On the implications of endogenous resistance to medications

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Abstract

Uniform treatment guidelines are often used in medicine to ensure that all physicians prescribe a safe, efficacious, and cost-effective drug in treating a medical condition. The main message of this paper is that a policy of uniform treatment based on the standard cost-effectiveness criterion may be inappropriate when drug resistance is endogenous, and selection pressure imposed by the use of any single drug (antibiotic, antiviral, or antimalarial) leads sooner or later to the evolution of resistance (by bacteria, viruses, or parasites) to that drug. The paper shows that a mixed treatment policy of multiple drug use is generally desirable, and characterizes analytically the conditions under which it is optimal. © 2002 Elsevier Science B.V. All rights reserved.

1. Introduction

From an economist's perspective, the treatment of infectious disease fundamentally differs from the treatment of non-infectious conditions such as arthritis, cardiovascular disease, or cancer in that infectious diseases treatment involves two social externalities—one positive and the other negative. Take the case of antimalarials. On the one hand, drug treatment[1] cures the patient, thereby reducing the probability that malaria will be transmitted to other individuals.[2] On the other hand, drug treatment selects in favor of harmful mutations or

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[1] The situation can be generalized to antibiotics and antivirals as well.

[2] It is useful to contrast *appropriate* drug treatment (or treatment for a bacterial infection that is likely to be cured faster as a result of that treatment) with *inappropriate* drug treatment, which does not cure the patient any

organisms that are resistant to the drug, increasing the likelihood that the drug will be less effective in the future. Since the individual patient fails to take into account either of these externalities when deciding to seek treatment, corrective public intervention is called for. The externality benefits of treating infectious diseases has been well-documented in earlier papers (Philipson, 1999; Laxminarayan and Brown, 2001). In this paper, we extend this literature to focus on the resistance externality, one that may require changes in the *choice* of drug treatment.[3]

When one examines the pattern of drug treatments for infectious diseases, one is struck by the degree of homogeneity in the choice of drug. For instance, in 1997, nearly 60% of all cases of acute ear infections (a common condition in young children) in the United States were treated with amoxicillin.[4] In fact, amoxicillin accounted for 35% of *all* antibiotics used by physician, and the five most commonly used antibiotics used accounted for 72% of *all* antibiotics used by physicians in this country. The degree of treatment homogeneity is even more striking in infectious disease treatment in the developing world. In most African countries, chloroquine has been the most commonly used drug to treat malaria for over five decades. In fact, in some countries, it was even mixed in with common salt to ensure widespread and uniform malarial prophylaxis.

There are at least three reasons why uniformity of drug treatment is frequently encountered. The first is institutional. In some developing countries, such as Swaziland for instance, the government centralizes and controls drug procurement, and thereby directly determines the choice of treatment for the entire country. The second reason for treatment homogeneity is that in both developing and developed countries, clinical treatment guidelines for community-level infections are typically issued by national public health bodies, such as the American Association of Pediatrics and the Centers for Disease Control and Prevention (CDC) in the United States. In addition, individual hospitals both set and follow uniform treatment guidelines based on the advice of the hospital's infection-control committee. There are important reasons why such homogeneity is actively promoted among the medical profession. Clinical guidelines and national treatment policy recommendations provide detailed guidance to individual physicians on drugs to use for first- and second-line treatments, thereby helping to ensure safe and accurate medical treatment while relieving the physician of some of the burden of medical decision-making.[5] Following uniform guidelines also reduces the liability associated with medical error for physicians.

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faster than if that treatment were not used. Although inappropriate drug treatment is a significant factor in the growing resistance of microbes to drugs, this paper focuses exclusively on optimal policies related to appropriate drug treatment. In practice, appropriate drug treatment is often linked to a guidelines-type policy under which physicians are expected to adhere uniformly to a predetermined sequence of drugs to be used for treatment.

