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Optimal Antibiotic Usage with Resistance and Endogenous Technological Change

Silvia Secchi
Iowa State University

Bruce A. Babcock
Iowa State University, babcock@iastate.edu

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Abstract
The use of antibiotics poses an impure public goods problem. Their utilization jointly generates a (positive) private characteristic, that is, the health of the individual who consumes the drug, and a (negative) public characteristic, that is, the reduction in susceptibility that renders the drug less effective over time. The authors use an expected utility model to explicitly identify these characteristics in a dynamic setting from a social planner perspective. The trade-off between present and future use of a drug and the allocation of resources to the development of new drugs is discussed. Results suggest that the optimal policy would limit the number of people treated with an existing antibiotic through time. Also, the model indicates that short bursts of high-level investment in research and development are optimal when the research process is certain, while a steady increase in investment over time is warranted when the discovery process is uncertain.

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Center for Agricultural and Rural Development
Iowa State University
Ames, Iowa 50011-1070
www.card.iastate.edu

Silvia Secchi is a postdoctoral research associate, Center for Agricultural and Rural Development, and Bruce A. Babcock is director, Center for Agricultural and Rural Development, and professor, Iowa State University.

For questions or comments about the contents of this paper, please contact Silvia Secchi, Center for Agricultural and Rural Development, 575 Heady Hall, Iowa State University, Ames, IA 50011-1070; Phone: 515-294-6173; Fax: 515-294-6336; E-mail: ssecchi@gcard.iastate.edu.

Abstract

The authors develop an expected utility model with heterogeneous individuals and apply some of the approaches developed in the energy literature to explicitly identify the public nature characteristics of susceptibility in a dynamic setting and to characterize the optimal intertemporal usage problem from a social planner perspective. The authors determine the optimal time path for the depletion of susceptibility to an existing drug and show that use of antibiotics should be rationed across the population and through time. The authors also discuss the impact of endogenous technological change and analyze the dynamics of research activities in backstop technologies both in a certain and in an uncertain world. The authors show that resources invested in R&D should increase through time if the discovery process is uncertain.

OPTIMAL ANTIBIOTIC USAGE WITH RESISTANCE AND ENDOGENOUS TECHNOLOGICAL CHANGE

Introduction

A recent review article in the *New England Journal of Medicine* stated that "the prevalence of antimicrobial-resistant human pathogens is rapidly increasing, but the discovery and development of new antimicrobial drugs that are active against multidrug-resistant organisms have slowed dramatically" (Gold and Moellering, p. 1446). As Table 1 shows, most of the antibiotic families known today were discovered in the 1940s, during the " antibiotic revolution" (Kingston).

More recently, discoveries have substantially slowed down: only one class, the quinolones, was discovered in the 1960s. A new class, the oxazolidinones, is presently undergoing clinical trials (Diekema and Jones).

The problem of resistance is not limited to bacteria; it also affects the treatment of viruses such as the ones responsible for AIDS (Fauci), and disease carriers, such as the *Anopheles* mosquito, which is a host for the malaria parasite. According to the World Health Organization and the World Bank, resistance is one of the main reasons why it has not been possible to eradicate malaria (World Health Organization/World Bank).[1]

The usage of these drugs[2] poses an impure public goods problem. Utilization jointly generates a (positive) private characteristic, which depends exclusively on the individual's consumption of the chemical, and a (negative) public characteristic, that is, the reduction in susceptibility. The magnitude of the reduction depends on the sum of all the individuals' use, both in the present and in the past, as in the case of an accumulating form of pollution. Susceptibility has a common-property nature because individual usage has a minimal impact on it; therefore, individuals tend to ignore the effect that their actions have on resistance. Susceptibility is a scarce resource, and although resistance

Table 1. Main antibiotic families and some of their characteristics

Family	Type	Usage	Date of First Discovery	Date of First Use
Aminoglycosides	Natural	Antitubercolosis agents	1944	1946
Cephalosporins	Natural	Broad spectrum	1945	1964
Chloranphenicol	Natural, synthetic	Broad spectrum	1947	1949
Macrolides	Natural	Pharyngitis, pneumonia	1952	1950s
Oxazolidinones	Synthetic	Broad spectrum	1987	Undergoing human trials
Penicillins	Natural, semi-synthetic	Broad spectrum	1929	1942
Quinolones	Synthetic	Broad spectrum	1962	1960s
Sulfonamides	Synthetic	Broad spectrum	1932	1935
Tetracyclines	Natural	Broad spectrum	1947	1966

Sources: Levy (1992); *Encyclopedia Britannica Online* (2000a, 2000b); Diekema and Jones; Kingston.

management plans that slow down resistance development are feasible, they can only reduce the impact of antibiotic usage on resistance development and not eliminate it.

In a first-best world, resistance buildup should affect optimal usage; benefits of antibiotic use in terms of improved health must be weighed against the costs of lower susceptibility in the future. Society also faces the decision of how many resources to invest in the discovery of new agents effective against the pest/microbe. Therefore, there is the need to examine the issues of resource allocation and availability of substitutes.

The objective of this paper is to explicitly identify the public nature characteristics of susceptibility in a dynamic setting and to characterize the optimal intertemporal usage problem from a social planner perspective. This allows us to discuss two essential social welfare issues. The first is the optimal number of people to treat while susceptibility to an existing drug lasts, that is, the trade-off between present and future use of a drug. The second issue is how many resources to allocate to the development of new drugs. The allocation of effort for the development of alternative technologies is an important social welfare issue, particularly in the case of pharmaceutical products because we are dealing with human health. The decision of how many resources to devote to research efforts

aimed at discovering new chemical compounds will depend on these activities' relative costs and benefits. These costs and benefits will in turn be a function of both stock and flow variables, such as the production costs of the chemicals, the level of susceptibility of the existing resource, and the overall amount of effort already spent on research.

Similarly, the determination of the optimal number of people to whom treatment should be administered is a significant issue, particularly because there is abundant anecdotal evidence of excessive and unnecessary usage of antimicrobials. According to the Centers for Disease Control and Prevention, for instance, around a third of the 150 million outpatient antibiotics prescribed each year are unneeded (Levy, 1998). Table 2 shows how some countries' antibiotic usage is much higher than others and includes a higher amount of broad spectrum antibiotics, for which the development of resistance is a greater concern. In Australia in particular, the situation has spurred various government inquiries (Doessel).[3]

Research on substitute technologies can be subdivided into two types: research on compounds similar to those already known, and basic research on new alternative technologies. The objective of the first type of activity is to discover antibiotics (or pesticides) that use a similar mode of action to those already known. This type of research is likely to involve a lower degree of uncertainty, since the existing drug provides a blueprint for scientists. Examples are the development of the semi-synthetic methicillin from penicillin, and the discovery of various pesticides all belonging to the same family, such as the chlorinated hydrocarbons, which include DDT, dieldrin, and endrin.

Table 2. Non-public sector antibiotic sales in 1983

Country	Defined Daily Dose[a] /1,000 Population/Day	Broad/Narrow Ratio
Sweden	7.01	1.72
UK	9.36	4.03
Canada	11.64	2.74
USA	13.22	2.07
Australia	17.12	4.69

Source: Doessel, 1998.
Note: Non-public sector sales exclude in-hospital use.
[a] The Defined Daily Dose is an aggregate measure of usage that allows comparisons.

In most of these cases, there is likely to be cross-resistance between the old and new compounds. Cross-resistance occurs when the development of resistance to a compound also confers at least partial resistance to another chemical, so that the second chemical is less effective than it would have been if it had been used first. The likelihood of cross-resistance depends on the fact that the chemicals have a similar mode of action or a resembling structure (Levy, 1992).

