Endogenous substitution between antibiotics under open access to the resource of antibiotic efficacy[1]

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Abstract

We analyze the use of multiple antibiotics when producers have open access to a common pool of antibiotic treatment efficacy. Patients derive demand for each antibiotic given its price, additional recovery rate (intrinsic quality) and level of treatment efficacy. The market outcome is compared to the social optimum and we characterize the dynamics of infected individuals, antibiotic efficacy and treatment rates. We show that the high-quality antibiotic drug loses its comparative advantage over time under both allocations making the low-quality drug the treatment of last resort. The switch to the last-resort treatment occurs at a later point of time in the social optimum and allows to better control for infection in the longer run. Accounting for the endogenous social cost of infection, we show that the socially optimal steady-state level of antibiotic efficacy is always lower than under open access. We also provide a taxation/subsidy policy allowing to correct these distortions.

Keywords: Antibiotic management; Non-renewable resource; Open access; Social optimum; Public health.

JEL classification: L1; Q3; I1

1 Introduction

There is a growing scientific consensus that antibiotic use to cure infectious diseases has the undesirable effect of causing the rise of resistant bacteria in hospitals and outpatient settings, entailing important economic costs via higher morbidity and mortality rates (see for instance, Holmberg et al., 1987; Phelps, 1989; Gersovitz and Hammer, 2004; Center for Disease Dynamics and Policy, 2011; World Health Organization, 2014). Economic research has looked at the positive and normative aspects of antibiotic use and modelled antibiotic treatment efficacy as a desirable natural resource and infection as an desirable or undesirable one depending on whether the industry's or society's point of view is adopted (for a review, see, Herrmann and Laxminarayan, 2010).

The price charged for antibiotics plays a crucial role in determining their use at a macro level.[1] In particular, the market power of the pharmaceutical industry to set antibiotic prices depends on whether *substitute drugs* are available, and whether the entry of generic firms in the market place has already occurred (Fisher Ellison et al., 1997; Scherer, 2000; Wiggins and Maness, 2004). Fisher Ellison and Snyder (2010) show how negotiation power between the pharmaceutical industry, health insurance companies and hospital or commercial retailers affects price.

In the context of bacterial resistance it is crucial to understand whether antibiotic drugs (or their biological formula) are linked to separate or common pools of antibiotic treatment efficacy as this influences the possible substitution between them. Most bio-economic research has abstracted from potential connections between pools or existence of a common pool which becomes relevant when antibiotics belong to the same family or class.[2] Epidemiological evidence indeed shows that antibiotic treatment efficacy can be lost at the class level

[1] At a micro level, antibiotic use is determined in a complex interaction between patients who demand them, physicians who prescribe them, and pharmacists who may substitute between brand and generic versions when both options are available. Hospitals and health organizations may also control which drugs are prescribed by their affiliated doctors. The analysis of these interactions lies outside the scope of this paper.

[2] The first, and well-known, out of around 20 antibiotic classes is penicillin. Others are cephalosporins, macrolides and quinolones.

(Coates et al., 2011; Prieto et al., 2002), as is demonstrated, e.g., by cephalosporin-resistant *N. gonorrhoea* or macrolide-resistant *S. pneumonia*.

The purpose of this paper is to examine how bacterial resistance evolves, when prices, and thus antibiotic use, are determined in a setting where antibiotic producers have open access to a common pool of antibiotic efficacy. We design a bio-economic framework where antibiotic use unavoidably leads to a decrease of treatment efficacy at the class level and where substitute drugs belonging to the same class are sold by a generic industry. Firms in such an industry have open access to the biological formulae of the drug and thus to the common pool of treatment efficacy, which leads to a complete dissipation of the economic rent. Although the assumed non-renewable character of treatment efficacy and the particular industry structure might seem restrictive at first sight, it represents a useful benchmark for addressing an era where more and more antibiotics go off patent and where it may become impossible to develop new classes (Coates et al., 2011; Becker et al., 2006). As in Laxminarayan and Brown (2001), Wilen and Msangi (2003) and Herrmann and Gaudet (2009) we build on an epidemiological model to address the spread of infection and rise of resistance. In contrast to these contributions, (i) antibiotics are connected to a common pool of antibiotic efficacy, (ii) endogenous substitution between antibiotics is considered from a positive and normative point of view and (iii) a regulatory tool inciting firms to produce in a socially optimal way is proposed.

The endogenous substitution between antibiotics affects critically the evolution of antibiotic efficacy and infection. The intertemporal substitution depends on producer characteristics, the *gross* quality (efficacy level) of the antibiotic class, as well as on the antibiotics' *intrinsic* quality defined by the additional recovery rate they procure to infected individuals. More precisely, our results indicate that when two drugs are in use, patients with high valuations of being in good health start using the high quality drug, while those with low valuations use the low quality drug. As the common pool of antibiotic efficacy decreases, the high quality drug loses its comparative advantage, such that the high quality drug is grad-

ually abandoned and patients turn to the low-quality drug. We also derive the conditions on bioeconomic parameters when either drug is dominated and not produced in the market equilibrium.

As in the open-access allocation, the low-quality drug is dominated and should never be used in the social optimum, when antibiotic quality per unit cost of production is greater for the high-quality drug. The socially optimal order of antibiotic use is identical to the open-access equilibrium, however the intensity of antibiotic use and the timing of abandoning an antibiotic differ. In particular, we determine the critical level of socially optimal economic viability of each antibiotic which depends on the social cost of infection and shadow price of the antibiotic class's treatment efficacy. Accounting also for the social cost of infection, we find that inter-temporal antibiotic use is such that the socially optimal steady-state level of antibiotic efficacy is lower than in the open-access allocation. Our numerical simulations indicate that a more parsimonious use of antibiotics is operated initially, while a more intensified use (and thus, better control of the prevalence of infection) occurs in the long run. We provide an economic instrument, which in addition to induce the socially optimal allocation, balances the social benefit of preserving antibiotic efficacy and the social cost of infection.

Our paper builds on theoretical bio-economic models developed by natural resource economists who address antibiotic efficacy as a natural resource, which may be – depending on the epidemiological specification – renewable or non-renewable.[3] The seminal paper by Laxminarayan and Brown (2001) examines the optimal use of two antibiotics, each having its own, *seperate*, pool of antibiotic efficacy. Considering antibiotic efficacy as a non-renewable resource, they find, among other things, that when unit costs of production are equal, it may exist an initial phase where only one antibiotic is used. Once the levels of antibiotic efficacy are equal, both antibiotics are used simultaneously. Herrmann and Gaudet (2009) concentrate on one antibiotic only with renewable efficacy when firms have open access to

[3]Empirical research on the economic cost of antibiotic resistance remains limited. An interesting contribution related to our work is Howard (2004) who estimates the increase in antibiotic spending to cure otitis media due to the rise of penicillin resistance as physicians turn to newer, more expensive antibiotics.

the resource pool of antibiotic efficacy. As firms do not account for the shadow prices of antibiotic efficacy and infection, antibiotic use necessarily differs from the social optimum leading to a steady-state level of antibiotic efficacy that may be greater or lower than its socially-optimal level, depending on the crucial bio-economic parameters of production cost and additional recovery.

Other contributions on antibiotic resistance and market structure relate to a monopolist selling an antibiotic. Mechoulan (2007) finds that while it may be socially optimal to eradicate the disease, it is not profit-maximizing for the monopolist to do so because infection represents its market size, a valuable asset. Herrmann (2010) shows that when the monopolist faces a finite patent life, his price dynamic is similar to that of a myopic monopolist as the end of the patent approaches. Both authors find conditions under which it is socially desirable to extent the duration of the patent.

The remainder of the paper is organized as follows. In Section 2, we present the biological and economic model. Section 3 examines antibiotic use under open access. Section 4 focuses on the socially optimal use of antibiotics. Section 5 contrasts the equilibrium trajectories obtained under open access with the socially optimal outcome. We conclude in Section 6.

2 The bio-economic model

We start by presenting the epidemiological constraints which will later be combined with an economic model of antibiotic use.

2.1 The SIS model

This section adapts an SIS epidemiological model to examine the use of two antibiotics $i = 1, 2$, which belong to the same antibiotic class. We assume that the total population N is constant and consists of healthy individuals $S(t)$, who are susceptible to infection and individuals who are infected $I(t)$. As we assume bacterial resistance to be class dependent, an infected individual is either susceptible or resistant to both antibiotic treatments. The infected population is thus constituted of individuals who are infected with a drug-susceptible

strain, $I_w(t)$, and those infected with a drug resistant strain, $I_r(t)$. It follows that, at any instant t, $I(t) = I_w(t) + I_r(t) = N - S(t)$.

