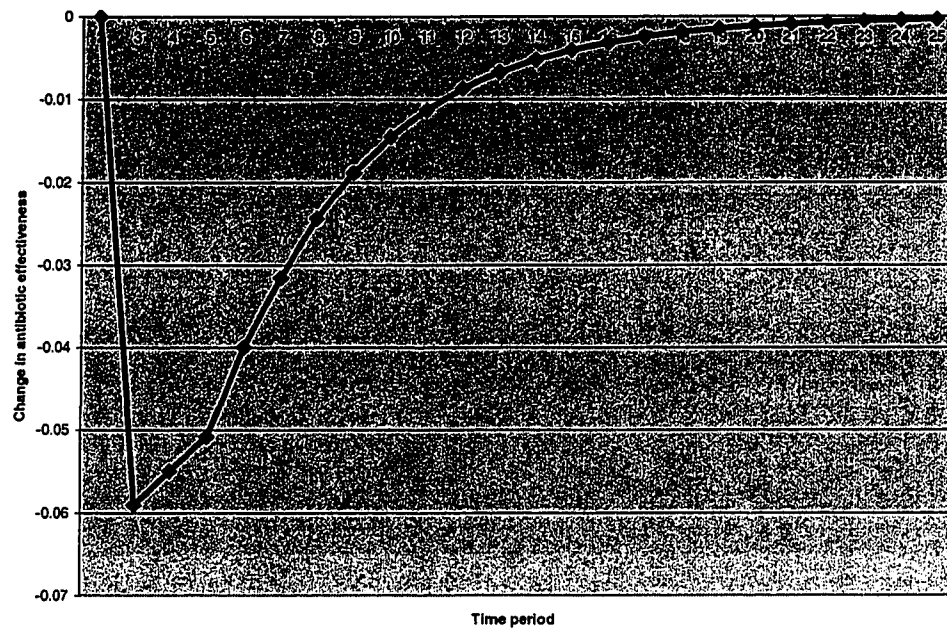


Figure 16: Response of GENT effectiveness to a one standard deviation increase in TREATG.

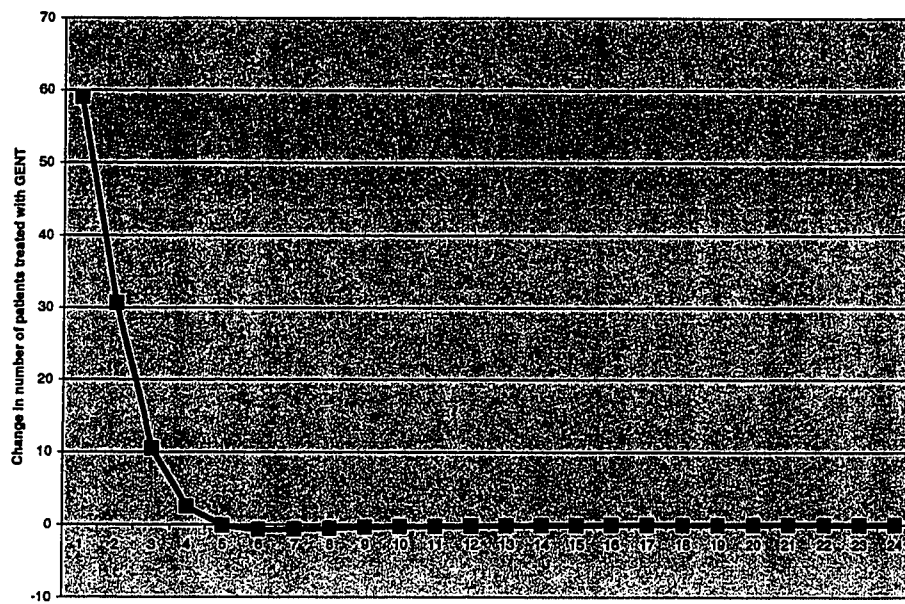


Figure 17: Response of TREATG to a one standard deviation increase in TREATG.