In the case of antibiotics, cross-resistance causes multidrug resistance to occur. This is a particularly dangerous phenomenon, because it can become impossible to treat an illness. The present emergence of multidrug-resistant tuberculosis worldwide is a case in point (Cohn, Bustreo, and Raviglione). Cross-resistance is particularly worrisome in antibiotics because resistance is transmitted from one strain of bacteria to another,[4] so that multidrug resistance in bacteria is the rule rather than the exception (Levy, 1992). Resistance has developed to all known antimicrobial drugs (Gold and Moellering) while, as we noted, the discovery of new classes of antibiotics has slowed down since the 1950s, making this a particularly important policy problem. According to the American Society for Microbiology (ASM), we are in an "incipient public health emergency, albeit one that is poorly appreciated and recognized" (ASM, p. 4).[5]

Resources can also be invested in the discovery of novel technologies, for which cross-resistance is not likely to be an issue. For example, vaccines are a cost-effective alternative to antibiotics. Other possible alternatives include both biospecific antibodies, which support the body's immune system in eliminating microbes, and bacteria-attacking viruses (Nemecek).[6]

In broad terms, the discovery of novel active ingredients and treatments is likely to involve a higher degree of pure research than the discovery of new antibiotics or pesticides that use a similar mode of action to those already known. Nowadays most pharmaceutical and chemical companies maintain substantial in-house research facilities,[7] and the traditional dichotomy of public sector/pure research and private sector/applied research is not clear-cut. However, the discovery of totally new compounds is likely to involve a high level of basic research, and this might have implications for both private and public research priorities and activities.

Both in the case of pests and of microorganisms, susceptibility could be modeled either as a nonrenewable or as a renewable resource. The choice impinges on the relative fitness of the resistant individuals compared to the susceptible ones. Should there be a fitness cost for the resistant organisms, it would tend to disappear once the usage of the chemical selecting for them had been stopped. There appears to be evidence that resistant bacteria do not suffer from any fitness cost (Stewart et al.).[8]

Limited literature exists on the common-property nature of susceptibility in the case of antibiotics. Tisdell provides a basic analysis, even though he frames the issue in terms of a prisoner's dilemma and not as a problem of the commons. Brown and Layton analyze the externalities involved in the use of antibiotics as growth promoters for animals, with a focus on the trade-offs. Both farmers and sick individuals choose the optimal level of medication, taking resistance as given, thereby overutilizing the antibiotic. Laxminarayan and Brown examine how to optimally utilize two antibiotics with different impacts on resistance without incorporating the development of backstop technologies, in a problem similar to that of the mining of various deposits of ore of different quality. Kile models the R&D expenditure in the private sector as a function of resistance. He finds some evidence that increases in the levels of resistance have a positive impact on the level of R&D expenditure, the rationale being that higher levels of resistance shorten the life span of existing drugs, so that their producers need to find alternative products.

Even though the economics literature has not focused on antibiotics use in optimal planning models, there is a large body of work on issues of common property and externalities in relation to exhaustible resources. Kamien and Schwartz (1982) provide an excellent literature review.

An extensive amount of economics literature, spurred by the energy crisis of the early 1970s, has analyzed the issues related to the use of a nonrenewable resource when the discovery of backstops is uncertain. Dasgupta and Heal's seminal paper (1974) analyzes the problem when there is uncertainty as to the date of discovery of the new, nonrenewable technology (and not on its characteristics). The probability of the discovery date is exogenous, and there are no investment efforts. They prove that in certain

circumstances the uncertainty is formally equivalent to an increase in the discount rate. Kamien and Schwartz (1978) and Dasgupta, Heal, and Majumdar extend the model to endogenize the level of investment that accelerates the time of discovery of the new technology. Davison uses essentially the same framework for the case in which the probability of discovering a backstop is a function of the flow of R&D and not its stock.

Next we develop an expected utility model with heterogeneous individuals and apply some of the approaches outlined in the energy literature to determine the optimal time path for the depletion of susceptibility to an existing drug. We assume that technological change is endogenous and analyze the dynamics of research in backstop technologies both in a certain and in an uncertain world.

The Basic Framework

When prescribing an antibiotic for an individual, the doctor or the manufacturer exogenously gives the dose. Therefore, we treat the choice of an individual drug as a discrete choice problem. Individuals are heterogeneous in their need for treatment, which allows analysis of the marginal impact of each treatment, the optimal number of individuals treated, and the externalities created by the increase in resistance induced by usage.

We will use the expected utility framework (Evans and Viscusi) to examine the issue of optimal use of antibiotics. We will also show how the model can be easily used for the case of pesticides. Preferences are quasilinear. Utility derived from the consumption of good *x* is contingent on good health, while utility obtained from the *numéraire* good *y* is independent of health. Therefore, each agent's utility is of the form: $a(x^i) + y^i$, where $a' > 0, a'' < 0$, and $\lim_{dx \to 0} a(x) = \infty$. Think of good *x* as any good that requires good health to provide positive utility; in bad health, the utility derived from *x* is zero (Fuchs and Zeckhauser).

The economy is either based on endowments or is such that the supply of labor is fixed over time: each individual *i* is given an identical endowment/wage *m* at each time *t.* In each time period each individual also faces a lump sum tax t to finance activities that prevent the buildup of resistance and the research in backstop technologies. We limit

ourselves to the case in which t is identical for everybody. This is consistent with the public nature of susceptibility and with the fact that the level of infection is independent of agents' actions. Alternatively, we could think that taxes are set *ex ante*, before people get sick, and, *ex ante*, individuals are identical in every respect.

Individuals maximize instantaneous utility. As discussed in more detail below, individuals cannot use their past sickness as a predictor for the future, and the development of resistance has a public good nature; thus each individual takes the existing stock of susceptibility E as given and his or her contribution to resistance development as negligible. There is no 'golden glow' effect on the part of untreated individuals with respect to the health levels of others in the economy, and susceptibility has no option value. We define treatment for individual i as $e^i = 1$ and the no treatment case as $e^i = 0$, with p as the price of the antibiotic. We assume that the marginal cost of production, ?, is constant, and the pharmaceutical industry is perfectly competitive[9], so that $p = ?$.[10]

The budget constraint for each agent is then $x^i + y^i + t + pe^i = m$. We can then rewrite the utility function as $a(x^i) + m - x^i - pe^i - t$.[11] Agents maximize expected utility:

$$EU^i = \Pr(\text{healthy})\left[a(x^i) + m - x^i - pe^i - t\right] + \Pr(\text{sick})\left[m - x^i - pe^i - t\right], \text{ and}$$

$$EU^i = \Pr(\text{healthy})a(x^i) + m - x^i - pe^i - t.$$

More specifically, we assume that the probability of being healthy for untreated agents is determined by an exogenous parameter $q^i \in \mathbb{N}, q^i \in [0, n]$,[12] which represents the severity of the infection. At 0, the agent is healthy; at n he is the sickest in the population, which has size $n + 1$. We assume that the sicker a person is, the less likely he is to recover without treatment. Therefore, the probability is a function of ?: pr(no recovery) = p(?), with p'(?) > 0, and pr(recovery) = 1 – p(?). In particular, to calculate explicit results, we will assume that pr(no recovery) = θ^2/n^2 and pr(recovery) =1 – (θ^2/n^2). We will also assume that, in each period of time, the probability that a particular individual is assigned a certain q^i is independent of the q^i of the previous period, so that neither the government nor the agents can use past sickness as a predictor.[13] This formulation therefore implies that the level of resistance each individual faces at any

point in time is the same and independent from each person's medical history. This is consistent with the fact that resistance spreads easily from one bacterium to another (Levy, 1992). Therefore, we can write

$$EU^i(m,q^i) = \left(1-\frac{q^2}{n^2}\right)a(x^i) + \frac{q^2}{n^2}0 + m - x^i - t = a(x^i) - \frac{q^2}{n^2}a(x^i) + m - x^i - t\ . \qquad (1)$$