Infection spreads at a transmission rate β between infected and healthy individuals, such that $\beta S(t)(I_w(t)+I_r(t)) = \beta S(t)I(t)$ is the total number of individuals becoming infected at time t. The infected individuals may recover naturally. However, this may occur at different rates. Let r_r and r_w represent, respectively, the natural rate of recovery from the drug-resistant and drug-susceptible strain. The difference $\Delta r = r_r - r_w$ is referred to the fitness cost incurred by drug-resistant strains and the bioeconomic literature generally assumes $\Delta r \geq 0$, a hypothesis which we will discuss shortly. Note that additional recovery due to antibiotic treatment occurs only when the individual is infected with a drug-susceptible strain. Treatment with antibiotic i then implies an increase in the recovery rate to $r_w + r_i$, while the recovery rate remains at its natural level, r_r, for individuals suffering from a drug-resistant strain. We assume without loss of generality that antibiotic 1 has a relatively higher recovery rate as compared to antibiotic 2, $r_1 > r_2$, *i.e.* antibiotic 1 has higher intrinsic quality than antibiotic 2.[4]

Denote by $f_i \in [0, 1]$ the fraction of the infected population being treated with antibiotic i. Recovery from the drug-susceptible infection is given by $r_w+f_1r_1+f_2r_2$, such that the total infected population decreases at the rate $r_rI_r(t) + (r_w + f_1r_1 + f_2r_2)I_w(t)$. The population dynamics are then given by

$$\begin{aligned} \dot{S} &= -\dot{I} = -\dot{I}_r - \dot{I}_w, \\ \dot{I}_w &= (\beta S - r_w - f_1r_1 - f_2r_2)I_w, \\ \dot{I}_r &= (\beta S - r_r)I_r. \end{aligned}$$

As in Laxminarayan and Brown (2001), we define $w = I_w/I$ as the level of antibiotic efficacy.

[4]The additional recovery rate of an antibiotic is an empirical measure, which may differ from the therapeutical value for a particular patient (Garrod, 1960). Following this author, the therapeutical value is related to the antibacterial activity of the drug, which is tested for *in vitro*, and can indeed differ between antibiotics belonging to a given class, like penicillin.

Making use of the definition of antibiotic efficacy, these equations can be transformed to

$$\dot{w} = w(1-w)(\Delta r - f_1 r_1 - f_2 r_2), \tag{1}$$

$$\dot{I} = (\beta(N-I) - r_r)I + wI(\Delta r - f_1 r_1 - f_2 r_2). \tag{2}$$

Note that when $\Delta r > 0$, antibiotic efficacy replenishes if both antibiotics are not used too intensively ($f_1 r_1 + f_2 r_2 < \Delta r$). As stated in Andersson and Hughes (2010), experimental studies support these theoretical findings, "but other processes, such as compensatory evolution and genetic co-selection complicate the picture and make reversibility [of antibiotic resistance] less probable in real-life settings (p.260)."[5] Based on this evidence, we will restrict our attention as in Laxminarayan and Brown (2001) to benchmark situations where the fitness cost is equal to zero (*i.e.* $r_r = r_w = r$), and hence, antibiotic treatment efficacy of the class is a non-renewable resource. Laws of motion (1) and (2) then become:

$$\dot{w} = -w(1-w)(f_1 r_1 + f_2 r_2), \tag{3}$$

$$\dot{I} = \beta I(N-I) - I(r + w(f_1 r_1 + f_2 r_2)), \tag{4}$$

As $r_1 > r_2$, increasing marginally the treatment with antibiotic 1, f_1, decreases more intensively antibiotic efficacy as compared to treatment with antibiotic 2. The evolution of infection is now easily determined by two opposite forces. The contagious effect is given by the first right-hand-side term of (4), while its second right-hand-side term is the recovery effect, consisting of natural and additional recovery due to antibiotic use. Infection can increase or decrease depending on which of both effects outweighs the other. Given our hypothesis that $r_1 > r_2$, note that the prevalence of infection is better controlled when marginally increasing the treatment with antibiotic 1 as compared to antibiotic 2.

[5] See Andersson and Hughes (2010) for a critical review on when experimental evidence suggests a positive fitness cost as a potential mechanism for reversing antibiotic resistance and when it is less clear. For economists comprehensible definitions of other biological patterns, such as compensatory evolution and co-selection are also provided by these authors.

2.2 Endogenous demands of antibiotics

Antibiotic resistance has been modeled in the economic literature as affecting in an ad-hoc manner antibiotic demand via the backstop price (Elbasha, 2003). Howard (2004) and Herrmann and Gaudet (2009) derive antibiotic demand on the grounds of a utility maximization problem, in which a patient knows the probability with which the antibiotic will be effective. In this paper as in those contributions, patients have full information about the level of antibiotic treatment efficacy. This can be motivated by the fact that the modeled antibiotic demand is induced by an altruistic physician who prescribes the drug and knows about its efficacy.

Let θ denote an individual's valuation to be in good health which is distributed according to the distribution function $F(\theta)$ over the total population N. When infected, each individual decides whether or not to purchase the antibiotic i at price p_i. We assume that an individual cannot be treated simultaneously with both antibiotics and that an infected individual does not know from which type of infection (resistant or susceptible) he is suffering.[6]

Following Herrmann and Gaudet (2009), the infected individual attributes probability $\frac{I_r}{I} = 1 - w$ of being infected with the resistant strain, and probability $\frac{I_w}{I} = w$ of being infected with the drug-susceptible strain, implying an expected natural rate of recovery given by $\pi(w) = (1-w)r_r + wr_w = r$, as we have assumed a zero fitness cost. Taking an antibiotic increases the chance of recovery of the individuals who are suffering from the drug-susceptible strain. Since there is a probability w that the bacterial strain is susceptible, the additional expected recovery rate of an individual is given by wr_i when he takes antibiotic i.

We write the following gross expected utility function for an individual of type θ

$$v(\theta) = \begin{cases} \theta, & \text{if in good health;} \\ \pi(w)\theta, & \text{if infected and not taking any antibiotic ;} \\ [\pi(w) + r_i w]\theta, & \text{if infected and taking antibiotic } i. \end{cases} \tag{5}$$

This is a model of vertical differentiation (Tirole, 1989). Since antibiotic 2 is of low quality

[6]Testing for the type of infection is possible in principle, but may be difficult, time consuming and costly depending on the type of infection. However, a physician may request testing when the prescribed antibiotic does not deliver any results and high morbidity costs are involved.

as compared to antibiotic 1, it will never be purchased if it is sold at the same price or is more expensive than antibiotic 1. Hence, in equilibrium, we will necessarily have $p_1 > p_2$.

Denote by $\tilde{\theta}_{12}$ the infected individual who is indifferent between buying either antibiotic 1 or antibiotic 2 and $\tilde{\theta}_i$ the individual who is indifferent between buying antibiotic i and nothing at all when infected. The value of $\tilde{\theta}_{12}$ is the solution of the equation

$$[\pi(w) + r_1 w]\theta_{12} - p_1 = [\pi(w) + r_2 w]\theta_{12} - p_2,$$

from which we obtain

$$\tilde{\theta}_{12} = \frac{p_1 - p_2}{w\Delta r_f}. \tag{6}$$

where $\Delta r_f = r_1 - r_2 > 0$ is the differential of additional recovery rates. The value of $\tilde{\theta}_i$ satisfies $\pi(w)\tilde{\theta}_i = [\pi(w) + r_2 w]\tilde{\theta}_i - p_i$, and hence

$$\tilde{\theta}_i = p_i/(wr_i), \;\; i = 1, 2. \tag{7}$$

In order to derive the demand for each antibiotic, first assume that $r_1/p_1 \geq r_2/p_2$ (that is, the "antibiotic quality per dollar" for antibiotic 1 is greater). In this case we have $\tilde{\theta}_2 \geq \tilde{\theta}_1$ so that individuals with $\theta \in [\tilde{\theta}_1, \tilde{\theta}_2]$ will buy antibiotic 1 while individuals with $\theta \geq \tilde{\theta}_2$ will buy either antibiotic 1 or antibiotic 2. However, as shown in the appendix, individuals with $\theta \geq \tilde{\theta}_2$ always prefer antibiotic 1 to antibiotic 2. Hence, all infected individuals with $\theta \geq \tilde{\theta}_1$ buy only antibiotic 1. The fraction of infected individuals who are willing to buy antibiotic 2 is equal to zero, while $[1 - F(\tilde{\theta}_1)]$ represents the fraction of those who are willing to buy antibiotic 1. Since individual demand is unitary, the total demand for antibiotic 1 in this case is $Q_1 = I[1 - F(\tilde{\theta}_1)]$.

The more interesting situation occurs when antibiotic 2 is not "dominated": $r_2/p_2 > r_1/p_1$. In this case, while individuals with $\theta \geq \tilde{\theta}_{12}$ will buy antibiotic 1, those with $\theta \in [\tilde{\theta}_2, \tilde{\theta}_{12}]$ will buy antibiotic 2 and the remaining individuals will not buy any of the two antibiotics. The fraction of infected individuals who are willing to buy antibiotic 2 is $[F(\tilde{\theta}_{12}) - F(\tilde{\theta}_2)]$, whereas the proportion $[1 - F(\tilde{\theta}_{12})]$ of individuals is willing to buy antibiotic 1. Unitary

demand then implies

$$\begin{aligned} Q_1 &= I[1 - F(\tilde{\theta}_{12})] \quad \text{and} \\ Q_2 &= I[F(\tilde{\theta}_{12}) - F(\tilde{\theta}_2)], \end{aligned}$$

where I is the potential market size for treatment with antibiotic i.