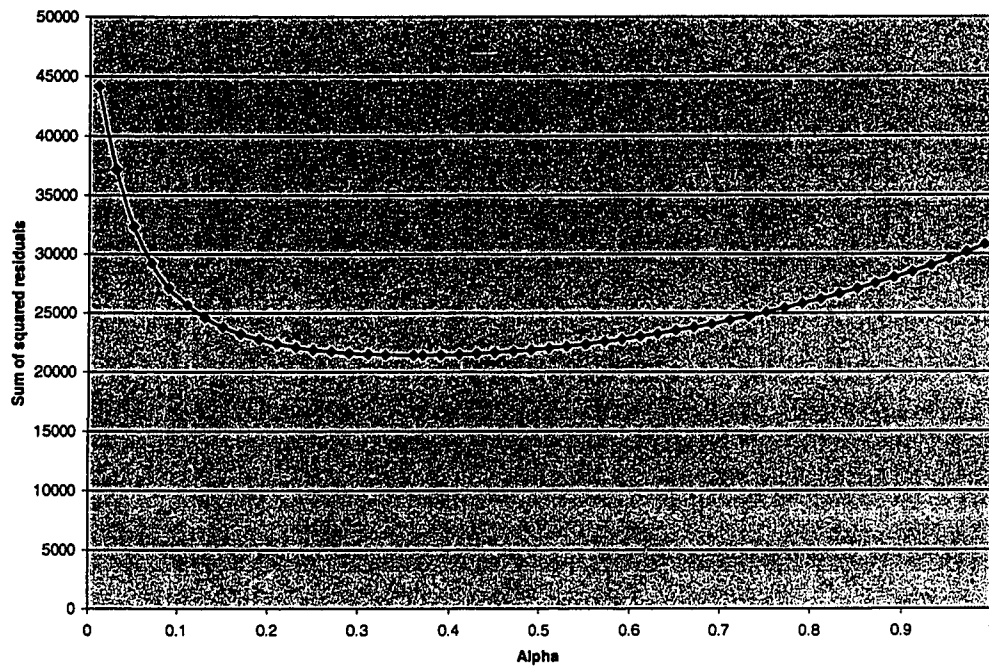


Figure 18: Plot of sum of squared residuals against range of values of α , the smoothing parameter for forecast model.