If agents receive treatment for their infection, their expected utility is no longer a function of the severity of the infection. Recovery depends on whether the infecting mechanism is susceptible to the treatment: the higher the level of susceptibility, the higher the probability of recovery. We normalize the stock of susceptibility *E* to the [0, 2^n-1] interval, and assume that the probability of recovering is $\frac{\ln(1+E)}{n\ln(2)}$, and the probability of no recovery is $1-\frac{\ln(1+E)}{n\ln(2)}$. If the treatment is effective, once again $U^i = a(x^i) + m - x^i - p - t$. If the treatment does not work, utility from *x* once again equals zero. Therefore,

$$EU^i(m,q^i) = \frac{\ln(1+E)}{n\ln(2)}\left[a(x^i) + m - x^i - p - t\right] + \left[1-\frac{\ln(1+E)}{n\ln(2)}\right]\left[0 + m - x^i - p - t\right],$$

and
$$EU^i(m,q^i) = \frac{\ln(1+E)}{n\ln(2)}a(x^i) + m - x^i - p - t. \qquad (2)$$

The agents' maximization then consists of a discrete choice problem:

$$EU^i(m,q^i,e^i=1) = \frac{\ln(1+E)}{n\ln(2)}a(x^i) + m - x^i - p - t,$$

versus

$$EU^i(m,q^i e^i=0) = \left(1-\frac{q^2}{n^2}\right)a(x^i) + \frac{q^2}{n^2}0 + m - x^i = a(x^i) - \frac{q^2}{n^2}a(x^i) + m - x^i - t,$$

$$\text{if } \frac{\ln(1+E)}{n\ln(2)}a(x^i) - p \geq a(x^i) - \frac{q^2}{n^2}a(x^i) \Rightarrow e^i = 1, \text{ and}$$

$$\text{if } \frac{\ln(1+E)}{n\ln(2)}a(x^i) - p < a(x^i) - \frac{q^2}{n^2}a(x^i) \Rightarrow e^i = 0.$$

Therefore, for agents with a serious infection, for whom pr(sickness) = $(\theta^2/n) \rightarrow 1$, treatment will be worthwhile even if the efficacy of the treatment is low. More specifically, for the sickest individual in the population, for whom pr(sickness) = 1, it will always be worthwhile to undergo treatment as long as $\frac{\ln(1+E)}{n\ln(2)}a(x^i) > p$:[14]

$$EU^i(m,n,e^i=1) = \frac{\ln(1+E)}{n\ln(2)}a(x^i) + m - x^i - p - t > EU^i(m,n,e^i=0) = m - x^i - t\ .$$

In a world of decentralized choices, the marginal individual is the one for whom

$$\frac{\ln(1+E)}{n\ln(2)}a(x^i) - p = a(x^i) - \frac{q_I^2}{n^2}a(x^i), \text{ that is,}$$

$$q_I = n\sqrt{1 + \frac{p}{a(x^i)} - \frac{\ln(1+E)}{n\ln(2)}}.$$

In this simple formulation, we are ignoring the fact that, at least in Western countries, antibiotics are not available over the counter, and a doctor must prescribe the medicine. One simple way to accommodate this would be to introduce a floor on the level of q^i below which doctors will not treat the patient, q_D^i. Given the evidence of antibiotic over-prescription discussed in the introduction, however, it is reasonable to assume that in practice this constraint does not bind: $q_D^i > q_I^i$.

The stock of susceptibility to antibiotics or pesticides used until time *t*, denoted by *E*, is such that its behavior through time can be described by the following equation of motion:

$$\dot{E} = \frac{-w\sum_{i=0}^{n+1} e^i}{\mathrm{P}+1}, \tag{3}$$

where *?* is the marginal impact of individual usage on resistance development, and *P* is the amount spent in resistance management activities such as education on the risks of resistance. The preventive activity is financed by the lump sum taxes *t* levied on each individual in the community, so that $(n + 1)t = P$. In the medical literature, activities that

could be included in *P* range from *ex ante* prevention to *ex post* containment of the infection (Murray). They include education on the risks of resistance and on the appropriate use of the chemical; techniques through which the chemical is put to use, such as one-, three-, or ten-day antibiotic cycles (*ex ante*), and containment of the infection or of the resistant pest population (*ex post*).

This specification follows Brown and Layton in that the effect of antibiotic usage on the stock of susceptibility is linear. We will discuss some of the consequences of a nonlinear specification later. This characterization of the problem's dynamics indicates that the increase in resistance taking place in each period affects only the future effectiveness of the antibiotic. This lag is due to the fact that resistance takes some time to spread.

In this formulation, if there is no usage of the chemical, resistance management is ineffective. The reason is that resistance management is not independent from utilization of the drug, which is essentially a way to minimize the impact of usage on the development of resistance. This will ensure that the stock of susceptibility *E* is effectively a nonrenewable resource and that, at each point in time, *E* is such that $E \leq E_0$, where E_0 is the initial stock of the resource. We are implicitly assuming that the level of preventive activity *P* is always as high as possible. The rationale for this is twofold. First, the effects of preventive activities are certain and immediate, and the benefits derived from a correct use of antibiotics are not limited to the slowing down of resistance but include better health for the individuals treated. Taking a course of antibiotics correctly improves a patient's chances of recovery in addition to reducing resistance buildup. Secondly, *P* is in practice of limited effectiveness and cannot eliminate the development of resistance, so an analysis of its dynamics is of limited interest.

Increases in the antibiotic price *p*, will decrease the number of people taking the medicine, because if $p_0 > p_1$,

$$q_I^0 = n\sqrt{1+\frac{p_0}{a(x^i)}-\frac{\ln(1+E)}{n\ln(2)}} \text{ and}$$

$$q_I^1 = n\sqrt{1+\frac{p_1}{a(x^i)}-\frac{\ln(1+E)}{n\ln(2)}}, \text{ so}$$

$$q_I^0 - q_1^1 = n\sqrt{1+\frac{p_0}{a(x^i)}-\frac{\ln(1+E)}{n\ln(2)}} - n\sqrt{1+\frac{p_1}{a(x^i)}-\frac{\ln(1+E)}{n\ln(2)}} > 0.$$

This is an expected result. It indicates that the magnitude of the change in *p* that would be needed to bring down overuse depends on $\frac{p_0}{a(x^i)}$, the real price of the medicine in utility terms. If income is large compared to the cost of the antibiotic, as is typically the case in Western countries, very large increases in price will be needed to substantially decrease overuse.

In a decentralized world, there is overuse of the antibiotic, but usage decreases with time as efficacy decreases. The socially optimal marginal individual is the one for whom

$$\frac{\ln(1+E)}{n\ln(2)}a(x^i) - p - m\frac{w}{\mathrm{P}+1} = a(x^i) - \frac{q_S^2}{n^2}a(x^i), \text{ that is,}$$

$$q_S = n\sqrt{1+\frac{p}{a(x^i)}-\frac{\ln(1+E)}{n\ln(2)}+m\frac{w}{a(x^i)(\mathrm{P}+1)}}.$$

And it is evident that

$$q_S > q_I = n\sqrt{1+\frac{p}{a(x^i)}-\frac{\ln(1+E)}{n\ln(2)}}.$$

This is similar to Brown and Layton's characterization. The difference between the social optimum and the decentralized case is given by the shadow value of susceptibility times the individual effective impact of usage on resistance, $\frac{w}{(\mathrm{P}+1)}$, weighted by the utility of consuming good *x*, $a(x^i)$. The higher the utility derived from the consumption

of good *x* which might be foregone if the agent is sick, the closer $?_S$ is to $?_I$, because the benefits of using the antibiotic in the present (the costs of delaying usage) are higher. As for the decrease in usage in the decentralized case,

$$\frac{\Delta q_I}{\Delta E} = -\frac{1}{2\ln(2)(1+E)}\left(1+\frac{p}{a(x^i)}-\frac{\ln(1+E)}{n\ln(2)}\right)^{-1/2} < 0.$$