As in Herrmann and Gaudet (2009) and Herrmann (2010), in the present paper, we restrict attention to a uniform distribution of θ across the population with support $[0, 1]$. Having assumed unitary demand, the quantity $f_i = Q_i/I$ is the fraction of infected individuals treated with antibiotic i. Thus, when antibiotic 2 is not "dominated" ($r_2/p_2 > r_1/p_1$), inverse demand functions for antibiotics can be rewritten in terms of f_1 and f_2 as

$$p_1(f_1, f_2) = w[r_1(1 - f_1) - r_2 f_2], \tag{8}$$

$$p_2(f_1, f_2) = w r_2[1 - f_1 - f_2]. \tag{9}$$

When antibiotic 2 is dominated, inverse demand for antibiotic 1 is merely the restriction of (8) to $f_2 = 0$. Notice that these inverse demand functions are linear in treatment rates, and that their choke prices depend on both, the intrinsic and class's quality, as well as the fraction of individuals purchasing its antibiotic substitute.[7]

3 Antibiotic use under open access

We assume that firms operating in the industry have open access to the common pool of antibiotic efficacy. This represents a benchmark analysis of a generic industry, in which the biological formulae of antibiotics are common knowledge and antibiotics are produced in a competitive environment. As in Laxminaryan and Brown (2001), Herrmann and Gaudet (2009) and Herrmann (2010), we consider a linear cost structure, given by $C_i(Q_i) = c_i Q_i$, where the production of Q_i units of antibiotic i by a firm occurs at a unit cost $c_i > 0$.

[7] As in the related literature (e.g., Laxminaryan and Brown, 2001; Herrmann and Gaudet, 2009), we abstract from health insurance here. However, if health insurance were to cover a part of the patient's drug spendings, antibiotic demand derived in our settings would correspond to the residual willingness-to-pay of patients for antibiotic drugs, once they have paid for their insurance plan.

In particular, we abstract from fixed costs incurred in the research and development of antibiotics, which are supposed to be sunk. Furthermore, we assume $r_i > c_i$ for both drugs to allow for a possibly positive economic value in each market when antibiotic efficacy is sufficiently high.

Antibiotic producers will enter until the economic rent gets dissipated in each market. Hence, at the open-access equilibrium, we must have

$$[p_i - c_i]f_i = 0, \;\; 0 \leq f_i \leq 1 \;\text{ and }\; p_i \leq c_i, \;\; i = 1, 2. \tag{10}$$

In order to derive the open-access equilibrium, it is helpful to distinguish two cases depending on the relative magnitude of the unit cost (and thus price) as compared to recovery rates. Consider first the case where $r_2/c_2 > r_1/c_1$. That is, antibiotic quality per unit cost is greater for antibiotic 2. In this situation, condition (10) along with (8) and (9) allow us to derive the fraction of the infected population that buys antibiotic 1. It is given by

$$f_1^{\infty}(t) = \begin{cases} 1 - \frac{c_1 - c_2}{w(t)\Delta r_f} & \text{if } w(t) > \frac{c_1 - c_2}{\Delta r_f}; \\ 0 & \text{otherwise }, \end{cases} \tag{11}$$

where the superscript ∞ stands for the open-access equilibrium. Likewise, the fraction of the infected population treated with antibiotic 2 is:[8]

$$f_2^{\infty}(t) = \begin{cases} \frac{1}{w(t)r_2\Delta r_f}(r_2c_1 - r_1c_2) & \text{if } w(t) > \frac{c_1 - c_2}{\Delta r_f}; \\ 1 - \frac{c_2}{w(t)r_2} & \text{if } \frac{c_2}{r_2} < w(t) \leq \frac{c_1 - c_2}{\Delta r_f} \; ; \\ 0 & \text{otherwise }. \end{cases} \tag{12}$$

Consider now the case where antibiotic quality per unit cost is greater for antibiotic 1, *i.e.* $r_1/c_1 \geq r_2/c_2$. In this situation, antibiotic 2 is dominated such that $f_2^{\infty}(t) = 0$ for all $t \geq 0$.[9] Using this in combination with conditions (10) and (8), we get:

$$f_1^{\infty}(t) = \begin{cases} 1 - \frac{c_1}{w(t)r_1} & \text{if } w(t) > \frac{c_1}{r_1}; \\ 0 & \text{otherwise }. \end{cases} \tag{13}$$

[8]Notice that the inequality $(c_1 - c_2)/\Delta r_f > c_2/r_2$ holds if and only if $r_2/c_2 > r_1/c_1$, which is our working hypothesis here.

[9]If antibiotic 2 was not dominated at date t, we would have $f_2^{\infty}(t) > 0$. This is not possible. Indeed, when $r_1/c_1 \geq r_2/c_2$ the interval $[\frac{c_2}{r_2}, \frac{c_1 - c_2}{\Delta r_f}]$ is empty. Hence, (12) indicates that $f_2^{\infty}(t)$ cannot be positive in such a case.

Three points merit discussion here, which will be used for a later complete characterization of antibiotic use in equilibrium. First, open-access treatment rates f_1 and f_2 do not depend explicitly on the stock of infected individuals (the market size). This result is intuitive because firms under open access behave as if they were myopic (they are unable to gain any rent from production). Second, there exists a critical level of antibiotic efficacy, below which no antibiotic is produced in the open-access equilibrium. This level of economic viability is given by $\min(c_1/r_1, c_2/r_2)$. Third, depending on the current level of antibiotic efficacy and model parameters, one of four possible regimes of antibiotic use, denoted by D, F and $A_i, i = 1, 2$, prevails. In regime D, both antibiotics are produced simultaneously, in regime F no individual buys an antibiotic and in regime A_i, only antibiotic i is produced.

3.1 The steady state under open access

The critical level of antibiotic efficacy, given by $\min(c_1/r_1, c_2/r_2)$, below which antibiotic use becomes uneconomical, suggests the existence of a steady state in the open-access equilibrium. Setting $f_1^\infty = f_2^\infty = 0$ into equation (2) gives $\dot{I} = (\beta(N-I)-r)I$. Solving this equation for $\dot{I} = 0$ yields the steady state for the stock of infected individuals: $I^\infty = (\beta N - r)/\beta$. Therefore, the steady state in the open-access equilibrium is

$$(f_1^{S\infty}, f_2^{S\infty}, I^\infty, w^\infty) = \left(0, 0, \frac{\beta N - r}{\beta}, \min\left(w_0, \frac{c_1}{r_1}, \frac{c_2}{r_2}\right)\right), \tag{14}$$

where w_0 is the initial value of antibiotic efficacy. In particular, we have $w^\infty = w_0$ in the case where the initial value of antibiotic efficacy is too low to sustain any antibiotic production over time such that antibiotic efficacy stays at its initial level.

3.2 The equilibrium dynamics under open access

In this section, we charaterize the evolution of the open-access equilibrium up to convergence to the steady state of the economy. We assume that the initial stock of infected population is $I(0) = I_0 \in (0, N)$ and the initial efficacy level is $w(0) = w_0 \in (0, 1)$. Since $\dot{w}(t) \leq 0$ and $w(t) \geq 0$, antibiotic efficacy decreases and converges to its steady state. Also note that,

having assumed $r_1 > r_2$, we always have

$$\frac{c_1 - c_2}{\Delta r_f} > \frac{r_2 c_1 - r_1 c_2}{r_2 \Delta r_f}. \tag{15}$$

As we will show, condition (15) and the particular structure of antibiotic use given in (11) and (12) suggest the existence of four possible cases for the dynamic behavior of the model.

In the first case, the initial level of antibiotic efficacy satisfies $w_0 > (c_1 - c_2)/\Delta r_f$, while additional recovery rates and unit costs satisfy $r_2/c_2 > r_1/c_1$. In this case, treatment rates defined in (11) and (12) indicate that regime D prevails and that antibiotic efficacy lies above $(c_1 - c_2)/\Delta r_f$ during the time interval $[0, t_1)$. Notice that t_1 is finite and defined by $w(t_1) = (c_1 - c_2)/\Delta r_f$. To see this, note that over the interval $(0, t_1)$, $f_1^\infty > 0$ and $f_2^\infty > 0$. Using (11) and (12) along with (3), we get $\dot{w} = (1 - w)(c_1 - r_1 w)$. Integration yields

$$w(t) = \frac{-c_1(1 - w_0) + (c_1 - r_1 w_0)e^{t(c_1 - r_1)}}{-r_1(1 - w_0) + (c_1 - r_1 w_0)e^{t(c_1 - r_1)}}, 0 \leq t \leq t_1. \tag{16}$$

Now, set $h(t) = w(t) - (c_1 - c_2)/\Delta r_f$, which is a continuous function. We have $h(0) = w_0 - (c_1 - c_2)/\Delta r_f > 0$ and $\lim_{t \to +\infty} h(t) = c_1/r_1 - (c_1 - c_2)/\Delta r_f < 0$.[10] Since w is monotone, so is h. Therefore, there exists a unique $t_1 \in (0, \infty)$ such that $w(t_1) = (c_1 - c_2)/\Delta r_f$. Equations (11)-(12) and (15) suggest that at instant t_1, regime A_2 starts. Suppose that this regime ends at t_2, which is characterized by $w(t_2) = c_2/r_2$. Recall that in A_2, we have $f_1^\infty = 0$ and $f_2^\infty > 0$, the efficacy dynamic is $\dot{w} = -w(1-w)r_2 f_2^\infty = -(1-w)(r_2 w - c_2)$, with the boundary condition $w(t_1) = (c_1 - c_2)/\Delta r_f$. Using a similar reasoning as for regime D, it can be shown that A_2 has a finite length. Since we have $w(t_2) = c_2/r_2$, (11) and (12) show that regime F prevails from t_2 on. Since in regime F, $f_1^\infty = f_2^\infty = 0$, the level of antibiotic efficacy remains constant and is given by $w(t) = c_2/r_2$ for all $t \geq t_2$.