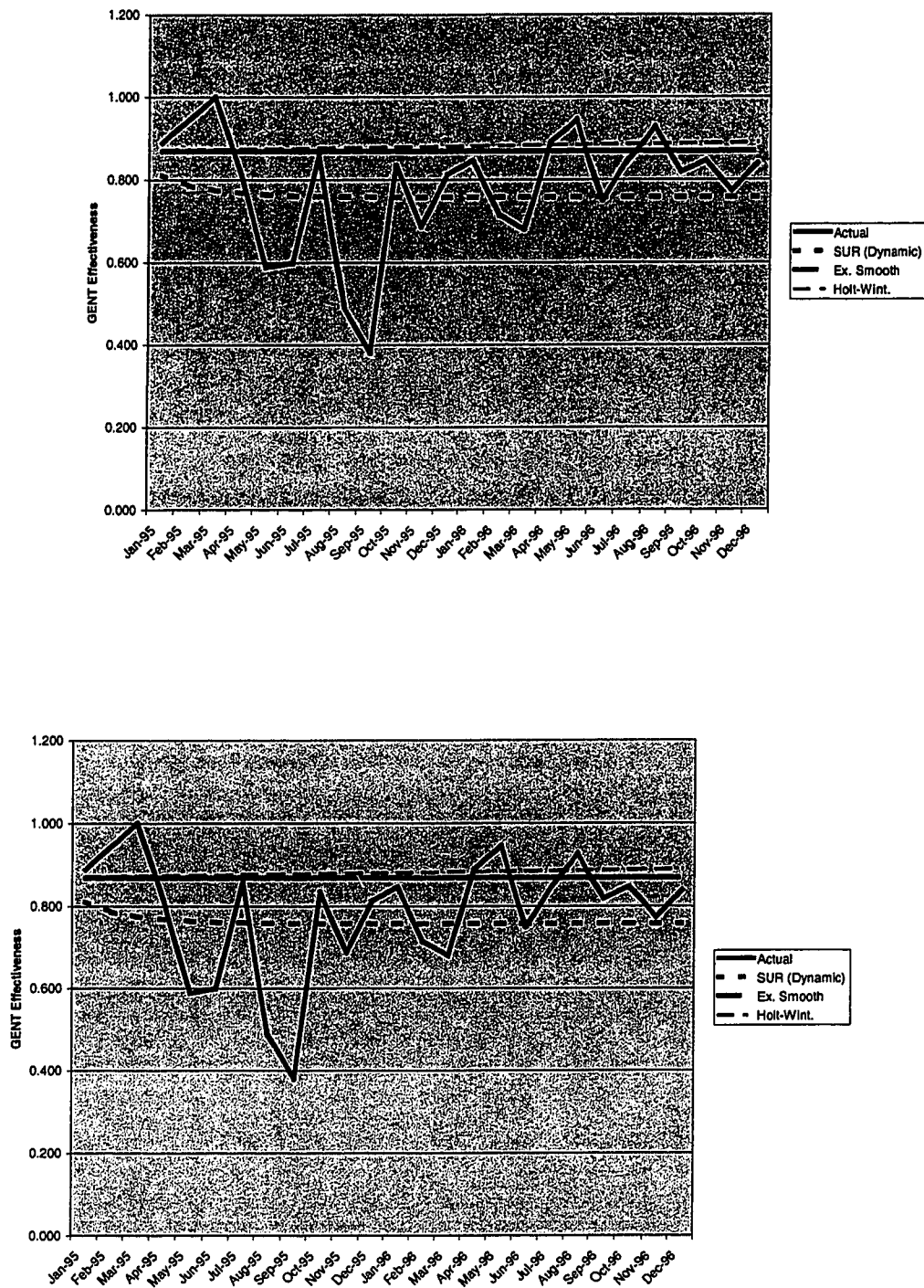


Figure 19: Dynamic forecasts using exponential smoothing, Holt-Winters and SUR.

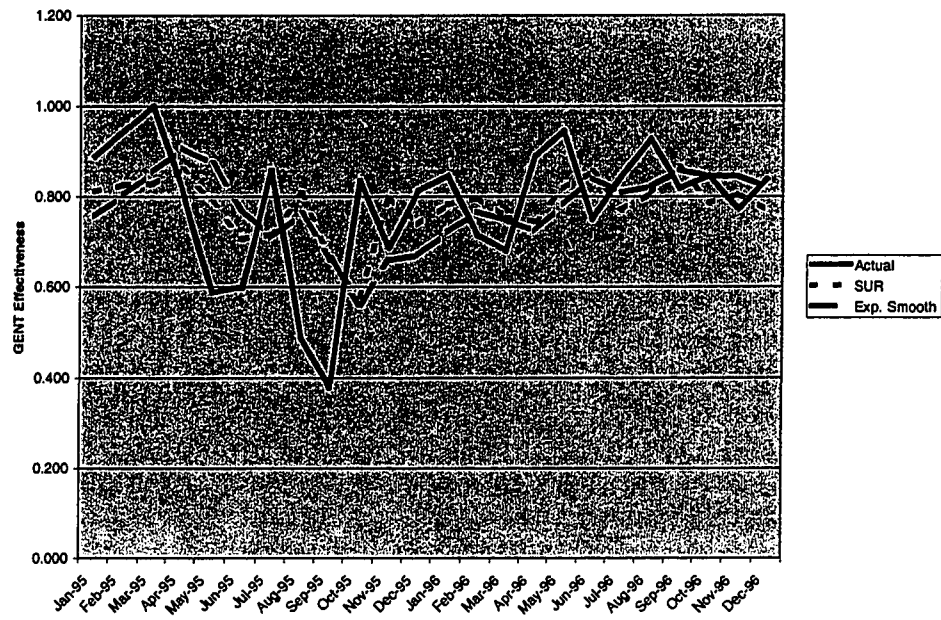


Figure 20: Static forecasts using SUR and exponential smoothing.

