Open access to the resource of antibiotic treatment efficacy subject to bacterial resistance[1]

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Abstract

In this paper, we are interested in how a pharmaceutical industry manages existing antibiotic drugs in the context of bacterial resistance. We consider a model based on an epidemiological framework where antibiotic recovery rates, *and thus intrinsic qualities*, may differ. Antibiotic efficacy is modeled as a common pool of a non-renewable resource to which antibiotic producers have open access. The paper derives antibiotic demands within a vertical differentiation model and characterizes the dynamics of infected individuals, antibiotic efficacy and treatment rates under the open-access and the socially optimal allocation. We show that the high-quality antibiotic drug loses its comparative advantage over time under both allocations, such that the low-quality drug should be used longer. This occurs at a later point of time in the social optimum and allows for a better control of infection in the longer run. In contrast with the ambiguous outcome reported in the literature, the socially optimal steady-state level of antibiotic efficacy is lower than that of the open-access allocation. We also extend our analysis to a strategic, duopolistic context.

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

JEL classification: L13; Q21; I18

1 Introduction

There is a growing scientific consensus that antibiotic use to cure infectious diseases causes the rise of resistant bacteria. The main driving mechanism is that of "natural selection." As bacteria get in contact with an antibiotic drug, only susceptible bacteria die, while naturally resistant ones may survive. Bacterial resistance entails economic costs and may have severe consequences for public health (see for instance, Holmberg et al., 1987; Phelps, 1989; Gersovitz and Hammer, 2004; Extending the Cure, 2011). In order to mitigate the cost of bacterial resistance, understanding the market allocation of antibiotic use and its potential distortions becomes crucial.

The purpose of this paper is to examine how bacterial resistance with respect to a class of antibiotics evolves, when there is open access on behalf of antibiotic producers to the common pool of antibiotic efficacy. We compare the market allocation with the socially optimal use of antibiotics. To do this, we incorporate an economic dimension into an epidemiological model of resistance introduced by Laxminarayan and Brown (2001) and Bonhoeffer et al. (1997), which allows to address the evolution of bacterial resistance, infection, and endogenous substitution between antibiotics. While antibiotics differ with respect to the additional recovery they procure to the infected individuals (their intrinsic quality), we assume that all antibiotics are linked to a common pool of treatment efficacy, which can be modelled as a non-renewable resource (see, Coates et al., 2011).[1] The market allocation resulting from firms having open access to the common resource pool and infected individuals substituting between antibiotics raises a number of research questions. How does the firms' behavior within a pharmaceutical industry affect antibiotic use and treatment efficacy over time? What is the socially optimal order of use of antibiotics? Can firms' output decisions sustain the socially optimal use of antibiotics?

In order to address these questions, we first characterize the open-access market allocation

[1] As an example, the penicillin class comprises a multitude of antibiotics. The treatment effectiveness of this class to fight several infections has been decreasing in recent years, which we model here as the decrease of a valuable bio-economic resource.

of antibiotics which results from firms entering the market as long as there is a positive rent. Our results indicate that when two drugs are in use, the fraction of individuals buying the high-quality antibiotic tends to decline, while the fraction of those buying the low-quality antibiotic tends to rise. This result can be attributed to the fact that as the overall antibiotic treatment efficacy decreases, antibiotic demand of the high-quality drug shifts down and the high-quality drug loses its comparative advantage from a consumer's point of view. When the low quality drug's ratio of additional recovery rate per unit cost is relatively lower as compared to the high quality one, the low quality drug is dominated and should never be produced.

We also look at the socially optimal use of antibiotics. Our analysis suggests that when antibiotic quality per unit cost of production is greater for the high-quality drug, the low-quality one is dominated and should never be used as in the open-access allocation. We find that inter-temporal antibiotic use is such that the socially optimal steady-state level of antibiotic efficacy is lower than that of the open-access case. When both antibiotics are initially used, the critical level of economic viability of the high quality antibiotic is reached first such that the exploitation of the low-quality antibiotic lasts longer within both, the open-access and socially optimal outcome. Numerical simulations indicate that the prevalence of infection remains lower in the long run in the social optimum, where a more intensive use of antibiotics is made as compared to the open access.