These consecutive regimes of antibiotic use are illustrated in Figure 1. As antibiotic efficacy tends to decrease, patients switch from antibiotic 1 to antibiotic 2, which provides relatively greater antibiotic quality per unit cost, $r_2/c_2 > r_1/c_1$. This pattern continues until antibiotic 1 loses its economic viability. After this instant, the fraction of individuals using

[10] Since $r_2 c_1 - r_1 c_2 > 0$, we have $\frac{c_1}{r_1} - \frac{(c_1 - c_2)}{\Delta r_f} = -\frac{r_2 c_1 - r_1 c_2}{r_1 \Delta r_f} < 0$. So, the sign of h changes over $(0, +\infty)$.

antibiotic 2 decreases until the level of antibiotic efficacy becomes too small rendering the use of antibiotic 2 economically nonviable. The switch from the antibiotic of high intrinsic quality to the one of low intrinsic quality occurs because prices in the open-access equilibrium cannot adjust ($p_1 = c_1$ and $p_2 = c_2$ and $c_1 > c_2$). As the overall quality of the antibiotic class decreases, individuals with a relatively high valuation of being in good health (high θ) are less willing to pay a premium for the high quality drug, as the intrinsic quality per price ratio is better for the antibiotic of low intrinsic quality ($r_2/c_2 > r_1/c_1$). From the consumers' point of view, the antibiotic with high intrinsic quality loses its comparative advantage in treating infected individuals.

The second case applies for an initial efficacy level w_0, satisfying $(c_1 - c_2)/\Delta r_f \geq w_0 > c_2/r_2$, and $r_2/c_2 > r_1/c_1$. In this situation, regime A_2 prevails initially. Let t_3 denote its length, which is characterized by $w(t_3) = c_2/r_2$. Since in A_2 we have $f_1^\infty = 0$ and $f_2^\infty > 0$, (3) indicates that the antibiotic efficacy dynamic is $\dot{w} = -w(1-w)r_2 f_2^\infty = -(1-w)(r_2 - c_2 w)$, with the boundary condition $w(0) = w_0$. A similar reasoning as for the first case allows us to find that t_3 is finite. Since we have $w(t_3) = c_2/r_2$, (11) and (12) suggest that regime F prevails from t_3 forever. Recall that in regime F, we have $f_1^\infty = f_2^\infty = 0$ so that w is constant. Therefore, we have $w(t) = c_2/r_2$ for all $t \geq t_3$.

The third case is for $w_0 > c_1/r_1$ and $r_1/c_1 \geq r_2/c_2$. Recall that in this case, antibiotic 2 is dominated, which implies ($f_2^\infty = 0$). Consequently, (3) and (13) show that the antibiotic efficacy dynamic is: $\dot{w} = (1-w)(c_1 - r_1 w)$. Using a similar method as for the first case, it can be shown that antibiotic efficacy approaches its steady state $w^s = c_1/r_1$ asymptotically. The fraction of infected individuals treated with antibiotic 1 decreases and converges asymptotically to a state where no individual buys antibiotic 1.

The fourth case corresponds to the situation where $c_1/r_1 > c_2/r_2 \geq w_0$ or $c_2/r_2 \geq c_1/r_1 \geq w_0$. Since antibiotic efficacy cannot replenish, (11), (12) and (13) show that in this case, the two antibiotics are not economically viable ($f_1^\infty = f_2^\infty = 0$). Consequently, (3) suggests that the level of antibiotic efficacy remains constant and is equal to its initial value.

Summarizing, the above results suggest four possible orders of use of antibiotics. (i) if $w_0 > (c_1 - c_2)/\Delta r_f$ and $r_2/c_2 > r_1/c_1$, then the sequence of use is $D \to A_2 \to F$. (ii) if $(c_1 - c_2)/\Delta r_f \geq w_0 > c_2/r_2$ and $r_2/c_2 > r_1/c_1$, then the order of use is $A_2 \to F$. (iii) if $w_0 > c_1/r_1$ and $r_1/c_1 \geq r_2/c_2$, then regime A_1 prevails forever. (iv) if $c_1/r_1 > c_2/r_2 \geq w_0$ or $c_2/r_2 \geq c_1/r_1 \geq w_0$, then regime F prevails forever.

Having derived so far the evolution of antibiotic treatment rates and antibiotic efficacy, we will next show in (I, w)-space, the evolution of antibiotic efficacy as function of the stock of infected individuals. Since antibiotics are not used in the fourth case described above, the stock of infected individuals evolves along a horizontal line up to convergence (in the (I, w)-space). In addition, for $f_1 = f_2 = 0$, (4) indicates that $\dot{I} \gtreqless 0$, if and only if $I \lesseqgtr I^{\infty}$. Hence, when starting below the biological steady state I^{∞}, the stock of infected individual rises monotonically and converges to I^{∞} defined in (14).

The dynamics of the open-access equilibrium for the first case as described above is illustrated in space (I, w) in Figure 2.[11] When initially located to the left of the isocline $\dot{I} = 0$, the contagious effect dominates the recovery effect, such that the stock of infected individuals rises and converges to the biological steady state given in (14). However, when initially located to the right of the isocline $\dot{I} = 0$, the stock of infected individuals evolves non-monotonically: it decreases and even falls below its steady-state level when the recovery effect dominates the contagious effect, before it starts to increase again up to convergence to its steady-state level.[12]

[11] The second and the third case have similar (I, w)-space representation as the first one.

[12] Note that the $\dot{I} = 0$ isocline is non stationary and moves in a similar way as in Herrmann and Gaudet (2009).

4 Socially optimal use of antibiotics

This section examines the optimal use of antibiotics 1 and 2. The instantaneous social welfare is the sum of gross expected surplus of individuals minus production costs. It is given by

$$\begin{aligned} W(f_1, f_2, w, I) &= N\int_0^1 v(\theta)d\theta - (c_1 f_1 + c_2 f_2)I \\ &= (N-I)\int_0^1 \theta d\theta + I\int_0^{\tilde{\theta}_2} \pi(w)\theta d\theta + I\int_{\tilde{\theta}_2}^{\tilde{\theta}_{12}} [(\pi(w)+r_2 w)\theta - p_2]d\theta \\ &\quad + I\int_{\tilde{\theta}_{12}}^1 [(\pi(w)+r_1 w)\theta - p_1]d\theta + (p_1-c_1)f_1 I + (p_2-c_2)f_2 I, \end{aligned}$$

where $\tilde{\theta}_{12}$ and $\tilde{\theta}_2$ are defined in expressions (6) and (7). Notice that these expressions depend on antibiotic prices p_1 and p_2, given in (8) and (9), and which are now to be interpreted at the optimum as *efficient prices*. We thus implicitly assume efficient rationing and that the set f_i, $i = 1, 2$ and p_i, $i = 1, 2$ can be used interchangeably to characterize the social optimum. Integration yields

$$\begin{aligned} W(f_1, f_2, w, I) &= \frac{1}{2}(N-I) + \frac{1}{2}rI + I[\frac{1}{2}r_2 w(\tilde{\theta}_{12}+\tilde{\theta}_2) - p_2](\tilde{\theta}_{12}-\tilde{\theta}_2) \\ &\quad + I[\frac{1}{2}r_1 w(1+\tilde{\theta}_{12}) - p_1](1-\tilde{\theta}_{12}) + (p_1-c_1)f_1 I + (p_2-c_2)f_2 I \\ &= \frac{1}{2}(N-I) + \frac{1}{2}rI + \frac{I}{2}r_2 w(2-2f_1-f_2)f_2 \\ &\quad + \frac{I}{2}r_1 w(2-f_1)f_1 - c_1 f_1 I - c_2 f_2 I, \end{aligned} \tag{17}$$

where the last equality follows by making use of inverse demand functions (8) and (9) in combination with (6) and (7). In particular, we characterize the critical consumers as $\tilde{\theta}_2 = 1 - f_1 - f_2$ and $\tilde{\theta}_{12} = 1 - f_1$. The first term in equation (17) corresponds to the average, expected surplus of the healthy population, the second one corresponds to the expected surplus of infected individuals recovering naturally, while the third and fourth terms correspond to the additional expected surplus accruing to infected individuals when buying antibiotic 1 or 2, and the last two terms are the production costs of antibiotics.