[3] Although, the resistance externality could be addressed using a tax on drug treatment, we would have to forego the ability to treat *all* infected patients. The impact of drug variety on resistance has received some exploratory discussion in an earlier paper by Ellison and Hellerstein (1999).

[4] This level of market concentration is remarkable considering the US$ 240 million market for antibiotics for this condition alone.

[5] National policies are especially useful in countries in which the primary health care provider is typically a health care worker with limited training. In countries in which government-run public health facilities are the primary sources of drugs, national policies determine which drugs are available at different levels of the health care system. For instance, a second-line drug may only be available at a hospital and not at a primary care clinic.

The final reason is that even in the absence of treatment guidelines, market forces that operate in the private treatment of disease ensure that the choice of drug treatment is, all other things being equal, often made on the basis of cost-effectiveness whereby the drug with the smallest ratio of treatment cost to effectiveness is the drug of first choice for *all* patients. (Weinstein and Fineberg, 1980). Physicians and individual patients acting in their own self-interest tend to prefer the most cost-effective drug option.

The starting point of this paper is the observation that to the extent that most patients in a region or country are treated with the same drug for a given infectious disease, the use of a single drug places "excessively" high selection pressure on organisms that are susceptible to that particular drug and increases the likelihood that a resistant strain will evolve and proliferate. As resistance to the recommended first-line drug builds up, that drug is replaced by an alternative that is used until resistance to this second drug also increases, and so on in succession. The main message of this paper is that the optimal solution may therefore be to use not just a *single* drug throughout the population as first-line agent, but to prescribe a variety of drugs, randomized over patients, to ensure that inordinate selection pressure is not placed on any single drug, or class or drugs. The precise fraction of patients that should be treated with these more effective drugs can be determined using fairly straightforward criteria, which we demonstrate in the sections that follow.

2. A model of endogenous resistance

This section of the paper presents our "core model" of endogenously-generated resistance to drug therapies. It goes without saying that such a model must of necessity be formulated at a very high level of abstraction. Nevertheless, the depth of analytical insight that emerges from even such a simple formulation will become clear presently.

Let there be available m possible drug therapies (indexed $i = 1, 2, \ldots, m$), each of which may be used to counter some particular infection. For analytical simplicity, we imagine that everyone in the population is treated with exactly one complete treatment dose of one of the drugs. Critical to our analysis is the idea that we are allowing a mixed treatment policy of different drugs to be used on different people and that the model should tell us when this strategy is optimal rather than excluding it a priori. Let x_i represent the fraction of the population treated with drug i, where

$$\sum_{i=1}^{m} x_i = 1, \tag{1}$$

and

$$0 \le x_i \le 1. \tag{2}$$

Let the cost (inclusive of non-drug treatment costs) of drug i (per unit of population) be given by

$$c_i > 0. \tag{3}$$

Resistance to drug i by the underlying pathogen is assumed to be a Poisson process with intensity parameter

$$\theta_i > 0, \tag{4}$$

where θ_i is a (very-small-valued) parameter representing the probability that resistance to drug i will develop endogenously (presumably by mutation) in the pathogen in any one person treated by that drug. (Here, we refer to *endogenously-acquired* resistance, which develops spontaneously by Poisson mutation in the pathogen in a patient being treated using the drug, as opposed to *epidemic* resistance by the pathogen, which results from infection by a drug-resistant pathogen from another person treated by that same drug.) The Poisson distribution describes the occurrence of discrete, random events, and is the classic model of choice in the biological literature to illustrate low probability events for which opportunities occur many times—see, for instance (Edelstein-Keshet, 1988).