Our paper fits in the literature developed by natural resource economists who have modelled antibiotic efficacy as a natural resource, which may be — depending on the epidemiological specification — renewable or non-renewable. A remarkable contribution is the seminal paper by Laxminarayan and Brown (2001), which 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. This regime prevails up to a point of time where the antibiotic efficacy levels are equal. After that,

it becomes efficient to use both antibiotics simultaneously. Our approach differs from that of Laxminarayan and Brown (2001) in three ways. First, these authors abstract from the individuals' behavior, and thus antibiotic demand in their analysis, which allows them to analyze the socially optimal use only. In contrast, this paper deals with a continuum of individuals choosing between two antibiotics, each individual having a different valuation of being in good health. We endogenously derive antibiotic demand for each antibiotic drug. Second, in contrast to the former study, antibiotics' recovery rates may differ in this paper. Finally, in addition to the socially optimal use of antibiotics examined by these authors, this paper asks as in Herrmann and Gaudet (2009) if the equilibrium outcome of firms producing antibiotics under open access may be socially optimal. Herrmann and Gaudet (2009) find that, when antibiotic efficacy is renewable, firms producing an antibiotic generate a steady-state level of antibiotic efficacy, which depending on parameter configurations, may be greater or lower than its socially-optimal level. Other interesting contributions examine the use of drugs produced by a monopolist in various contexts. 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. 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. Our model generalizes the three contributions mentioned before to the case where substitution between two antibiotics of different intrinsic quality is possible.

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. Section 6 presents an extension of the basic model, where strategic effects are considered in a duopolistic setting. We conclude in Section 7.

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 $i = 1, 2$. 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 $I(t)$. An infected individual is susceptible to either antibiotic treatment or resistant to both, which allows us to concentrate on the substitution occurring between antibiotics for the treatment of a given infection. 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, $I(t) = I_w(t) + I_r(t) = N - S(t)$.

Infected individuals can infect the healthy population through contact with them. Let β represent the transmission rate of each type of infection 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. While the natural rate of recovery is r_r for those infected with the drug-resistant strain, the natural rate of recovery for those infected with the drug-susceptible strain is r_w. In the epidemiological literature, the difference $\Delta r = r_r - r_w$ is referred to as the fitness cost associated to the resistant strains and is generally assumed to be positive. The knowledge of the some bacteria to resist antibiotic treatment comes at the cost that they survive at a lower rate (*i.e.*, lower fitness) when no antibiotic is used (an individual naturally recovers at a higher rate when infected with a resistant strain). 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 high recovery rate as compared to antibiotics 2, $r_1 > r_2$, *i.e.* antibiotic 1 is of higher quality than antibiotic 2.

Denote by $f_i \in [0,1]$ the fraction of the infected population that is being treated with antibiotic i. Recovery from the drug-susceptible infection is given by $r_w + f_1 r_1 + f_2 r_2$, such that the total infected population decreases at the rate $r_r I_r(t) + (r_w + f_1 r_1 + f_2 r_2) I_w(t)$. The population dynamics are then given by

$$\dot{S} = -\dot{I} = -\dot{I}_r - \dot{I}_w, \tag{1}$$

$$\dot{I}_w = (\beta S - r_w - f_1 r_1 - f_2 r_2) I_w, \tag{2}$$

$$\dot{I}_r = (\beta S - r_r) I_r. \tag{3}$$

As in Laxminarayan and Brown (2001) and Herrmann and Gaudet (2009), we define $w = I_w/I$ as the level of antibiotic efficacy. Making use of the definition of antibiotic efficacy, these equations can be transformed to

$$\dot{w} = w(1-w)(\Delta r - f_1 r_1 - f_2 r_2), \tag{4}$$

$$\dot{I} = (\beta(N - I) - r_r) I + wI(\Delta r - f_1 r_1 - f_2 r_2). \tag{5}$$

Note that increasing marginally the treatment rate of antibiotic 1, f_1, slows down more intensively the possible regeneration of antibiotic efficacy, while it improves the control of infection, as compared to the treatment rate of antibiotic 2. Antibiotic 1 thus exerts a relatively higher selection pressure on drug-susceptible infection.

The dynamic system given by (4) and (5) suggests the existence of three possible steady states. First, for a particular combination of treatment rates, such that $\Delta r = f_1 r_1 + f_2 r_2$, antibiotic efficacy remains constant at a level $\hat{w} \in [0,1]$. This results in the steady state

$$(I^S, w^S) = (N - r_r/\beta, \hat{w}). \tag{6}$$

If $\Delta r \neq f_1 r_1 + f_2 r_2$, there are two other steady states associated to the efficacy levels $w = 0$ and $w = 1$, which are

$$\left(I^S, w^S\right) = \left(N - r_r/\beta, 0\right) \tag{7}$$

and

$$(I^S, w^S) = ([N\beta - r_w - f_1 r_1 - f_2 r_2]/\beta, 1)\,. \tag{8}$$

2.2 Endogenous demands of antibiotics

Let θ denote an individual's valuation to be in good health, with θ being 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 the two antibiotics and that the infected individual does not know from which type of infection (resistant or susceptible) he is suffering, but knows the level of antibiotic efficacy, w. It follows that the infected individual attributes probability $\frac{I_r}{I} = 1 - w$ of being infected with the resistant strain, implying a recovery rate r_r whether he consumes an antibiotic or not. Furthermore, there is a probability $\frac{I_w}{I} = w$ of being infected with the drug-susceptible strain. In the latter situation, if he does not take any antibiotic, he can expect to recover naturally at the rate r_w. The expected natural recovery rate of an individual without any antibiotic treatment is then given by