The social optimum is determined by treatment paths $0 \leq f_1 \leq 1$ and $0 \leq f_2 \leq 1$

maximizing

$$\int_0^{+\infty} e^{-\rho t} W(f_1(t), f_2(t), w(t), I(t)) dt, \tag{18}$$

subject to (3), (4), $w(0) = w_0$, $I(0) = I_0$, where $W(f_1, f_2, w, I)$ is defined by (17) and where ρ is the social discount rate. The Hamiltonian in current value for this optimization problem is

$$\begin{aligned}\mathcal{H} = &\frac{1}{2}(N - I) + \frac{1}{2} rI + \frac{I}{2} r_2 w(2 - 2f_1 - f_2) f_2 + \frac{I}{2} r_1 w(2 - f_1) f_1 \\ &- c_1 f_1 I - c_2 f_2 I - \lambda[w(1 - w)(f_1 r_1 + f_2 r_2)] + \mu[(\beta(N - I) - r)I - wI(f_1 r_1 + f_2 r_2)],\end{aligned}$$

where λ and μ are costate variables associated to antibiotic efficacy and infection, respectively. As antibiotic efficacy is a desirable resource for society, we conjecture that λ is positive and reflects the shadow price of antibiotic efficacy. This contrasts with μ, which represents the shadow cost of infection for society, and should be non-positive.[13]

Necessary conditions for maximizing (18) require for antibiotic $i = 1, 2$

$$\frac{\partial \mathcal{H}}{\partial f_i} \leq 0, \quad f_i \geq 0, \quad \frac{\partial \mathcal{H}}{\partial f_i} f_i = 0, \text{ or } \frac{\partial \mathcal{H}}{\partial f_i} \geq 0, \quad f_i \leq 1, \quad \frac{\partial \mathcal{H}}{\partial f_i}(1 - f_i) = 0, \tag{19}$$

where

$$\begin{aligned}\frac{\partial \mathcal{H}}{\partial f_1} &= [w(1 - f_1) r_1 - w f_2 r_2 - c_1] I - w r_1 [\lambda(1 - w) + \mu I], \\ \frac{\partial \mathcal{H}}{\partial f_2} &= [w r_2 (1 - f_1 - f_2) - c_2] I - w r_2 [\lambda(1 - w) + \mu I],\end{aligned}$$

as well as

$$\begin{aligned}\dot{\lambda} - \rho\lambda &= -\frac{I}{2} r_2 (2 - 2f_1 - f_2) f_2 - \frac{I}{2} r_1 (2 - f_1) f_1 \\ &\quad + (f_1 r_1 + f_2 r_2)(\lambda(1 - 2w) + \mu I), \qquad (20) \\ \dot{\mu} - \rho\mu &= \frac{(1 - r)}{2} - \frac{r_2}{2} w(2 - 2f_1 - f_2) f_2 - \frac{r_1}{2} w(2 - f_1) f_1 \\ &\quad + c_1 f_1 + c_2 f_2 - \mu[\beta(N - 2I) - r - w(f_1 r_1 + f_2 r_2)], \qquad (21) \\ \lim_{t \to +\infty} e^{-rt} \lambda(t) w(t) &= 0 \quad \text{and} \quad \lim_{t \to +\infty} e^{-rt} \mu(t) I(t) = 0. \qquad (22)\end{aligned}$$

[13] Numerical simulations confirm our conjecture as will be shown later.

Let f_1^* and f_2^* denote the socially optimal treatment rates. For an interior solution, static efficiency in (19) implies

$$w(1-f_1^*)r_1 - wr_2f_2^* = c_1 + r_1\nu(w,I,\lambda,\mu) \equiv \hat{c}_1, \tag{23}$$

$$w(1-f_1^*-f_2^*)r_2 = c_2 + r_2\nu(w,I,\lambda,\mu) \equiv \hat{c}_2, \tag{24}$$

with $\nu(w,I,\lambda,\mu) \equiv w[\frac{\lambda}{I}(1-w)+\mu]$ and where $\hat{c}_i$ is defined as the augmented marginal cost of treatment with antibiotic i. The left-hand sides of (23) and (24) can be interpreted as the price allowing for efficient rationing of antibiotic drug i, and is noted for later reference p_i^*. Hence, conditions (23) and (24) state that when in use, antibiotic i's price should be equal to its augmented marginal cost of treatment. Note that the shadow price of antibiotic efficacy adds to the augmented marginal cost, as antibiotic use involves a negative externality: current antibiotic use implies forgone efficacy in the future. However, there is also a positive externality related to antibiotic use as it allows to control for future prevalence of infection, diminishing the augmented marginal cost of antibiotic treatment. The term $\nu(w,I,\lambda,\mu)$ accounts for these two externalities and may either be positive or negative.

It can be shown that antibiotic 2 should never be produced when the antibiotic intrinsic quality per unit cost is greater for antibiotic 1 (*i.e.* $r_1/c_1 \geq r_2/c_2$). To see this, dividing (23) and (24) respectively by r_1 and r_2 results in two equations, which subtracting side by side yield

$$\frac{p_1^*}{r_1} - \frac{p_2^*}{r_2} = \frac{r_2c_1 - r_1c_2}{r_1r_2},$$

which is negative as long as $r_2c_1 - r_1c_2 \leq 0$ (*i.e.* $r_1/c_1 \geq r_2/c_2$). This finding implies that antibiotic 2 is always dominated ($r_1/p_1^* \geq r_2/p_2^*$ or equivalently $f_2^* = 0$) when $r_1/c_1 \geq r_2/c_2$. In particular, antibiotic 2 should never be used when antibiotics have the same unit cost of production (*i.e.* $c_1 = c_2$).

Notice that, given our specification, antibiotics are in a common pool of antibiotic efficacy. By contrast, Laxminarayan and Brown (2001) propose a separate pool of antibiotic efficacy. In the latter, the authors show that when unit costs of production are identical, there may

exist a phase characterized by simultaneous use of the two antibiotics as the socially-optimal outcome. This does not hold in our context as the low-quality antibiotic is then necessarily dominated.

4.1 The socially optimal steady state

The socially optimal steady state is characterized by $\dot{\mu} = \dot{\lambda} = \dot{w} = \dot{I} = 0$. Given $w_0 \in (0, 1)$ and $\dot{w} = -w(1-w)(r_1 f_1 + r_2 f_2)$, antibiotic treatment rates must satisfy $f_1 = f_2 = 0$ in steady state where $\dot{w} = 0$. Using this in equations (20) and (21) allows us to determine the shadow prices of antibiotic efficacy and infection: $\lambda^s = 0$ and $\mu^s = -(1-r)/2(\rho + N\beta - r)$, which, combined with (19) allows us to derive the steady-state level of antibiotic efficacy. It is given by the minimum of w_0 and the socially optimal viability level of each antibiotic,

$$w^s = \min(w_0, \hat{c}_1/r_1, \hat{c}_2/r_2) = \min(w_0, (c_1/r_1)/(1-\mu^s), (c_2/r_2)/(1-\mu^s)), \tag{25}$$

or, explicitly,

$$w^s = \min\left(w_0, \quad \frac{2c_1(\rho + N\beta - r)/r_1}{2(N\beta + \rho - r) + (1-r)}, \frac{2c_2(\rho + N\beta - r)/r_2}{2(N\beta + \rho - r) + (1-r)}\right). \tag{26}$$

Finally, given the evolution of infection in (4) and setting $\dot{I} = 0$ with $f_1 = f_2 = 0$ yields the steady-state level of infection $I^s = (\beta N - r)/\beta$.

Hence, the steady state in the social optimum is

$$(f_1^s = 0, f_2^s = 0, I^s, w^s). \tag{27}$$

Conditions (26) and (27) suggest that the steady-state level of antibiotic efficacy is given by the initial level w^0, whenever this lies below the minimum level of socially optimal economic viability.[14] The more interesting case arises when the steady-state level of antibiotic efficacy is endogenous and depends on initial antibiotic use, such that $w^s < w_0$.

Suppose that antibiotic 2 has the minimum level of socially optimal antibiotic viability, *i.e.* $\hat{c}_1/r_1 > \hat{c}_2/r_2$. A higher production cost, c_2, increases the minimum level of viability,

[14]Note that in this case, any of the two antibiotics should be used over the whole planning horizon.

while a higher additional recovery rate, r_2, decreases it. Clearly, a more costly antibiotic cannot sustain too low levels of antibiotic efficacy, while a more effective antibiotic can. Furthermore, the higher the social cost of infection (high values of $|\mu^s|$), the lower is the minimum level of antibiotic efficacy which can be sustained in steady state. Note that an increase in the social discount rate and disease transmission rate decreases the social cost of infection in steady state, as the future is less valued and less infection can be avoided in steady state (see later discussion on Figure 5). This, in turn, increases the minimum value of socially optimal antibiotic viability which can be sustained in steady state.[15]

4.2 The socially optimal dynamics

Given the complexity of the static and dynamic efficiency conditions (19)-(21), we run numerical simulations in order to address the dynamics of the socially optimal treatment rates, of antibiotic efficacy and infection, as well as their shadow values. As in Laxminarayan and Brown (2001), we consider a discrete time version of the model presented above and assume a finite horizon $T = 100$.[16] Note that the finite horizon impacts on the dynamics of all variables. However, for a sufficiently long time horizon, we find that dynamics exhibit the turnpike pattern, which represents a good characterization of the infinite horizon problem. We observe numerical convergence of the dynamic system to the steady state defined in (27). In particular, shadow prices of infection and antibiotic efficacy approach their steady-state levels before satisfying appropriate transversality conditions ($\lambda(T) = \mu(T) = 0$, see the appendix).