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APPENDIX A: DERIVATION OF RESISTANCE DYNAMICS

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

$$\text{A.2.1} \quad I = I_1 + I_2 + I_{12} + I_w$$

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:

$$\text{A.2.2} \quad \dot{I}_w = \beta SI_w - r_w I_w - (f_1 + f_2) I_w$$

$$\dot{I}_1 = \beta SI_1 - r_1 I_1 - f_2 I_1$$

$$\dot{I}_2 = \beta SI_2 - r_2 I_2 - f_1 I_2$$

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

f_a and f_b are the fractions of the infected population treated with antibiotics a and b. We assume that no one is treated using both antibiotics. The effectiveness of antibiotic a 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.2.3

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

$$\text{A.2.4 } \frac{\dot{I}}{I} = \beta S - w_1(f_1 + r_2 - r_{12}) - w_2(f_2 + r_1 - r_{12}) + w_{12}(r_1 + r_2 - r_{12} - r_w) - r_{12}$$

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

$$\text{A.2.5 } \frac{\dot{I}}{I} = \beta S - w_1 f_1 - w_2 f_2 - r$$

The rate at which effectiveness declines over time is given by

$$\begin{aligned} \dot{w}_1 &= \frac{\partial \left(\frac{I_2 + I_w}{I} \right)}{\partial t} \\ &= \frac{\dot{I}_2}{I} + \frac{\dot{I}_w}{I} - \left(\frac{I_2 + I_w}{I} \right) \left(\frac{\dot{I}}{I} \right) \end{aligned}$$

$$\begin{aligned}
\text{A.2.6} \quad &= [\beta S - r_w - (f_1 + f_2)]w_{12} + [\beta S - r_2 - f_1][w_1 - w_{12}] \\
&- w_1[\beta S - w_1 f_1 - w_2 f_2 - r_1(w_2 - w_{12}) - r_2(w_1 - w_{12}) - r_w w_{12} - r_{12}(1 - w_1 - w_2 + w_{12})]
\end{aligned}$$

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

$$\text{A.2.7} \quad \dot{w}_1 = f_1 w_1 (w_1 - 1) - f_2 (w_{12} - w_1 w_2)$$

By symmetry,

$$\text{A.2.8} \quad \dot{w}_2 = f_2 w_2 (w_2 - 1) - f_1 (w_{12} - w_1 w_2)$$

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

$$\text{A.2.9} \quad \dot{w}_1 = f_1 w_1 (w_1 - 1)$$

$$\text{A.2.10} \quad \dot{w}_2 = f_2 w_2 (w_2 - 1)$$

The evolution of multi-drug resistance can be written as,

$$\begin{aligned}
\text{A.2.11} \quad &\dot{w}_{12} = \frac{\partial \left(\frac{I_w}{I} \right)}{\partial t} = \frac{\dot{I}_w}{I} - \frac{I_w}{I} \frac{\dot{I}}{I} \\
&= [\beta S - r - (f_1 + f_2)]w_{12} - [\beta S - w_1 f_1 - w_2 f_2 - r]w_{12} \\
&= w_{12}[f_1(w_1 - 1) + f_2(w_2 - 1)]
\end{aligned}$$

APPENDIX B: CHARACTERIZING COSTATE VARIABLES

Proof:

From equations (8.3) and (8.4), we have

$$\text{A.1.1} \quad \frac{\dot{\mu}_1}{\mu_1} = \rho - kf_1(2w_1 - 1) - \frac{(x - \varphi)If_1}{\mu_1}$$