First Scenario: No Substitutes for the Antibiotic

We start by discussing the simplest case. In this scenario, there are no alternatives to the antibiotic, and resistance management is the only activity that can slow down the mining of susceptibility. This is not necessarily a realistic scenario, because it assumes that no technological change is possible, but it is useful in setting the stage for the problem. The social planner seeks to maximize[15]

$$\underset{e^i \forall i}{\text{Max}} \int_0^{\infty}\left[\sum_{i=0}^{g} EU^i(\text{untreated}) + \sum_{i=g+1}^{n+1} EU^i(\text{treated})\right] e^{-rt},$$

$$\text{s.t. } \dot{E} = \frac{-w(n-g)}{\text{P}+1}.$$

Assuming that *n* is large, so that the proportion of population not taking the drug, *?/n*, can be treated as a continuous variable, and remembering that

$$\sum_{i=1}^{K} i^2 = \frac{1}{6}K(K+1)(2K+1),$$

we can reformulate the problem as

$$\underset{\frac{g}{n}}{\text{Max}} \sum_{i=0}^{g} EU^i(\text{untreated}) + \sum_{i=g+1}^{n+1} EU^i(\text{treated}).$$

We can rearrange the maximand as follows:

$$\sum_{i=0}^{g}\left[\left(1-\frac{q^2}{n^2}\right)a(x^i)+m-x^i-t\right]+\sum_{i=g+1}^{n+1}\left[\frac{\ln(1+E)}{n\ln(2)}a(x^i)+m-x^i-p-t\right]=$$

$$(g+1)a - \frac{g(g+1)(2g+1)}{6n^2}a + (g+1)(m - x^i - t) + \frac{\ln(1+E)}{n\ln(2)}(n-g)a$$
$$+(n-g)(m - x^i - p - t) =$$

$$(g+1)a - \frac{g(g+1)(2g+1)}{6n^2}a + \frac{\ln(1+E)}{n\ln(2)}(n-g)a + (n+1)(m - x^i) - p(n-g) - (n+1)t =$$

$$(g+1)a - \frac{g(g+1)(2g+1)}{6n^2}a + \frac{\ln(1+E)}{n\ln(2)}(n-g)a + (n+1)(m - x^i) - p(n-g) - \mathrm{P}.$$

In this problem the presence of a positive discount rate for the future, *r*, is a debatable assumption. As Ramsey wrote, the discounting of future generations is "ethically indefensible and [originating] merely from the weakness of the imagination" (Ramsey, p. 543). We can view this as a general formulation of the problem that allows for the particular case of $r = 0$.[16] The present-value Hamiltonian is then

$$H = \left[(g+1)a - \frac{g(g+1)(2g+1)}{6n^2}a + (n-g)\frac{\ln(1+E)}{n\ln(2)}a + (n+1)(m - x^i) - p(n-g) - \mathrm{P}\right]e^{-rt}$$
$$-m\frac{w(n-g)}{\mathrm{P}+1}.$$

We rewrite the Hamiltonian in terms of the proportion of people treated:

$$H = \int_0^{\infty}\left[\left(\frac{g}{n}n+1\right)a - \frac{\left(\frac{g}{n}n\right)\left(\frac{g}{n}n+1\right)\left(2\frac{g}{n}n+1\right)}{6n^2}a \cdot \right.$$
$$\left. +\left(n-\frac{g}{n}n\right)\frac{\ln(1+E)}{n\ln(2)}a + (n+1)(m - x^i) - p\left(n-\frac{g}{n}n\right) - \mathrm{P}\right]e^{-rt} - m\frac{w\left(n-\frac{g}{n}n\right)}{\mathrm{P}+1}.$$

We can simplify this to

$$H = \int_0^{\infty} \left[\begin{array}{l} \left(\frac{g}{n}n+1\right)a - \left[\left(\frac{g}{n}\right)^3\frac{n}{3}+\left(\frac{g}{n}\right)^2\frac{1}{2}+\left(\frac{g}{n}\right)\frac{1}{6n}\right]a - \mathrm{P} \\ +\left(1-\frac{g}{n}\right)\frac{\ln(1+E)}{\ln(2)}a + (n+1)(m-x^i) - pn\left(1-\frac{g}{n}\right) \end{array} \right] e^{-rt} \qquad (4)$$
$$-m\frac{nw\left(1-\frac{g}{n}\right)}{\mathrm{P}+1}.$$

The first-order conditions are

$$0 = \frac{\partial H}{\partial g/n} = \left[na - \left[\left(\frac{g}{n}\right)^2 n + \left(\frac{g}{n}\right) + \frac{1}{6n}\right]a - \frac{\ln(1+E)}{\ln(2)}a + np \right] e^{-rt} + mn\frac{w}{\mathrm{P}+1}, \qquad (5)$$

$$m = \frac{\mathrm{P}+1}{w}\left[-a + \left[\left(\frac{g}{n}\right)^2 n + \left(\frac{g}{n}\right) + \frac{1}{6n}\right]\frac{a}{n} + \frac{\ln(1+E)}{n\ln(2)}a - p \right] e^{-rt}, \qquad (6)$$

$$\dot{m} = -\frac{\partial H}{\partial E} = -\left(1-\frac{g}{n}\right)\frac{a}{(1+E)\ln(2)}e^{-rt}. \qquad (7)$$

PROPOSITION 1. *The proportion of untreated people increases over time if the discount rate is positive.*

Proof. We take the derivative of (6) with respect to time, and equate it to (7):

$$\dot{m} = \frac{\mathrm{P}+1}{w}\left\{ \left[2\left(\frac{g}{n}\right)n+1 \right]\frac{a}{n}\left(\frac{\dot{g}}{n}\right) - \frac{a}{n(1+E)\ln(2)}\frac{w(n-g)}{\mathrm{P}+1} \right\} e^{-rt}$$
$$-r\frac{\mathrm{P}+1}{w}\left\{ -a + \left[\left(\frac{g}{n}\right)^2 n + \left(\frac{g}{n}\right) + \frac{1}{6n}\right]\frac{a}{n} + \frac{\ln(1+E)}{n\ln(2)}a - p \right\} e^{-rt},$$

and because $\dot{m} = -\frac{\partial H}{\partial E} = -\left(1-\frac{g}{n}\right)\frac{a}{(1+E)\ln(2)}e^{-rt}$, we can write

$$\left[2\left(\frac{g}{n}\right)n+1\right]\frac{a}{n}\left(\frac{\dot{g}}{n}\right)=r\left\{-a+\left[\left(\frac{g}{n}\right)^{2}n+\left(\frac{g}{n}\right)+\frac{1}{6n}\right]\frac{a}{n}+\frac{\ln(1+E)}{n\ln(2)}a-p\right\} \qquad (8)$$

This result implies that, if the discount rate is zero, the optimal policy is to have a constant percentage of the population receiving treatment through time. The level of social welfare will, however, decrease over time as the efficacy of the antimicrobial declines. If, on the other hand, $r > 0$, then $\left(\frac{\dot{g}}{n}\right)\geq 0$, as the term in brackets is positive.

Note the result that $\dot{g}=0$ for $r=0$ is independent from the specification of the dynamics of resistance but depends on resistance development being linear. We could see resistance buildup as exponential, because resistance in bacteria is transferred not only via reproduction but also through gene exchange. Therefore, "One [surviving bacterium] can produce new copies of itself, as well as recruit new resistant neighbors" (Levy 1992, p. 78), and resistance spreads faster as more people are treated. If the erosion of susceptibility is specified as $\dot{E}=-\frac{\exp\left[w\left(n-g\right)\right]}{\mathrm{P}+1}$, individual use has increasingly high costs in terms of resistance. In this case, the optimal policy would be to increase the proportion of untreated people through time, even if the discount rate is zero. Therefore, the conclusion that, when the discount rate is zero, the optimal policy is to have a constant percentage of the population receiving treatment is a conservative one.