Unless specified differently, we use baseline parameter values $\rho = 0.04; c_1 = 0.004; c_2 = 0.001; r_1 = 0.17; r_2 = 0.154; r = 0.2; \beta = 0.7; N = 1; w_0 = 0.8$ and $I_0 = 0.8$. Given this set of parameters, $r_2/c_2 > r_1/c_1$, such that antibiotic 2 is not dominated. Treatment fractions f_1^* and f_2^* are shown in Figure 6 (ignore, for now, the trajectories corresponding to the open

[15]The effect of natural recovery rate, r, on the social cost of infection is ambiguous and depends on the disease transmission rate and the social discount rate. For low values of β and ρ, the natural recovery rate has the opposite effect on the social cost of infection as has the disease transmission rate.

[16]Conditions for optimality of the discrete time version with a finite horizon of this model are presented in the appendix.

access). Initially, antibiotic 1 should be used more intensively as compared to antibiotic 2, as it procures a higher additional recovery rate ($r_1 > r_2$) to individuals. As the level of antibiotic efficacy decreases, treatment with antibiotic 1 is reduced, while treatment with antibiotic 2 is intensified. Since antibiotic 2 reduces antibiotic efficacy less and is also less costly, its social desirability is increasing over time. The socially optimal level of economic viability is reached first for antibiotic 1, and later on for antibiotic 2 (because $\hat{c}_1/r_1 > \hat{c}_2/r_2$). When $I_0 = 0.5$ (graph not shown), the contagious effect dominates the recovery effect up to convergence to steady state. As a result a more intensive use is made of antibiotics, in particular of antibiotic 1, as compared to the case described above where the recovery effect initially dominates. The qualitative evolution of substitution between antibiotics is however similar to the case described above where $I_0 = 0.8$.

The robustness of the qualitative evolution of our dynamic system can be addressed via a comparative dynamic analysis. Higher values of r_1 imply a decrease of the critical level of economic viability for antibiotic 1, whereas the one associated with antibiotic 2 tends to rise. While this causes the use of antibiotic 1 to last longer, it reduces the extraction duration for antibiotic 2. These results are illustrated in Figure 3.

We also examine the effects of the infection transmission rate on treatment rates. In response to an increase in β, treatment rates decrease, which leads to a slow depletion of antibiotic efficacy during an initial phase allowing to sustain a high level of treatment rates later on. Moreover, such an increase of β leads to a longer lasting exploitation of antibiotic efficacy as illustrated in Figure 4.

We have also investigated the evolution of the shadow prices of infection and antibiotic efficacy, μ and λ. In particular, we find a negative relation between the level of infection and the shadow cost of infection as shown in Figure 5 for various values of the transmission rate β. Consider the baseline parameter case with $\beta = 0.7$. In the left panel of Figure 5, we have $I_0 = 0.5$ and as infection moves towards its steady-state level, the shadow cost of infection decreases. At the margin, an additional infected individual causes less social

cost, the smaller the gap between the current and the unavoidable, steady-state level of infection. Also note that the higher the transmission rate of infection, the lower is the social cost of infection. While this result may appear counterintuitive at first sight, it is due to the fact that the infection can be controlled at a lesser extent, such that an additional infected individual causes relatively less social cost. The right panel of Figure 5 shows the evolution of the social cost of infection, whenever the initial value of infection is relatively high ($I_0 = 0.8$). Its evolution is now non-monotonic, reflecting the pattern of undershooting below the steady-state level of infection. Notice that in both panels, the shadow price (social cost) of infection shows the turnpike pattern: it remains close to its steady-state level, before converging to zero satisfying the transversality condition $\mu(T) = 0$.

With respect to the shadow price of antibiotic efficacy, numerical simulations (graph not shown) suggest a positive relationship between antibiotic efficacy and λ. As the level of antibiotic efficacy decreases, the inverse demand function pivots inside (antibiotic consumption is less valued), which is reflected by a decreasing shadow price of antibiotic efficacy. In particular, we also find that the higher the initial level of infection, the higher will be the shadow price of antibiotic efficacy.

5 Comparing the open-access equilibrium with the social optimum

This section compares in order, the steady state and the trajectories of the open-access equilibrium with the socially optimal allocation.

5.1 Comparing steady states

Consider the case where w_0 is sufficiently high to warrant antibiotic production in the open-access and socially optimal allocation, such that $w^\infty < w_0$ and $w^s < w_0$. For $\rho < \infty$, it can be shown by comparing (14) and (25) that the steady-state level of antibiotic efficacy under open access is always greater than in the social optimum.[17] In both cases, the steady-state

[17]For the limiting case $\rho = \infty$, the level of antibiotic efficacy in steady state is identical in the open-access socially optimal allocation. This occurs because no weight is attributed to future welfare in the social optimum, such that socially optimal and open-access allocation collapse into one and the same. When

level of antibiotic efficacy corresponds to the respective level of economic viability, which in the social optimum accounts for the social cost of infection. When w_0 lies below the respective level of economic viability, no antibiotic will be used under either allocations. This implies that the steady-state antibiotic treatment rates necessarily coincide in the socially optimal and open-access allocation. Note that the steady-state levels of infection always coincide.

5.2 Comparing dynamics

When both drugs are simultaneously used, it can be shown that the socially optimal treatment fraction with antibiotic 2 coincides with the open-access equilibrium at the initial date $t_0 = 0$ regardless of the parameter values *i.e.*, $f_2^*(0) = f_2^\infty(0)$. Indeed, combining (23) and (24), we can eliminate f_1^* and obtain: $f_2^*(0) = (r_2\hat{c}_1 - r_1\hat{c}_2)/(w_0 r_2 \Delta r_f)$. Substituting for the augmented marginal cost of antibiotic use yields the desired result. However, treatment fractions of antibiotic 1 do not coincide under both allocations, *i.e.* $f_1^*(0) \neq f_1^\infty(0)$. Since $\tilde{\theta}_{12} = 1 - f_1$ and $\tilde{\theta}_2 = 1 - f_1 - f_2$, individuals characterized by θ buying either antibiotic differ even at the initial date. Furthermore, when $c_1/r_1 > c_2/r_2$, antibiotic 2 is not dominated and we also have $\hat{c}_1/r_1 > \hat{c}_2/r_2$. This result implies that antibiotic 1 always has a higher critical level of economic viability. In other words, when the two drugs are initially in use, the production of antibiotic 1 lasts less than that of antibiotic 2 under both the open-access and socially optimal allocation. Numerical simulations confirm the validity of these analytical results.

Figure 6 shows the evolution of treatment fractions in the open-access equilibrium and social optimum when $I_0 = 0.8$, while Figure 7 shows the evolution of the state variables, (I, w) for initial state $I_0 = 0.5$ and $I_0 = 0.8$. Although the smallest level of infection prevalence is obtained in the open-access equilibrium, because more intensive use is made of antibiotics initially as compared to the social optimum, the prevalence of infection is lower in the long run in the social optimum as can be seen from Figure **??**.

$\rho = \infty$, we need the shadow prices to be equal to zero for the dynamic efficiency conditions to hold in steady state.

The numerical results described here are robust for a large range of parameter values when both antibiotics are produced initially. After this phase, only antibiotic 2 is produced. In particular, both antibiotics tend to be used on a longer time scale in the social optimum as compared to the open access. It also turns out that the use of both antibiotics tends to be higher initially under open access as compared to the social optimum, whereas the opposite tends to hold later on as can be seen in Figure 6. The above results suggest that open access creates a social distortion of antibiotic efficacy, antibiotic use and infection. We will next provide an incentive mechanism allowing to correct such a distortion.

Given the particular structure of conditions given in (10), (19), (23), and (24) the tax/subsidy scheme $\tau_i = r_i \nu(w^*, I^*, \lambda^*, \mu^*), i = 1, 2$, allows to correct the distortion caused under open access. θ defined in (23) accounts for externalities (positive and negative) associated with antibiotic use along the socially optimal allocation. Whenever $\nu > 0$, the social benefit of preserving antibiotic efficacy outweighs the social cost of infection. In this case, since $r_1 > r_2$, we have $\tau_1 > \tau_2 > 0$ such that a tax should be applied to both antibiotics and the tax rate levies on antibiotic 1 should be greater. The contrary holds when $\nu < 0$.

6 Conclusion

This paper has addressed the management of antibiotics belonging to the same class used to fight an infection. While antibiotics may have different recovery rates (intrinsic qualities), they are linked to a common resource pool of antibiotic efficacy, which is endogenously determined by antibiotic use over time. We model the demand system for two antibiotics which are substitutes in fighting a given infection. The combination of the economic model with a biological model of disease transmission allows us to capture the evolution of bacterial resistance (a non-desirable bio-economic resource). While a full dynamic solution of the open-access equilibrium could be derived, we relied on numerical simulations to illustrate certain results for the social optimum as analytical solutions were not tractable. When antibiotic quality per unit cost is greater for the high-quality antibiotic, the low-quality antibiotic

should never be used under both, the open access and social optimum. However, when at least one antibiotic is initially used, open access leads to a long-run level of antibiotic efficacy, which is greater than the socially optimal level. This is the case because in the longer run, the socially optimal treatment rates are greater which allows to fight the undesirable infection. When both antibiotics are used initially, the level of economic viability of the high quality antibiotic is reached first such that the exploitation of the low-quality antibiotic lasts longer. In this context, we also find that the initial treatment rate with the low-quality antibiotic under the open-access equilibrium is socially optimal. We derive a tax/subsidy mechanism correcting potential distortions caused by open access to the resource of antibiotic efficacy.