We can substitute from equations (8.1) and (8.2) to get,

$$\text{A.1.2} \quad \frac{\dot{\mu}_1}{\mu_1} = \rho - kf_1w_1$$

Differentiating equation (8.1) with respect to time,

$$\text{A.1.3} \quad \dot{\mu}_1 = \frac{(x - \varphi)I\dot{\omega}_1 + (x - \varphi)\dot{I}\omega_1 - \dot{\varphi}I\omega_1 + \mu_1 k\omega_1(2\omega_1 - 1)}{k\omega_1(1 - \omega_1)}$$

Substitute for $\dot{\mu}_1$ from equation (A.1.2) and for \dot{w}_1 , \dot{I} , $\dot{\varphi}$ from equations (7.1), (7.3) and (8.5) to get,

$$\text{A.1.4} \quad \beta I(x + \varphi) = x(\beta - r - \rho)$$

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

$$\text{A.1.5} \quad \varphi = \frac{x(\beta(1 - I) - r - \rho)}{\beta I}$$

we see that $\varphi < 0$ when $\beta < \rho + r$. Estimates of β (both in our data and in earlier studies) are on the order of 0.01 persons/month. The estimate of r is in the order of 0.7. Therefore, the $\beta < \rho + r$ is a reasonable one to make even for fairly low discount rates.

From equation 8.5,

$$\text{A.1.6} \quad \frac{\dot{\varphi}}{\varphi} = (\rho + r + 2\beta I - \beta) - \frac{(x - \varphi) \sum w_i f_i + c_I + \bar{c} f_1}{\varphi}$$

Since $\varphi < 0$, $\frac{(x - \varphi) w f}{\varphi}$ is negative for all values of w . Therefore, the sufficient

condition for $\frac{\dot{\varphi}}{\varphi} > 0$ is that $(\rho + r + 2\beta I - \beta) > 0$. The equivalent condition is that

$I > \frac{\beta - \rho - r}{2\beta}$. This condition holds as long as the now familiar condition,

$\beta < \rho + r$ holds.

APPENDIX C: PROOFS FOR CHAPTER 2

PROOF 1.1 FOR PROPOSITION 1 TO SHOW THAT $q_{1A}^ < q_{1A}^{**}$*

Consider the intertemporal profit function under Case 1

$$(20.1) \quad \pi_A = \pi_{1A}(w_1, q_{1A}) + \delta \pi_{2A}(w_2, q_{2A})$$

Then we determine the optimal second period quantity by setting

$$(20.2) \quad \frac{\partial \pi}{\partial q_{2A}} = \frac{\partial \pi_{2A}}{\partial q_{2A}} = 0$$

The firm then assumes the optimal level of production in period 2, q_{2A}^* to determine the optimal quantity to produce in period 1, q_{1A}^* , by setting

$$(20.3)$$

$$\frac{\partial \pi^1}{\partial q_{1A}} = \frac{\partial \pi_1^1}{\partial q_{1A}} - \delta \left(\frac{\partial g(w_1, q_{1A})}{\partial q_{1A}} \frac{\partial \pi_2^1(w_2, q_2^*)}{\partial w_2} + \frac{\partial \pi_2^1(w_2, q_2^*)}{\partial q_2} \frac{\partial q_2^*(q_{1A}, w_1)}{\partial q_{1A}} \right) = 0$$

But the second term within parentheses equals zero, by definition of q_{2A}^* .

Therefore, we can rewrite equation (20.3) as

$$\frac{\partial \pi^1}{\partial q_{1A}} = \frac{\partial \pi_1^1}{\partial q_{1A}} - \delta \frac{\partial g(w_1, q_{1A})}{\partial q_{1A}} \frac{\partial \pi_{2A}^1(w_2, q_2^*)}{\partial w_2} = 0$$

The corresponding equation for Case 2 is given by

$$\frac{\partial \pi^2}{\partial q_{1A}} = \frac{\partial \pi_1^2}{\partial q_{1A}} - \delta \frac{\partial g(w_1, q_{1A})}{\partial q_{1A}} \frac{\partial \pi_{2A}^2(w_2, q_2^{**})}{\partial w_2} = 0$$