When a fraction x_i are treated by drug i, the probability that a resistant strain emerges is (to a first-order approximation)

$$[\theta_i x_i]. \tag{5}$$

If such a resistant strain emerges, it will put at risk of epidemic resistance all x_i people treated by drug i. Let the social loss *per person* of being placed 'at risk" by resistance developing in the drug by which they are being treated be denoted

$$L > 0. \tag{6}$$

Then, combining (5) with (6), the expected social loss *per person* of being put 'at risk' by drug i is

$$L[\theta_i x_i], \tag{7}$$

Note that in the static model we have described, the cost L is incurred because a fraction x_i individuals continue to be treated with drug i even after resistance develops to the drug.[6] ,[7] However, the size of L would depend on the speed at which treatment policies adjust to the emergence of resistance. In a world where patients are treated strictly in sequence, and there is perfect information regarding the emergence of resistance following the treatment of each patient, L would equal zero. In this world, variety has no value and the optimal strategy would be to prescribe the most cost-effective drug to each patient.

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[6] To be sure, the static framework is an artificial one and it is possible that treatment policies could be adjusted so that a different drug is used once resistance has emerged (and has been observed) in a population. However, in practice, there are may be significant informational and institutional barriers to instantaneously adjusting treatment policies. Even in the United States, where medical practice is, arguably, very responsive to available surveillance information, the process of changing treatment policy can take anywhere between a few months and a couple of years, and is often motivated by a significant level of resistance. In the case of malaria and other diseases in developing country contexts, resistance typically rises to very high levels and results in a great many treatment failures before treatment policy is changed because there may be large fixed costs (in addition to informational and institutional barriers) of adjusting treatment policies.

[7] This resistance cost is proportional to the size of the population taking this drug because of the likelihood that epidemic transmission of resistance would result in treatment failure.

The *total* expected social loss from being put 'at risk' by being exposed to pathogens that are resistant to drug i is

$$[Lx_i][\theta_i x_i]. \tag{8}$$

In other words, we assume that it takes time to change these treatment fractions and that individuals who continue to be treated with drug i after a resistant strain has emerged are at risk for treatment failure.

Let

$$N_i = \frac{1}{\theta_i} \tag{9}$$

be the average number of people that use drug i before resistance can be expected to set in. Then the total expected social loss expression (8) can be rewritten as

$$\frac{Lx_i^2}{N_i}. \tag{10}$$

We are now ready to formulate the *optimal drug combination problem* in this model as a simple quadratic programming problem. It is to *minimize*

$$\sum_{i=1}^{m} \left[c_i x_i + \frac{L}{N_i} x_i^2 \right] \tag{11}$$

subject to

$$\sum_{i=1}^{m} x_i = 1, \tag{12}$$

and

$$0 \le x_i \le 1. \tag{13}$$

3. Characterizing the optimal drug combination

The effectiveness of all drugs is assumed to be identical. Without loss of generality suppose the drugs are arrayed from least to most expensive, so that

$$c_1 \le c_2 \le \cdots \le c_n. \tag{14}$$

It is quite obvious that it will never be optimal to use (to prescribe positive amounts of) a *more* expensive drug while not using (prescribe zero amount of) a *less* expensive drug. To see beyond this what is the form of an optimal policy, and what it depends upon, let us begin by analyzing in full detail the situation for *two* drugs ($m = 2$).

There are two possible solutions—an interior solution and a corner solution of the form $x_1 = 1, x_2 = 0$. The latter corresponds to the necessary and sufficient first-order corner condition

$$c_2 > c_1 + \frac{2L}{N_1}. \tag{15}$$

From Eq. (15) we may say that a "mixed" interior solution using both drugs is optimal if and only if the following condition is met:

$$(c_2 - c_1)N_1 < 2L. \tag{16}$$

The economic intuition behind result (16) is as follows. The precise economic condition under which it is optimal to include drug 2 to our menu is that the increase in cost associated with treating with the more expensive drug in place of the cheaper drug is less than or equal to the expected benefit from using two drugs in place of one. The term on the right hand side is $2L/N_1$ represents the marginal expected social cost per person associated with treating another patient with drug 1. As long as the increase treatment cost of using drug 2 in place of 1 is less than the expected increase in cost associated with endogenously generated resistance if drug 1 were to be used, it makes economic sense to use drug 2.