Second Scenario: The Existence of Certain Exhaustible Substitutes

In this case, we will assume that there exists an alternative technology to the original antibiotic. Specifically, it is possible to develop another antibiotic that is superior technologically to the existing one because it mines susceptibility more slowly than the original one. That is, the new chemical has a lower impact on resistance: $w_1 > w_2$, where w_1 is the impact of the old technology on resistance and w_2 is the impact of the new one. The development of this substitute is certain but it requires investment in a capital stock. The structure of this model is similar to that of the second model developed by Vousden

in the case of oil. We have three control variables: $\frac{g}{n}$; the proportion of people treated with the new chemical, $\frac{d}{n}$; and the level of investment, *I*. Two state variables are *E* and the capital stock *K*. Investment increases capital, so that $\dot{K} = f(I)$, and $f' > 0$, $f'' < 0$, and investment presents increasing marginal costs because of the nature of the research and development process, so the cost of investment, $g(I)$, is such that $g' > 0$, $g'' > 0$. Because of the quasilinearity of the utility functions, the formulation is the same whether we assume that agents treated with the newer antibiotics still pay the same price *p* and the government finances the difference or whether agents pay the full price for the newer treatment. Initially, the costs of using a new drug are very high: clinical trials require expensive Food and Drug Administration approvals and are conducted by highly trained medical personnel. In addition to that, the production of new drugs itself is often very costly. As more resources are invested in the research of the new drug, costs decline. Therefore, we model the cost of the new antibiotic as an increasing function of the number of people treated with it, *d*, and a decreasing function of the level of capital *K*: $c(d, K)$, such that $c_1(d, K) > 0$, $c_2(d, K) < 0$, $c_{11}(d, K) > 0$, $c_{22}(d, K) > 0$, $c_{12}(d, K) < 0$ for *d* and $K > 0$, $c(d, 0) = c_2(d, 0) = 8$, and $c(0, K) = c_1(0, K) = c_{11}(0, K) = 0$. Note that there is no capital depreciation, so the nonnegativity constraint for capital is always satisfied. For simplicity, we will assume that $K_0 = 0$. The social planner problem is then

$$\underset{\frac{g}{n},\frac{d}{n},I}{\text{Max}} \int_0^{\infty} \left\{ \left[\begin{array}{l} \left(\frac{g}{n}n+1\right)a - \left[\left(\frac{g}{n}\right)^3\frac{n}{3} + \left(\frac{g}{n}\right)^2\frac{1}{2} + \left(\frac{g}{n}\right)\frac{1}{6n}\right]a \\ + \frac{\ln(1+E)}{\ln(2)}\left(1-\frac{g}{n}\right)a \\ +(n+1)(m-x^i) - p\left(n-\frac{g}{n}n\right) - \mathrm{P} - c\left(\frac{d}{n}n, K\right) - g(I) \end{array} \right] \right\} e^{-rt}dt,$$

$$\text{s.t. } \dot{E} = \frac{-w_1\left(n - \frac{g}{n}n - \frac{d}{n}n\right) - w_2\left(\frac{d}{n}n\right)}{\mathrm{P}+1},$$
$$\dot{K} = f(I).$$

The Hamiltonian is

$$H = \begin{bmatrix} \left(\frac{g}{n}n+1\right)a - \left[\left(\frac{g}{n}\right)^3\frac{n}{3} + \left(\frac{g}{n}\right)^2\frac{1}{2} + \left(\frac{g}{n}\right)\frac{1}{6n}\right]a + \frac{\ln(1+E)}{\ln(2)}\left(1-\frac{g}{n}\right)a \\ +(n+1)(m-x) - p\left(n - \frac{g}{n}n\right) - \mathrm{P} - c\left(\frac{d}{n}n, K\right) - g(I) \end{bmatrix} e^{-rt} \\ +m\frac{-w_1\left(n - \frac{g}{n}n - \frac{d}{n}n\right) - w_2\left(\frac{d}{n}n\right)}{\mathrm{P}+1} + u\,f(I). \tag{9}$$

The first-order conditions are

$$0 = \frac{\partial H}{\partial g/n} = \left[na - \left[\left(\frac{g}{n}\right)^2 n + \left(\frac{g}{n}\right) + \frac{1}{6n}\right]a - \frac{\ln(1+E)}{\ln(2)}a + np\right]e^{-rt} + mn\frac{w_1}{\mathrm{P}+1}, \tag{10}$$

that is,

$$m = \frac{\mathrm{P}+1}{w_1}\left[-a - p + \left[\left(\frac{g}{n}\right)^2 n + \left(\frac{g}{n}\right) + \frac{1}{6n}\right]\frac{a}{n} + \frac{\ln(1+E)}{n\ln(2)}a\right]e^{-rt}, \tag{11}$$

$$0 \geq \frac{\partial H}{\partial I} = -g'(I)e^{-rt} + u\,f'(I), \tag{12}$$

$$0 \geq \frac{\partial H}{\partial d/n} = -nc_1\left(\frac{d}{n}n, K\right)e^{-rt} + mn\frac{w_1 - w_2}{\mathrm{P}+1}, \tag{13}$$

$$\dot{m} = -\frac{\partial H}{\partial E} = -\left(1-\frac{g}{n}\right)\frac{a}{(1+E)\ln(2)}e^{-rt}, \tag{14}$$

$$\dot{u} = -\frac{\partial H}{\partial K} = c_2\left(\frac{d}{n}n, K\right)e^{-rt}. \tag{15}$$

Note that (10) is the same condition as in the first scenario (no technological change) as long as $w = w_1$ (see equation [5]).

If $-nc_1\left(\frac{d}{n}n, K\right)e^{-rt} + mn\frac{w_1 - w_2}{\mathrm{P}+1} = 0$, then $m = \frac{\mathrm{P}+1}{w_1 - w_2}c_1\left(\frac{d}{n}n, K\right)e^{-rt}$.

PROPOSITION 2. *The dynamic path of the proportion of untreated people is the same as in the first scenario if the impact of the existing antibiotic on resistance is the same ($w = w_1$). This is due to the fact that the optimal policy is independent from the distribution of wealth.*

Proof. We take the derivative of (10) with respect to time, and equate it to (11):

$$\dot{m} = \frac{\mathrm{P}+1}{w_1}\left\{\left[2\left(\frac{g}{n}\right)n + 1\right]\frac{a}{n}\left(\frac{\dot{g}}{n}\right) - \frac{a}{n(1+E)\ln(2)}\frac{w_1(n-g)}{\mathrm{P}+1}\right\}e^{-rt}$$

$$-r\frac{\mathrm{P}+1}{w_1}\left\{-a + \left[\left(\frac{g}{n}\right)^2 n + \left(\frac{g}{n}\right) + \frac{1}{6n}\right]\frac{a}{n} + \frac{\ln(1+E)}{n\ln(2)}a - p\right\}e^{-rt}, \text{ and also,}$$

$$\dot{m} = -\frac{\partial H}{\partial E} = -\left(1 - \frac{g}{n}\right)\frac{a}{(1+E)\ln(2)}e^{-rt}, \text{ therefore}$$

$$\left[2\left(\frac{g}{n}\right)n + 1\right]\frac{a}{n}\left(\frac{\dot{g}}{n}\right) = r\left\{-a + \left[\left(\frac{g}{n}\right)^2 n + \left(\frac{g}{n}\right) + \frac{1}{6n}\right]\frac{a}{n} + \frac{\ln(1+E)}{n\ln(2)}a - p\right\}. \quad (16)$$