Our first task is to show that $q_{2A}^* > q_{2A}^{**}$. By definition of q_{2A}^* and q_{2A}^{**}

$$\frac{\partial \pi_{2A}(g(w_1, q_{1A}), q_2^*)}{\partial q_{2A}} = \frac{\partial \pi_{2A}(g(w_1, q_{1A}, q_{1B}), q_2^{**})}{\partial q_{2A}} = 0,$$

Since decreasing patent breadth can only increase the total quantity of antibiotics produce, $q_{1A} < q_{1A} + q_{1B}$ and $g(w_1, q_{1A}) > g(w_1, q_{1A} + q_{1B})$.

We know that $\frac{\partial \pi_2(w_2, q_2^*)}{\partial q_2 \partial q_2} < 0$ (concavity condition) and $\frac{\partial \pi_2(w_2, q_2^*)}{\partial q_2 \partial w_2} > 0$ (by definition). Therefore, we can deduce that $q_{2A}^* > q_{2A}^{**}$. How?

An increase in w_2 increases the value of $\frac{\partial \pi_2(w_2, q_2^*)}{\partial q_2}$. However, an increase in

q_2 decreases $\frac{\partial \pi_2(w_2, q_2^*)}{\partial q_2}$. Since $w_2^1 > w_2^2$, q_{2A}^* must exceed q_{2A}^{**} so that (20.6)

holds. If $q_{2A}^* = q_{2A}^{**}$, then $\frac{\partial \pi_{2A}(g(w_1, q_{1A}), q_2^*)}{\partial q_{2A}} < \frac{\partial \pi_{2A}(g(w_1, q_{1A} + q_{1B}), q_2^{**})}{\partial q_{2A}}$ which

violates (20.6).

We continue on our proof that $q_{1A}^* < q_{1A}^{**}$

Equation (20.3) can be rewritten as

$$(21.1) \quad \frac{\partial \pi^1}{\partial q_{1A}} = \frac{\partial \pi_1^1}{\partial q_{1A}} - \delta \left(\frac{\partial g(w_1, q_{1A})}{\partial q_{1A}} \frac{\partial \pi_2^1(w_2, q_2^*)}{\partial w_2} \right) = 0$$

For the two firm case,

$$(21.2) \quad \frac{\partial \pi^2}{\partial q_{1A}} = \frac{\partial \pi_1^2}{\partial q_{1A}} - \delta \left(\frac{\partial g(w_1, q_{1A}, q_{1B})}{\partial q_{1A}} \frac{\partial \pi_2^2(w_2, q_2^{**})}{\partial w_2} \right) = 0$$

The marginal impact of antibiotic sales by firm A remains unchanged even with firm B's production, if

$$(22.1) \quad \frac{\partial g(w_1, q_{1A}, q_{1B})}{\partial q_{1A}} = \frac{\partial g(w_1, q_{1A})}{\partial q_{1A}}$$

But

$$(22.2) \quad \frac{\partial \pi_2^1(w_2^1, q_2^*(q_{1A}, w_1))}{\partial w_2} > \frac{\partial \pi_2^2(w_2^2, q_2^{**}(q_{1A}, w_1))}{\partial w_2}$$

since $w_2^1 > w_2^2$ and $q_2^*(q_{1A}, w_1) > q_2^{**}(q_{1A}, w_1)$, by earlier proof.