Next, consider the more general case where m is a arbitrary positive integer (>2). The first-order condition for a fully interior solution is the existence of a positive multiplier λ, which is dual to Eq. (12), that satisfies for positive x_i the conditions

$$c_i + \frac{2Lx_i}{N_i} = \lambda. \tag{17}$$

The multiplier, λ can therefore be interpreted as the "user cost" of any drug that is being used in the menu. Therefore, for any drug i that is being used, the total user cost equals the sum of the treatment cost c_i and the resistance cost $(2x_i/N_i)L$, where the resistance cost equals the marginal probability of inducing a resistant infection with another treatment multiplied by L, the associated social cost of inducing resistance in the population. While the treatment costs of drugs in our optimal menu can vary greatly, their user cost is identical. In other words, if two drugs are included in our optimal menu and one costs less than the other, then the resistance cost of the cheaper drug must exceed that of the more expensive drug so that the user cost of the two drugs is identical.

The astute reader may have guessed where we are headed. The optimal decision rule is to use the lowest cost drug(s) first, as standard economic intuition would dictate. What is not so standard, however, is to explicitly include, in addition to the treatment cost which the individual patient faces, the additional cost associated with the increased probability of drug resistance associated with each use of the drug, which is endogenously determined by the fraction of the infected population that is administered the drug in question. Therefore, the optimal menu design is such that the sum of treatment and resistance costs of *all* drugs on the menu is identical, thus, ensuring that some drugs may find their way into this menu even if they are not the least expensive from a treatment cost perspective.

Combining Eq. (12) with (17), we can solve for λ. With our expression for λ, and the "interiorness" condition $x_i > 0$ is equivalent to the condition $c_i > \lambda$, we have,

$$\sum_{j \neq i}(c_i - c_j)N_j < 2L, \tag{18}$$

which is the appropriate generalization of (16). From an economic perspective, it is optimal to include any drug i, in the menu of the drugs so long as the cost of the drug is less than or equal to the benchmark user cost, λ. It is now intuitively clear what is an easy-to-apply myopic algorithm for determining optimal drug use. Suppose by induction it is known that

an optimal solution includes a positive use of all drugs j where $j < i$ for some i. The next question to ask is whether it is additionally optimal to use drug i at a positive level. The answer is "yes" if and only if

$$\sum_{j<i}(c_i - c_j)N_j < 2L. \tag{19}$$

By repeatedly asking the induction question in the form of expression (19), it is possible to build up an optimal solution inductively, using a simple recursive algorithm based on this easily-interpretable economic criterion. We can rewrite the "interiorness" condition (19) as follows:

$$c_i < \frac{\sum c_j N_j}{\sum N_j} + \frac{2L}{\sum N_j}. \tag{20}$$

Inequality Eq. (20) means that drug i will be used as long as the marginal cost of using this drug is less than the weighted average cost of all drugs that are already under use. The weights are expected lifespan, measured in number of treatments before resistance evolves, plus the average cost of treatment failure associated with each additional treatment. Even if the resistance cost represented by the second term on the right hand side of Eq. (20) is small, we could still want to use more than one drug, which is quite unlike the standard cost-effectiveness criterion—where drugs are used strictly in the order of lowest to highest cost, and only one drug is used at any given time. When this second term is large, then we may want even to use drugs whose marginal cost *exceeds* the average cost of all drugs weighted by their expected lifespans. From Eqs. (17) and (18), for any two drugs j and k being used in positive amounts, we can write

$$\frac{x_j}{x_k} = \frac{\left(2L + \sum c_i N_i - c_j \sum N_i\right) N_j}{\left(2L + \sum c_i N_i - c_k \sum N_i\right) N_k}. \tag{21}$$

As noted earlier, the parameter N_i does not ever invert the order in which a drug i is included in the overall drug menu. However, from (21), we note that the average useful lifetime parameters $\{N_i\}$ could result in a relatively less cost-effective drug being used on a larger fraction of patients, such that $x_k > x_j$ even while $c_k > c_j$, so long as N_j is sufficiently smaller than N_k.