PROPOSITION 3. *Investment declines over time if the discount rate is zero. If the discount rate is positive, the time path of investment will depend on the importance that the stock of capital has on the reduction in the cost of producing the new drug.*

Proof. Investment will not start as long as $g'(0)e^{-rt} > u\,f'(0)$. Once

$g'(I)e^{-rt} - u\,f'(I) = 0$,

$$\dot{u} = \frac{g''(I)f'(I) - g'(I)f''(I)}{[f'(I)]^2}\dot{I}\,e^{-rt} - r\frac{g'(I)}{f'(I)}e^{-rt}, \text{ and } \dot{u} = c_2(d, K)e^{-rt}, \text{ therefore}$$

$$\dot{I} = \frac{[f'(I)]^2}{g''(I)f'(I) - g'(I)f''(I)}\left[c_2(d,K) + r\frac{g'(I)}{f'(I)}\right]. \tag{17}$$

If $|c_2(d,K)| > r\frac{g'(I)}{f'(I)}$, investment will decline over time. In this case, because the benefits of investment are certain, the level of investment will be initially high, so that its benefits can be captured as soon as possible, and then taper off.

The start of investment will not, in general, coincide with the beginning of use of the new technology. The date at which sufficient capital has been accumulated to make use of the new technology economically viable will depend on the structure of the cost function *c*. Specifically, treatment with the new technology will be delayed as long as $c_1 > m\frac{w_1 - w_2}{\mathrm{P}+1}e^{rt}$. If, for low levels of capital stock, the marginal cost of treating even very few patients is high, adoption of the technology will be deferred. Figure 1 suggests a possible cost structure. For levels of capital below K_0, the cost of treatment is prohibitively high.

PROPOSITION 4. *The time path of the proportion of agents treated with the new antibiotic depends on the net effect of a capital increase in the cost of administering the new drug and the impact of the use of the new drug on resistance.*

Proof. We rearrange (13) and take its derivative with respect to time, and equate it to (11):

$$\dot{m} = \frac{\mathrm{P}+1}{w_1 - w_2}\left[c_{11}\left(\frac{d}{n}n,K\right)\left(\frac{\dot{d}}{n}\right)n + c_{12}\left(\frac{d}{n}n,K\right)f(I) - rc_1\left(\frac{d}{n}n,K\right)\right]e^{-rt}, \text{ and}$$

$$\dot{m} = -\frac{\partial H}{\partial E} = -\left(1-\frac{g}{n}\right)\frac{a}{(1+E)\ln(2)}e^{-rt}, \text{ therefore}$$

$$\left(\frac{\dot{d}}{n}\right) = -\frac{c_{12}}{c_{11}n}f(I) + r\frac{c_1}{c_{11}n} - \frac{w_1 - w_2}{\mathrm{P}+1}\left(1-\frac{g}{n}\right)\frac{a}{c_{11}n(1+E)\ln(2)}. \tag{18}$$

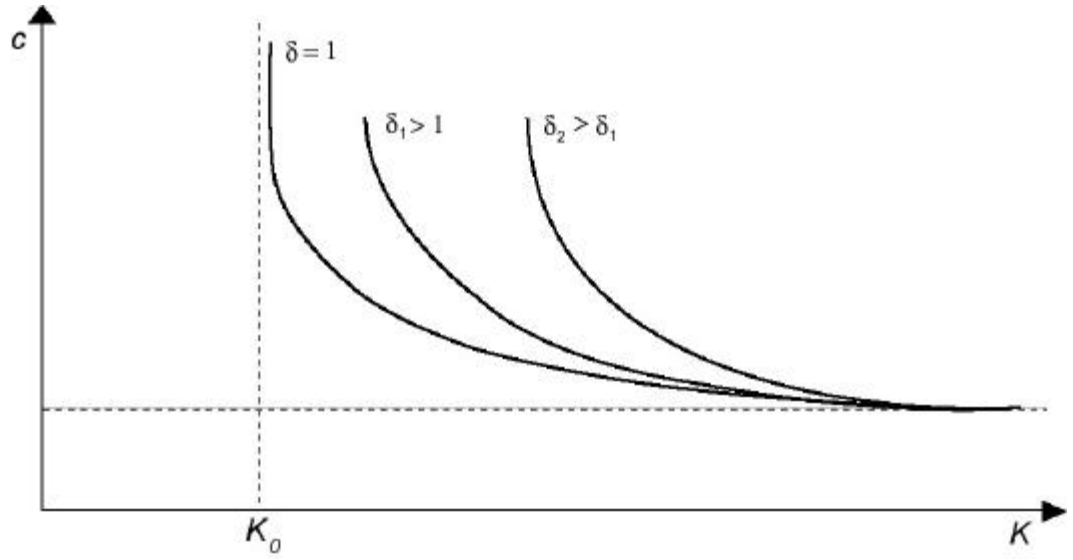

FIGURE 1. A possible structure of the cost function for the new technology

The long-run behavior of the percentage of population treated with the new technology will depend on the difference between the reduction in costs brought about by a capital increase and the net effect of the use of the new drug on resistance buildup. Figure 2 shows a possible path for the portion of people treated with the old and new chemical, with a positive interest rate, and $(\dot{d}/n) > 0$ globally. In this case, since the number of untreated people keeps increasing, as does the number of people treated with the second antibiotic, the slope of the latter must be flatter, or $\dot{d} < \dot{g}$. If, on the other hand, the discount rate for the future were zero, the number of untreated people would be constant but the number of people treated with the new antibiotic might still increase through time, albeit more slowly (see [18]).

Third Scenario: Uncertain Nonrenewable Substitutes

In this scenario, the discovery of a backstop technology is not certain, and the probability of developing a new (nonrenewable) technology is endogenous, depending positively on the cumulative amount of R&D effort. We suppose that the new technology is a real breakthrough, so that it renders the stock of susceptibility remaining at the time of the discovery

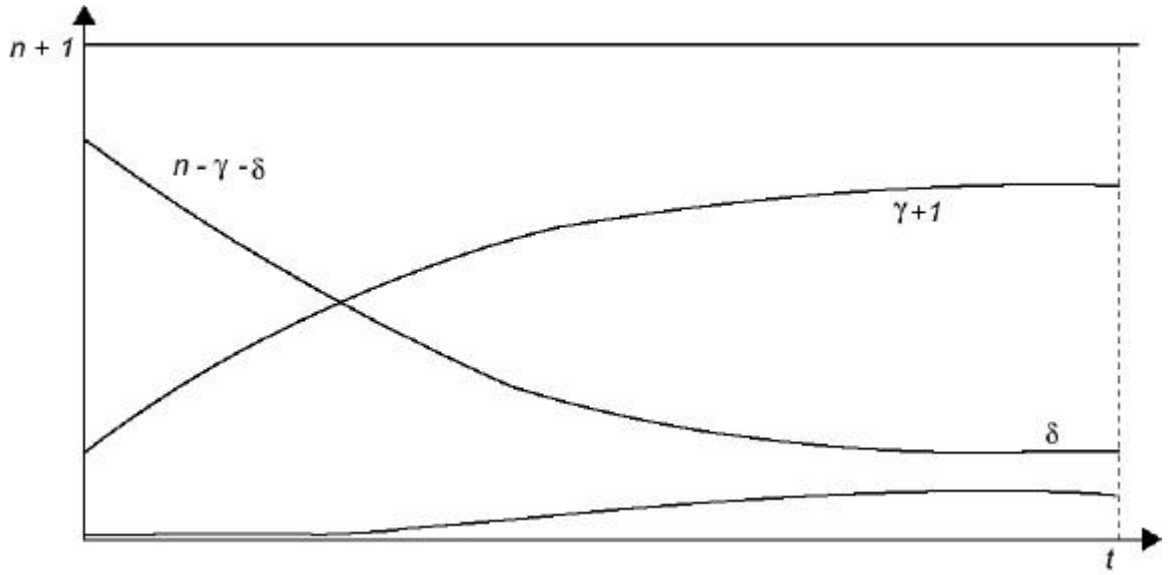

FIGURE 2. Treatment with a positive discount rate in the second scenario

worthless. A good example would be the discovery of "biospecific antibodies," which recognize harmful bacteria and take them to the human cells that can eliminate them (Nemecek). Define T as the time at which the new technology becomes available, and W as the maximum social welfare possible after the new technology is

$$W = \max \int_{T}^{\infty} \left(\sum_{i=1}^{n} U^i \right) e^{-r(t-T)} dt \,. \tag{19}$$