Our results shed new light on the socially optimal order of use of antibiotics as compared to Laxminarayan and Brown (2001). When each antibiotic has its own pool of antibiotic efficacy (separate antibiotic "classes" or resource pools), the findings of these authors suggest that antibiotics may be produced simultaneously when they have the same unit cost of production. In a common class however, we have shown analytically the non validity of that result. In particular, our model suggests that in a common class of antibiotic efficacy, when antibiotic unit production costs are equal, it is not socially optimal to use the low-quality antibiotic.

We should mention that our findings are obtained under particular assumptions concerning the market structure. Other interesting considerations include a Stackelberg-type market structure where a leader produces a "brand" antibiotic and a competitive fringe provides the rest of the market with a generic version after observing the leader's production level. Furthermore, in many situations, patients have the possibility to purchase an insurance coverage which may help them buying drugs if they are infected. Incorporating these features in our model might affect the antibiotics' prices and treatment rates and ultimately, the evolution of antibiotic efficacy. How exactly these features would influence the results is however a matter for future research.

Appendix

• Proof that antibiotic 2 is dominated when $r_1/p_1 \geq r_2/p_2$

Assume that $r_1/p_1 \geq r_2/p_2$.

$$\begin{aligned}
&\{[\pi(w) + r_1 w]\theta - p_1\} - \{[\pi(w) + r_2 w]\theta - p_2\} \\
&= p_1(\frac{\theta r_1 w}{p_1} - 1) - p_2(\frac{\theta r_2 w}{p_2} - 1) \\
&\geq (p_1 - p_2)(\frac{\theta r_2 w}{p_2} - 1),
\end{aligned}$$

which is positive if $\theta \geq p_2/w r_2 \equiv \tilde{\theta}_2$.

• Discrete time numerical analysis

In a discrete time framework with a finite horizon T, given I_0 and w_0, optimality conditions for (18) require

$$\begin{aligned}
&\frac{\partial \mathcal{H}}{\partial f_1} \leq 0, f_1 \geq 0, \frac{\partial \mathcal{H}}{\partial f_1} f_1 = 0, \text{ or } \frac{\partial \mathcal{H}}{\partial f_1} \geq 0, f_1 \leq 1, \frac{\partial \mathcal{H}}{\partial f_1}(1 - f_1) = 0, \\
&\Delta\lambda - \rho\lambda = -\frac{I}{2} r_2(2 - 2f_1 - f_2) f_2 - \frac{I}{2} r_1(2 - f_1) f_1 + (f_1 r_1 + f_2 r_2)(\lambda(1 - 2w) + \mu I), \\
&\Delta\mu - \rho\mu = \frac{(1 - r)}{2} - \frac{r_2}{2} w(2 - 2f_1 - f_2) f_2 - \frac{r_1}{2} w(2 - f_1) f_1 + c_1 f_1 + c_2 f_2 \\
&- \mu[\beta(N - 2I) - r - w(f_1 r_1 + f_2 r_2)], \\
&\Delta w = -w(1 - w)(f_1 r_1 + f_2 r_2), \\
&\Delta I = [\beta(N - I) - r - w(f_1 r_1 + f_2 r_2)] I, \\
&\lambda(T) = 0; \quad \mu(T) = 0.
\end{aligned}$$

where $\Delta\mu(t) = \mu(t+1) - \mu(t)$, $\Delta w(t) = w(t+1) - w(t)$, $\Delta I(t) = I(t+1) - I(t)$ and $\Delta\lambda(t) = \lambda(t+1) - \lambda(t)$ for $t = 0, 1, ...T - 1$.

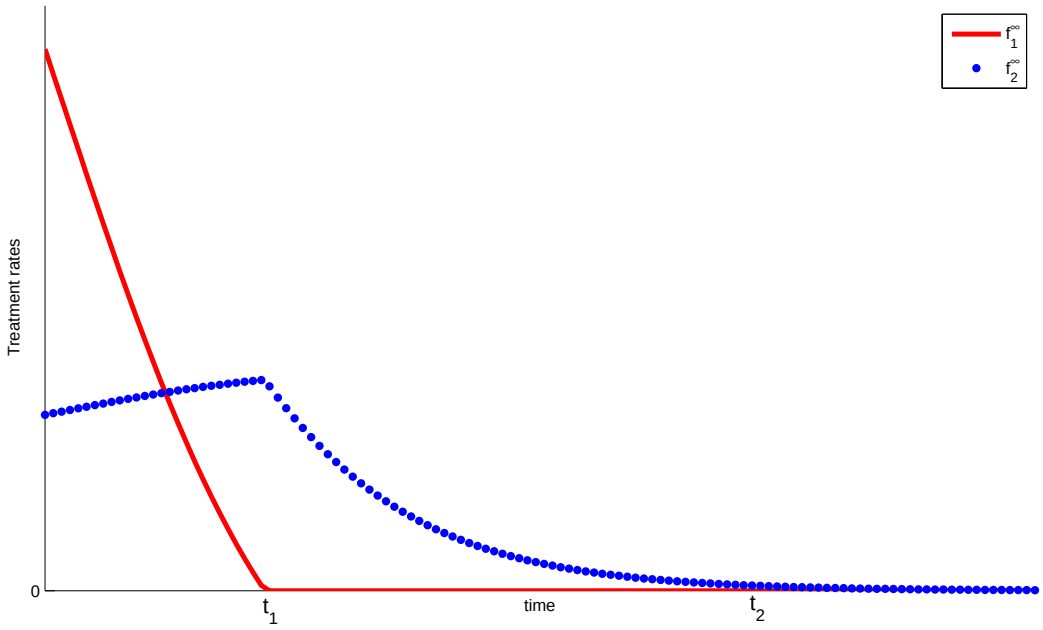

Figure 1: Treatment rates in open access when $w_0 > (c_1 - c_2)/\Delta r_f$ and $r_2/c_2 > r_1/c_1$.

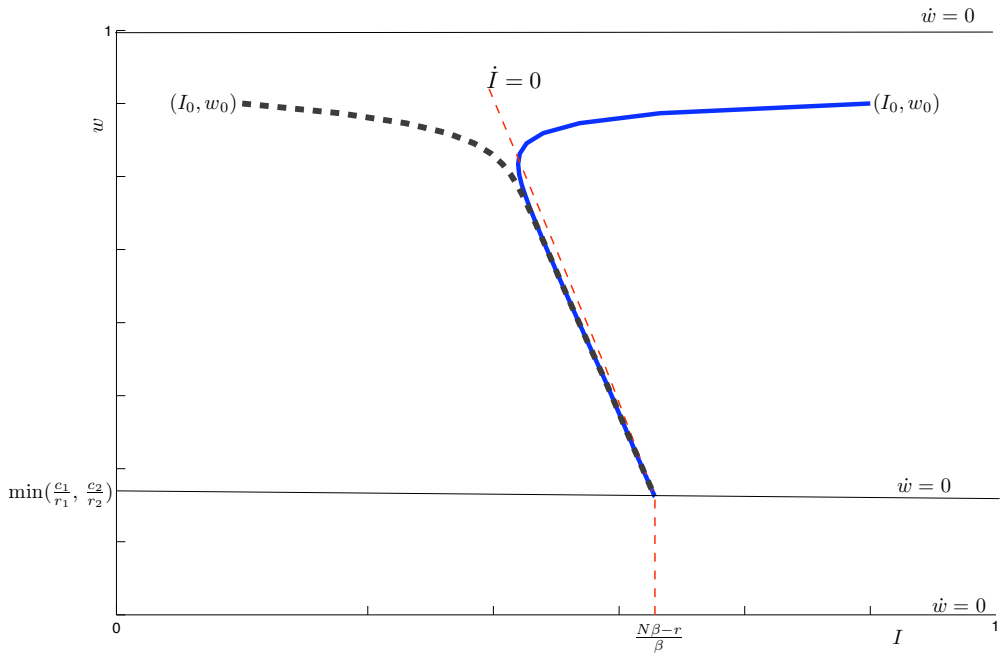

Figure 2: Phase diagram representing (I, w)-space in open access.