Referring back to expression (14), if one were to follow the traditional medical cost-effectiveness criterion of moving sequentially in strict order of increasing cost-effectiveness ratios, then treating all patients with the same drug can be myopically ineffective whenever we take account of the inescapable fact that resistance is endogenous. In fact, it may not even be optimal to use the most cost-effective drug on the largest number of patients as we have just shown.

4. The case of malarial treatment

In recent years, the ability of public health agencies to treat malaria in Africa has been seriously compromised by the increasing resistance of malarial parasites to the most commonly

Table 1
Resistance frequency and drug cost of commonly used antimalarial drugs

Drug name	Initial frequency of resistant allele	Cost (US$)
Chloroquine	1 in 10^{19}	0.01
Sulfadoxine-pyrimethamine (SP)	1 in 10^{11}	0.2
Amodiaquine/artemisinin	1 in 10^{20}	1.2
Mefloquine	1 in 10^{14}	2.4

used antimalarial drug, chloroquine. As chloroquine associated treatment failures mount, African countries are faced with the policy problem of selecting their malaria treatment strategy for the future. South Africa, Malawi, Botswana and Kenya have already switched to sulfadoxine-pyrimethamine (SP), the next least costly antimalarial, and a number of other countries are considering this option. In this section, we apply the iterative decision algorithm to the policy problem of selecting optimal treatment for malaria in Africa. Needless to say, this application is purely illustrative and by no means should be taken literally.

From a mathematical perspective, malaria is a convenient disease to model in some respects since it is possible to estimate the number of parasites in an infected patients body (White and Olliaro, 1996; White, 1998, 1999; White et al., 1999). This permits to directly calculate the probability of encountering a resistant parasite, each time a patient is treated with an anti-malarial (see Table 1). We can calculate that if we were to treat a million patients with artemisinin, we would encounter one patient in whom we could expect a resistant infection to develop.[8]

If we were to use the standard cost-effectiveness paradigm then the recommended strategy would be to treat *all* patients with SP, the least expensive drug. However, if we were to apply the iterative decision algorithm developed in this paper, we would begin by including SP in our optimal drug menu, since it is the cheapest drug among available antimalarials. The probability of encountering a resistant infection with SP use is one in a hundred. (We assume that the effectiveness of all drugs is identical and that the cost per person associated with a resistant infection is US$ 1000). The next step is to see if we would want to treat some fraction of our patients with amodiaquine/artemisinin. From the information in Table 1 and Eq. (19), we know that it is optimal to include this drug combination on our menu as long as its price is less than US$ 10.20. Next, in similar fashion, we consider the use of mefloquine. We can easily show that it is *not* optimal to include this drug since the cost of the drug exceeds the hurdle cost dictated by the cost of SP and amodiaquine/artemisinin and their

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[8] We arrive at this number in the following way. In malaria endemic areas, an adult patient who has between 10^{10} and 10^{11} parasites will show symptoms of malaria. A total biomass over 10^{12} in adults is likely to result in lethal malaria and mortality can be expected when the number of parasites exceeds 10^{13}. Therefore, while we are virtually certain of encountering a resistant parasite when treating a single, adult infected patient with atovaquone (a drug with initial frequency of resistant allele in the order of 1×10^{-12}), the equivalent probability in the case of treatment with artemisinin is roughly 0.000001. In general, the chance of a resistant mutant malaria parasite being selected by that antimalarial drug depends on the total number of parasites, the mutation frequencies, the elimination profile of the drug, and the drug-susceptibility and fitness of the mutants. For the purpose of this illustration, we assume that if more than 1000 parasites in the patient are resistant, then we have a resistant infection that can endanger the patient and can be transmitted to other individuals.

respective frequencies of resistant allele. The underlying economic reason is of course that the probability of encountering a strain resistant to amodiaquine/artemisinin is so small that the benefit of increasing drug heterogeneity by including mefloquine on our menu is not large enough to offset its higher cost.