As we said above, the probability of discovering a backstop technology is endogenous, and depends positively on the cumulative amount of R&D effort. Define the level of R&D in each time period as I, and the cumulative level of R&D, or stock of knowledge capital, as K. We will assume that the dynamic relationship between stock and flow of knowledge has the same structure as in the previous scenario:

$$\dot{K} = g(I)\,, \tag{20}$$

$$\text{s.t.} \quad K(0) = 0,\ f(0) = 0, f' > 0,\ \text{and } f'' < 0.$$

We define the probability of discovering the backstop as $f(K)$. Expression $f(K)$ is such that $f(0)=0$, $f'(0)=0$, $f'\geq 0$, and $\lim_{z\to\infty} f(z)=1$. This is the same structure of the R&D function specified in Kamien and Schwartz (1978). The probability of discovering the new technology in the interval *dt* equals

$$df(K(t)) = f'(K(t))\dot{K}(t)dt = f'(K(t))f(I)dt\,.$$

In their seminal 1974 paper, Dasgupta and Heal prove that if $W_E = 0$, as we have assumed here, a certain kind of certainty equivalence results, so that the maximization can be rewritten as

$$\underset{\frac{g}{n},I}{\text{Max}} \int_0^{\infty} \left\{ \begin{bmatrix} \left(\frac{g}{n}n+1\right)a - \left[\left(\frac{g}{n}\right)^3\frac{n}{3}+\left(\frac{g}{n}\right)^2\frac{1}{2}+\left(\frac{g}{n}\right)\frac{1}{6n}\right]a \\ +\frac{\ln(1+E)}{\ln(2)}\left(1-\frac{g}{n}\right)a \\ +(n+1)(m-x)-p\left(n-\frac{g}{n}n\right)-\mathrm{P}-g(I) \end{bmatrix} \left(1-f(K)\right)+f'(K)f(I)W \right\} e^{-rt}dt,$$

$$\text{s.t. } \dot{E} = \frac{-w\left(n-\frac{g}{n}n\right)}{\mathrm{P}+1} \qquad \text{(multiplier } m\text{), and}$$

$$\dot{K} = f(I) \qquad \text{(multiplier } h\text{).}$$

The optimal control problem has two control variables: γ/n and *I*, and two state variables, *E* and *K*. In general terms, utilization of the antibiotic shall cease in finite time at, say, *T** because the susceptibility that makes it effective is nonrenewable. The presence of uncertainty might modify the optimal *T**, but, because the discovery of a backstop in the period [0, *T**] cannot be guaranteed, it might be the case that the susceptibility of the antibiotic is exhausted before an alternative technology is invented. We define the social welfare function before the introduction of the backstop as

$$\Gamma\left(\frac{g}{n}, I, E\right)=\left(\frac{g}{n}n+1\right)a-\left[\left(\frac{g}{n}\right)^3\frac{n}{3}+\left(\frac{g}{n}\right)^2\frac{1}{2}+\left(\frac{g}{n}\right)\frac{1}{6n}\right]a+\frac{\ln(1+E)}{\ln(2)}\left(1-\frac{g}{n}\right)a$$
$$+(n+1)(m-x)-p\left(n-\frac{g}{n}n\right)-\mathrm{P}-g(I).$$

Then the Hamiltonian is

$$H=\left\{\Gamma\left(\frac{g}{n}, I, E\right)(1-f(K))+f'(K)f(I)W\right\}e^{-rt}+m\frac{-w\left(n-\frac{g}{n}n\right)}{\mathrm{P}+1}+hf(I).$$

The first-order conditions are

$$0=\frac{\partial H}{\partial g/n}=\left[na-\left[\left(\frac{g}{n}\right)^2 n+\left(\frac{g}{n}\right)+\frac{1}{6n}\right]a-\frac{\ln(1+E)}{\ln(2)}a+np\right](1-f(K))e^{-rt}$$
$$+mn\frac{w}{\mathrm{P}+1}, \tag{21}$$

$$0\geq\frac{\partial H}{\partial I}=[-g'(I)](1-f(K))e^{-rt}+f'(K)f'(I)We^{-rt}+hf'(I), \tag{22}$$

$$h=\frac{g'(I)}{f'(I)}(1-f(K))e^{-rt}-f'(K)We^{-rt}, \tag{23}$$

$$\dot{h}=-\frac{\partial H}{\partial K}=f'(K)\Gamma\left(\frac{g}{n}, I, E\right)e^{-rt}-f''(K)f(I)e^{-rt}W, \tag{24}$$

$$\dot{m}=-\frac{\partial H}{\partial E}=-\left(1-\frac{g}{n}\right)\frac{a}{(1+E)\ln(2)}(1-f(K))e^{-rt}, \tag{25}$$

$$m=\frac{\mathrm{P}+1}{w}\left\{-a+\left[\left(\frac{g}{n}\right)^2 n+\left(\frac{g}{n}\right)+\frac{1}{6n}\right]\frac{a}{n}+\frac{\ln(1+E)}{n\ln(2)}a-p\right\}(1-f(K))e^{-rt}. \tag{26}$$

PROPOSITION 5. *The proportion of untreated people increases through time.*

Proof. We take the derivative of (26) with respect to time, and equate it to (25):

$$\dot{m} = \frac{\mathrm{P}+1}{w}\left\{\left[2\left(\frac{g}{n}\right)n+1\right]\frac{a}{n}\left(\frac{\dot{g}}{n}\right) - \frac{a}{n(1+E)\ln(2)}\frac{w(n-g)}{\mathrm{P}+1}\right\}\left(1-f(K)\right)e^{-rt}$$

$$-r\frac{\mathrm{P}+1}{w}\left\{-a+\left[\left(\frac{g}{n}\right)^2 n+\left(\frac{g}{n}\right)+\frac{1}{6n}\right]\frac{a}{n}+\frac{\ln(1+E)}{n\ln(2)}a-p\right\}\left(1-f(K)\right)e^{-rt}$$

$$-\frac{\mathrm{P}+1}{w}\left\{-a+\left[\left(\frac{g}{n}\right)^2 n+\left(\frac{g}{n}\right)+\frac{1}{6n}\right]\frac{a}{n}+\frac{\ln(1+E)}{n\ln(2)}a-p\right\}f'(K)f(I)e^{-rt}, \text{ and}$$

$$\dot{m} = -\frac{\partial H}{\partial E} = -\frac{(n-g)a}{n(1+E)\ln(2)}\left(1-f(K)\right)e^{-rt}, \text{ therefore}$$

$$\left[2\left(\frac{g}{n}\right)n+1\right]\frac{a}{n}\left(\frac{\dot{g}}{n}\right) = r\left\{-a+\left[\left(\frac{g}{n}\right)^2 n+\left(\frac{g}{n}\right)+\frac{1}{6n}\right]\frac{a}{n}+\frac{\ln(1+E)}{n\ln(2)}a-p\right\}$$
$$+\left\{-a+\left[\left(\frac{g}{n}\right)^2 n+\left(\frac{g}{n}\right)+\frac{1}{6n}\right]\frac{a}{n}+\frac{\ln(1+E)}{n\ln(2)}a-p\right\}\frac{f'(K)f(I)}{(1-f(K))}. \qquad (27)$$

Note that the first term is identical to the expression on the right-hand side of equations (8) and (16) in the certainty cases. In this case, however, if $r = 0$, then $(\dot{g}/n) > 0$, because we can rewrite (27) as

$$\left(\frac{\dot{g}}{n}\right) = \frac{w}{\mathrm{P}+1}\frac{m}{\left[2\left(\frac{g}{n}\right)n+1\right]\frac{a}{n}}\frac{f'(K)f(I)}{\left(1-f(K)\right)^2}e^{rt},$$

and m, the shadow value of susceptibility, is positive. The presence of uncertainty modifies a result that held for both the certainty cases. Because the date of discovery of an alternative technology is now unpredictable, the use of the existing technology is more prudent.