Therefore, from equations (21.1) and (21.2), we have

$$(23.1) \quad \frac{\partial \pi_1^1}{\partial q_{1A}} - \frac{\partial \pi_1^2}{\partial q_{1A}} = \delta \left(\frac{\partial g(w_1, q_{1A})}{\partial q_{1A}} \frac{\partial \pi_2^1(w_2, q_2^*)}{\partial w_2} \right) - \delta \left(\frac{\partial g(w_1, q_{1A}, q_{1B})}{\partial q_{1A}} \frac{\partial \pi_2^2(w_2, q_2^{**})}{\partial w_2} \right)$$

Combining this with equations (22.1) and (22.2), we have

$$(23.2) \quad \frac{\partial \pi_1^1}{\partial q_{1A}} - \frac{\partial \pi_1^2}{\partial q_{1A}} > 0$$

Recall that the greater the value of $\frac{\partial \pi_1}{\partial q_1}$, the greater the extent to which antibiotic production in period 1 is lower than the optimal in the absence of resistance. Therefore, equation (8.2) implies that the rate of antibiotic use in period 1 in the one firm case is lower and the corresponding rate for the two firm case, as illustrated in figure A.21.

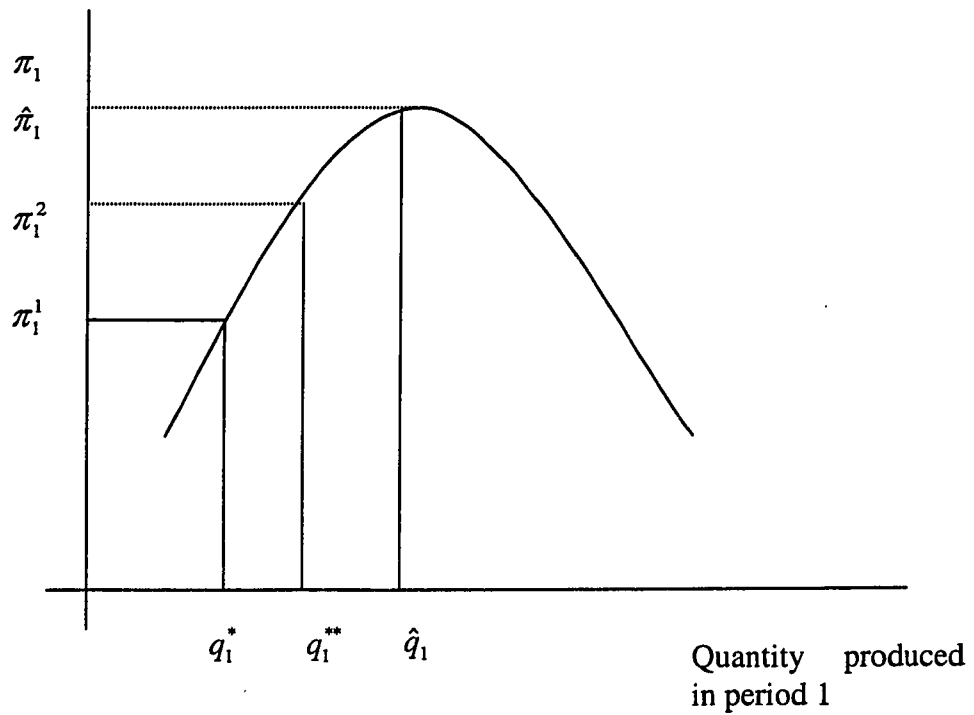


Figure A.21: Plot of first period profits made by incumbent in the absence of the resistance problem ($\hat{\pi}_1$) and for Cases 1 and 2.

Figure A.21 illustrates the essence of this proposition. In the absence of resistance, period 1's quantity set at \hat{q}_1 corresponding to $\frac{\partial \hat{\pi}_1}{\partial q_1} = 0$ since there is no incentive to conserve effectiveness for period 2. When we introduce the problem of resistance, use in the first period drops to q_1^* in recognition of the economic value of conserved effectiveness. With entry by other firms, the incentive to conserve effectiveness for period 2 is diminished. Therefore, production in period 1 increases to q_1^{**} since $\frac{\partial \pi_1^*}{\partial q_1} > \frac{\partial \pi_1^{**}}{\partial q_1}$.