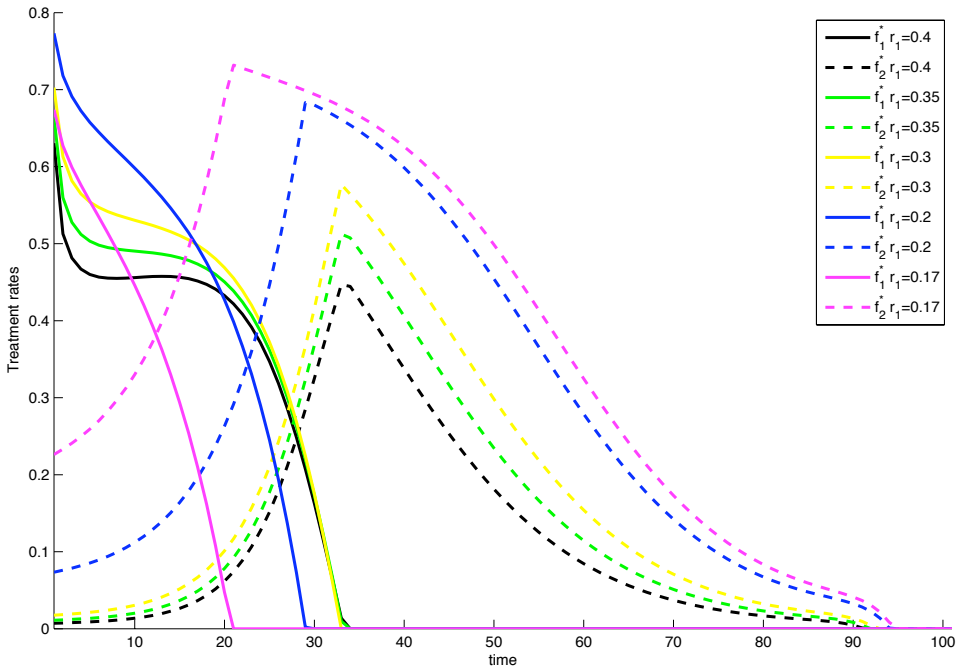

Figure 3: Effects of varying r_1 on the socially-optimal treatment rates

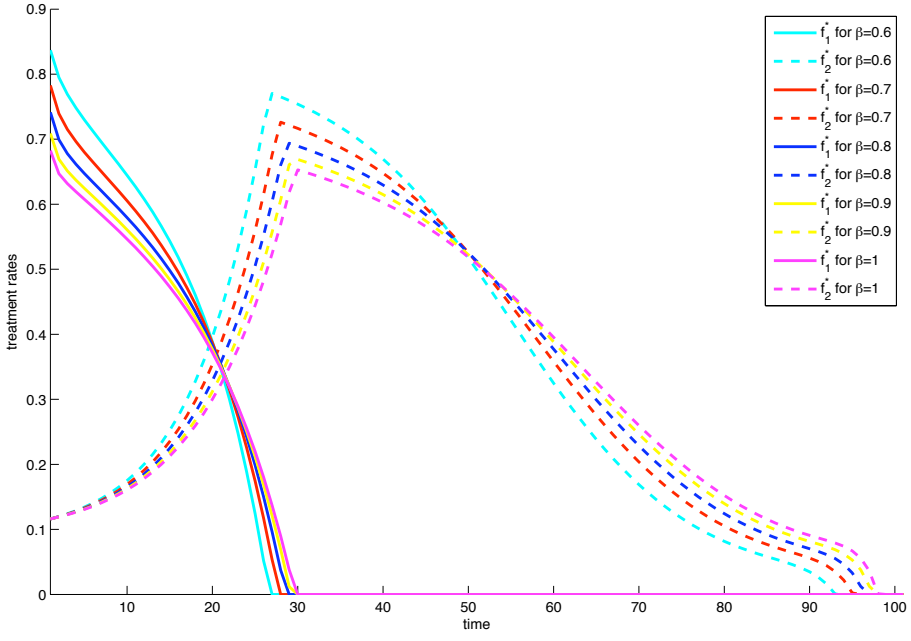

Figure 4: Effects of varying β on the socially-optimal treatment rates

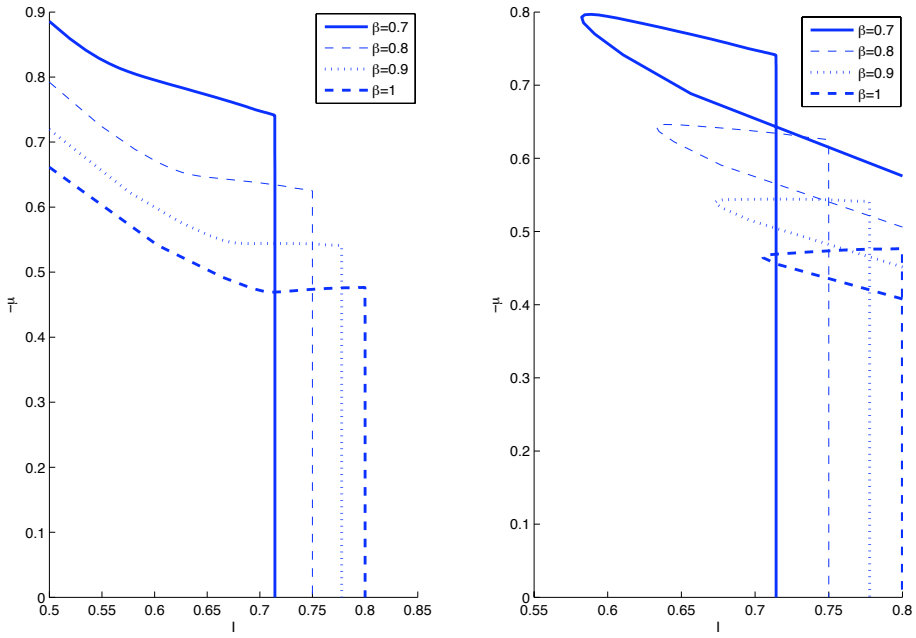

Figure 5: Effects of varying β on the evolution of $(I, -\mu)$.

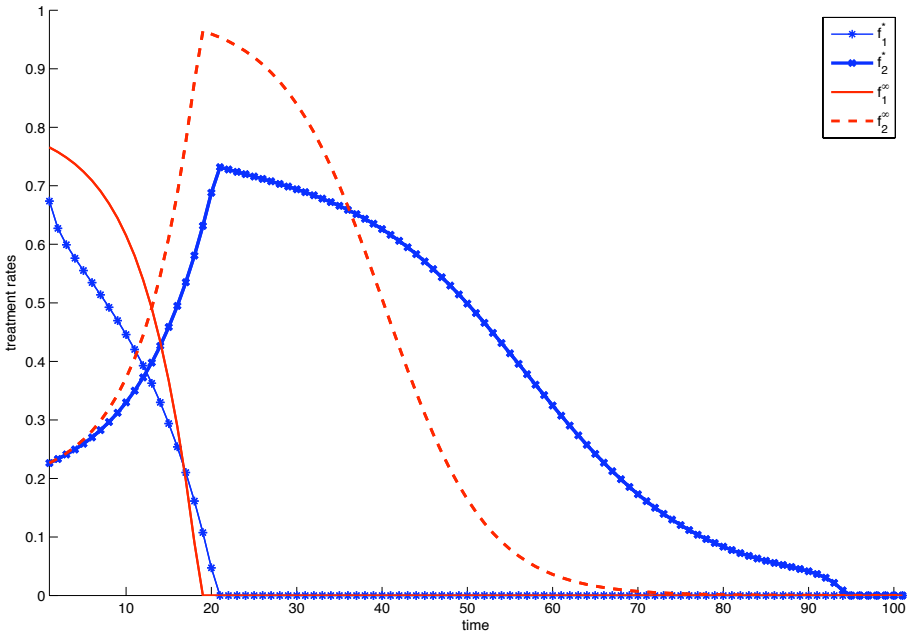

Figure 6: Comparing socially optimal and open-access treatment rates for $I_0 = 0.8$.

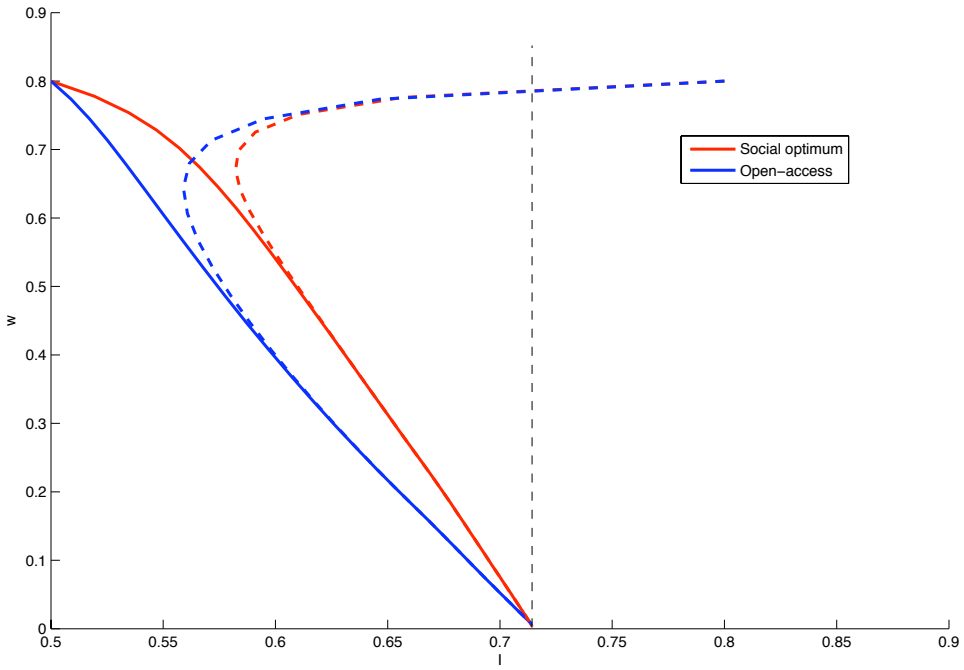

Figure 7: Comparing socially optimal and open-access evolution of (I, w).

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