PROPOSITION 6. *The level of investment increases through time. The increase is higher if the discount rate is positive*.

Proof. We take the derivative of (23) with respect to time, and equate it to (24):

$$\dot{h} = \left[\frac{g''(I) f'(I) - g'(I) f''(I)}{f'(I)^2} \dot{I} \left(1 - f(K)\right) - \frac{g'(I)}{f'(I)} f'(K) f(I) - f''(K) f(I) W \right] e^{-rt}$$

$$-r \left[\frac{g'(I)}{f'(I)} \left(1 - f(K)\right) - f'(K) W \right] e^{-rt}, \text{ and}$$

$$\dot{h} = -\frac{\partial H}{\partial K} = f'(K) \Gamma\left(\frac{g}{n}, I, E\right) e^{-rt} - f''(K) f(I) W e^{-rt}, \text{ therefore}$$

$$\dot{I} = \frac{\left[f'(I)\right]^2}{g''(I) f'(I) - g'(I) f''(I)} \left\{ \begin{array}{l} \dfrac{f'(K)}{\left(1 - f(K)\right)} \left[\dfrac{g'(I) f(I)}{f'(I)} + \Gamma\left(\dfrac{g}{n}, I, E\right) \right] \\ + r \left[\dfrac{g'(I)}{f'(I)} - \dfrac{f'(K)}{\left(1 - f(K)\right)} W \right] \end{array} \right\}. \qquad (28)$$

Conclusions

The model's results on the use of existing antibiotics are, in general, extremely robust to changes in the specification of the nature of the research. They suggest that, no matter what the nature of the alternative technology to invest in, the optimal policy would limit the number of people treated with the existing antibiotic. In practice, however, it appears that the number of people treated with the existing antibiotics is on the increase, at least in Western countries. This is particularly worrisome in the context of the results of the last scenario, which suggest that if the nature of the discovery process is uncertain, the number of people treated should be restricted through time, even in the more intergenerationally equitable case of a zero discount rate for the future.

The model also indicates that if the research process is certain, short bursts of high-level investment might be optimal, while resources invested in R&D should increase through time if the discovery process is uncertain.

According to the American Society for Microbiology, in the mid 1990s, the short- and medium-term prospects of availability of new drugs were not very good. More recently, the report of the July 1997 workshop of the Forum on Emerging Infections, created by a joint initiative of the Centers for Disease Control and Prevention (CDC) and

the National Institute of Allergy and Infectious Diseases (NIAID), states that "Also, because general confidence in the existing antibiotic toolkit had muted any sense of urgency, there has been a distinct lag in producing new classes of antimicrobials, despite great advances in the fundamental science that is fueling pharmaceutical innovation in many other areas. This situation is changing, and the pharmaceutical industry has in the past few years expanded its investment substantially, but public-sector investment awaits reinvigoration. What is needed now is sustained, sufficient support—for basic pioneering research, for the clinical research required to move truly new products from the laboratory to the pharmacy, and for the infrastructure underpinning both" (Harrison and Lederberg). This quote suggests that research might be underfunded; both the level of investment and its time path appear to be suboptimal.

Linked to the issue of funding is the question of investment choice. We have been implicitly assuming that science determines in each instance the specific nature of investment to which research efforts should be directed. The social planner is presented with only one type of investment possibility and can choose only the (continuous) amount of resource to devote to it. However, if various choices of investment were possible concurrently, the model could still be utilized to determine the optimal combination of investments.

Endnotes

1. Another instance of the importance of resistance is the case of agricultural pesticides. According to the National Audubon Society, in 1993, 504 insect species were known to be resistant to at least one formulation of pesticide, while 150 fungi and other plant pathogens had developed resistance to fungicides (Cate and Tinkle). As for weeds, 212 herbicide resistant weed biotypes were reported to be in existence in 1998 (Heap).

2. We will use the terms *drug*, *antimicrobial*, and *antibiotic* interchangeably.

3. In agriculture, there exists a corresponding problem. Because of the mobility of the pest population and the common property nature of susceptibility, farmers may exhibit myopic behavior toward the future development of resistance, which results in overapplication of the pesticide. In case of overutilization of the chemicals, be they antimicrobials or pesticides, the first step is to determine optimal usage to help devise policies that reduce suboptimal utilization.

4. This occurs via mobile pieces of DNA, called plasmids or transposons, which move from one bacterium to another and become part of the new host's genetic material.

5. In the case of pesticides, the transmission of resistance occurs only via reproduction, so the time path of resistance development is easier to predict, and multipesticide resistance is not the norm. However, cross-resistance is a concern at the core of the policy debate today, as it is the rationale for the Environmental Protection Agency's (EPA) unprecedented policy of mandatory refuges for *Bacillus thuringiensis* (*Bt*) plant pesticides, genetically engineered to produce pesticides (EPA, 1998).

6. In the pesticide field, novel pesticides, which combine lower toxicity for humans and alternative modes of actions, range from chemical modifiers of development and behavior (pheromones, growth regulators) to artificial analogues of natural elements, such as the chloronicotinyls (from nicotine) to insect-tolerant plants and genetically modified crops (Pedigo).

7. See Gambardella for the pharmaceutical industry and Hammock and Soderlund for the pesticide industry.

8. As for pests, there are various instances of lack of fitness costs; see, for instance, Andrews and Morrison; Croft and Whalon; Penrose; and Romero and Sutton.

9. The pharmaceutical industry is also myopic in its behavior toward resistance, because E is a public good.

10. This is a simplification in the case of patented drugs, but it reflects reality for older drugs.

11. We will not concern ourselves with nonnegativity constraints for y.

12. It would be possible to choose a more complex distribution that puts some mass at q^1. This would not change the quality of the results.

13. Alternatively, we could interpret this as having a stationary population of size n with individuals living only one time period.

14. In the case of pesticides, this basic framework could be used to analyze the behavior of risk-neutral farmers who receive an endowment *m* in each time period and whose crops are produced by a composite input *x* via a concave production function *a*. The application of pesticides can be considered a discrete problem, either because the farmers follow the recommended dosage instructions or because they do not have a choice over the dosage, as in the case of the recently introduced Bt crops, which are genetically engineered to produce a pesticide. We indicate the level of infestation by *?*; the stock of susceptibility as $E \in [0, 2^n\text{-}1]$; the cost of the pesticide application as *p;* and the efficacy of the pesticide, a function of susceptibility, as $\frac{\ln(1+E)}{n\ln(2)}$. Then the expected profits have the same form as the expected utilities specified above.

15. Note that this maximization indicates the lack of credit markets for both the government and individual agents.

16. Note that a negative discount rate could be advocated in this context because the future generations will necessarily be poorer than the present ones, as the stock of susceptibility at their disposal is lower. See Goodin for arguments against the use of discounting, particularly when human health is concerned.

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