Next, assume for a moment that the marginal impact of antibiotic use in humans on resistance is greater if they are also used in animals. Here, we are relaxing the assumption that effectiveness in the second period is a linear function of use in the first period and are allowing for a non-linear dose response relationship. Therefore equation (22.1) is now modified as

$$(24.1) \quad \frac{\partial g(w_1, q_{1A}, q_{1B})}{\partial q_{1A}} > \frac{\partial g(w_1, q_{1A})}{\partial q_{1A}}$$

From equations (24.1), (22.2) and (23.1) we see that the effect demonstrated in equation (23.2) is only enhanced. Introducing non-linearity to the dose-response function only increases the early depletion effect demonstrated earlier. Use of antibiotics as growth promoters not only increases overall resistance, but it also

has the effect of increasing the marginal impact of antibiotic use in humans on future resistance⁴⁴.

This implies that extending patent breadth decreases the rate of antibiotic use for humans in the first period, and has important policy implications in the case of antibiotic patents. Narrower patents for antibiotics would permit the use of antibiotics patented for use in humans as growth promoters in livestock. As noted in proposition 1, this encourages greater use of antibiotics in humans than would be the case when patents are so broad that they cover an entire class of antibiotics.

PROOF 1.2 FOR PROPOSITION 2

Turning to incentives for investment, the profit functions for the two cases where second period quantities are chosen optimally can be written as

(30.1)

$$\pi_A^1 = \pi_{1A}^1(w_1, q_{1A}) - c_{1A}q_{1A} - c(I^1) + \delta\pi_{2A}^1(g(w_1, q_{1A}), q_{2A}^*) - f(c_{1A}, I^1)q_{2A}$$

(30.2)

$$\pi_A^2 = \pi_{1A}^2(w_1, q_{1A}) - c_{1A}q_{1A} - c(I^2) + \delta\pi_{2A}^2(g(w_1, q_{1A}, q_{1B}), q_{2A}^{**}) - f(c_{1A}, I^2)q_{2A}$$

⁴⁴ The convexity of the dose-response relationship

When the patent awarded to the innovator is broad, and there is only one firm in the picture, the optimal level of investment to undertake in period 1 that reduces the marginal cost of production in period 2, is given by

$$(31.1) \quad \frac{\partial \pi_A^1}{\partial I^1} = -c'(I^1) - \delta \left(\frac{\partial f(c_{1A}, I^1)}{\partial I^1} q_{2A} \right) = 0$$

For the two firm case,

$$(31.2) \quad \frac{\partial \pi_A^2}{\partial I^2} = -c'(I^2) - \delta \left(\frac{\partial f(c_{1A}, I^2)}{\partial I^2} q_{2A} \right) = 0$$

From equations (31.1) and (31.2), we see that

$$(32.3) \quad -c'(I^1) - \delta \left(\frac{\partial f(c_{1A}, I^1)}{\partial I^1} q_{2A}^* \right) = -c'(I^2) - \delta \left(\frac{\partial f(c_{2A}, I^2)}{\partial I^1} q_{2A}^{**} \right)$$

$$(32.4) \quad c'(I^1) - c'(I^2) = \delta \left(\frac{\partial f(c_{2A}, I^2)}{\partial I^1} q_{2A}^{**} \right) - \delta \left(\frac{\partial f(c_{1A}, I^1)}{\partial I^1} q_{2A}^* \right)$$

First of all, the marginal impact on future production costs of period 1 investment is identical for the two cases. Further, any investment in the first period only reduces marginal production costs in the second period. Therefore

$$(32.5) \quad \frac{\partial f(c_{1A}, I^1)}{\partial I^1} = \frac{\partial f(c_{1A}, I^2)}{\partial I^2} < 0$$

Moreover, since $\frac{\partial \pi_{2A}^1}{\partial q_{2A}} = \frac{\partial \pi_{2A}^2}{\partial q_{2A}}$ and $q_{2A}^* > q_{2A}^{**}$, as shown earlier, the RHS of equation (32.4) is positive. Therefore,

$$c'(I^1) > c'(I^2)$$

Since $c'(I) > 0$, we have $I^1 > I^2$.

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