5. Discussion

The externality problem associated with the treatment of infectious diseases—one that is related to a treatment's dual properties of reducing contagion and increasing drug resistance—has a reduced-form structure that is extremely familiar to any economist. Externalities are a common problem, whether they are related to highway congestion or air pollution. Always, a negative externality calls for using less of the privately-optimal good, and more of the privately-more expensive alternatives. What is unusual about drug resistance is that this problem has not been widely recognized as a social externality—possibly of enormous consequence. Following this line of thinking we arrived at simple criteria for choosing an optimal antibiotic policy, which contrasts sharply with the conclusion of the standard conventional health economists' individualistic cost-effectiveness analysis.

Under the standard cost-effectiveness approach, the economic criteria most commonly used in offering an economic perspective on the optimal choice of first line-treatment is that the drug with the lowest ratio of cost to effectiveness is selected as the primary or first-line drug. When this criterion is followed, it ignores the possibly large negative externality of overusing a particular drug. There are a large number of papers in the medical literature using the private-cost approach to determine the "optimal" treatment for a communicable disease. But the very nature of a communicable disease means there is a potentially large externality associated with drug treatments. The standard approach fails to recognize the externality problem associated with the uniform use of a single drug.[9]

Without a doubt, there may be practical problems with using a variety of drugs at the health care setting for a single disease. For instance, a physician may have to explain to individual patients why they are getting different drugs. The specific treatment given by different doctors will differ depending on their (different) assessments of probability weights. This is potentially problematic since patients typically look to doctors to resolve uncertainty by prescribing the "single best" treatment. Herein lies the dilemma. We have boxed ourselves into a certain particular way of reasoning that there is a "best" treatment for an ailment, one that is attributable to the fact that we are not used to having externalities in medicine. Once we become aware of the nature of the particular externality in infectious disease treatment as one that requires the physician to also consider society's best interests, while determining what is in the best interest of the patient, then an optimal strategy may well involve a mixture of less and more expensive drug therapies.

The starting point of this paper is that drug resistance is endogenous. The current strategy has been to wait for resistance to evolve before being surprised each time it appears, as if

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[9] In recent years, there has been greater recognition of the link between treatment strategies and resistance, and policies such as antibiotic rotation have received increased attention. While such policies introduce some degree of heterogeneity in antibiotic use, they are still far from being standard medical practice.

it were an ad hoc problem requiring some quick fix. Economists can contribute to the formulation of strategies that would internalize the cost of endogenously-generated resistance into the process of treatment decision-making. This paper tries to take a first step in such a direction.

Acknowledgements

References

Edelstein-Keshet, L., 1988. Mathematical Models in Biology, Birhauser Mathematical Series. McGraw-Hill, New York.

Ellison, S.F., Hellerstein, J., 1999. The Economics of Antibiotics: An Exploratory Study. Measuring the Prices of Medical Treatment. J.E. Triplett, Brookings, Washington, DC.

Laxminarayan, R., Brown, G.M., 2001. Economics of antibiotic resistance: a theory of optimal use. Journal of Environmental Economics and Management 42 (2), 183–206.

Philipson, T., 1999. Economic Epidemiology and Infectious Diseases. NBER, Cambridge, MA.

Weinstein, M.C., Fineberg, H.V., 1980. Clinical Decision Analysis. Saunders, Philadelphia.

White, N.J., 1998. Preventing antimalarial drug resistance through combinations. Drug Research Updates 1, 3–9.

White, N.J., 1999. Antimalarial drug resistance and combination chemotherapy. Philosophical Transactions of Royal Society of London B 354, 739–749.

White, N.J., Nosten, F., et al., 1999. Averting a malaria disaster. Lancet 353, 1965–1967.

White, N.J., Olliaro, P.L., 1996. Strategies for the prevention of antimalarial drug resistance: rationale for combination therapy for malaria. Parasitology Today 12 (10), 399–401.