$$\pi(w) = (1 - w)r_r + wr_w.$$

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 expect utility function for an individual of type θ

$$v(\theta) = \begin{cases} \theta & \text{if in good health;} \\ \pi(w)\theta & \text{if infected and not taking any antibiotic ;} \\ [\pi(w) + r_i w]\theta & \text{if infected and taking antibiotic } i. \end{cases} \tag{9}$$

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

$$\tilde{\theta}_{12} = \frac{p_1 - p_2}{w\Delta r_f}. \tag{10}$$

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

$$\tilde{\theta}_i = p_i / w r_i, i = 1, 2. \tag{11}$$

First, assume that $r_1/p_1 \geq r_2/p_2$ (that is, the "antibiotic grade 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 so that antibiotic 2 is not purchased. 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. Since

individual demand is unitary, the total demand for antibiotics 1 and 2 are respectively

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

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

$$p_1(f_1, f_2) = w[r_1(1 - f_1) - r_2 f_2], \tag{12}$$
$$p_2(f_1, f_2) = w r_2[1 - f_1 - f_2]. \tag{13}$$

Notice that these inverse demand functions are linear in the treatment fraction, and that a variation in antibiotic efficacy makes them pivot around the point where price is zero. Furthermore, for a given value of $f_2 \in [0, 1)$, $w(r_1 - r_2 f_2)$ is the antibiotic 1 choke price, which is the price at which its demand falls to zero. Likewise, for a given value of $f_1 \in [0, 1)$, the choke price for the antibiotic 2 is $w r_2(1 - f_1)$. If the quality of the two drugs is equal to zero ($w = 0$), so will be the price ($p_1 = p_2 = 0$) individuals are willing to pay such that demand is zero ($f_1 = f_2 = 0$). However, when antibiotic 2 is dominated (*i.e.* $r_1/p_1 \geq r_2/p_2$) we always have $f_2 = 0$, and the inverse demand for antibiotic 1 in terms of f_1 is:[2]

$$p_1(f_1) = w r_1(1 - f_1). \tag{14}$$

In this study, as in Laxminarayan and Brown (2001), we will restrict our attention to situations where the fitness cost is equal to zero (*i.e.* $r_r = r_w = r$).[3] In such a case (*i.e.*

[2]Notice that the inverse demands associated to the case where antibiotic 2 is dominated are merely the restriction of (12) and (13) to $f_2 = 0$.

[3] Certain bacteria can be virulent without losing their of resistance (see for instance Björkman et al., 1998).

$\Delta r = 0$), laws of motion (4) and (5) become:

$$\dot{w} = -w(1-w)(f_1 r_1 + f_2 r_2), \tag{15}$$

$$\dot{I} = (\beta(N-I) - r)I - wI(f_1 r_1 + f_2 r_2), \tag{16}$$

Furthermore, let $C_i(Q_i) = c_i Q_i$ denote the cost associated to the production of Q_i units of antibiotic i by a firm, where $c_i > 0$ is the unit production cost of antibiotic i.

3 Antibiotic use under open access

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

$$[p_i - c_i]f_i = 0, \;\; 0 \leq f_i \leq 1 \;\text{ and }\; p_i \leq c_i, \;\; i = 1, 2. \tag{17}$$

In order to derive the open-access equilibrium, it is helpful to distinguish two cases depending on the relative magnitude of the unit cost 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 (17) along with (12) and (13) allow us to derive the fraction of the infected population that buys antibiotic 1. It is given by

$$f_1^{\infty}(t) = \begin{cases} 1 - \frac{c_1 - c_2}{w(t)\Delta r_f} & \text{if } w(t) > \frac{c_1 - c_2}{\Delta r_f}; \\ 0 & \text{otherwise }, \end{cases} \tag{18}$$

where the superscript ∞ stands for the open-access equilibrium. Likewise, the fraction of the infected population treated with antibiotic 2 is:[4]

$$f_2^{\infty}(t) = \begin{cases} \frac{1}{w(t) r_2 \Delta r_f}(r_2 c_1 - r_1 c_2) & \text{if } w(t) > \frac{c_1 - c_2}{\Delta r_f}; \\ 1 - \frac{c_2}{w(t) r_2} & \text{if } \frac{c_2}{r_2} < w(t) \leq \frac{c_1 - c_2}{\Delta r_f}\ ; \\ 0 & \text{otherwise }. \end{cases} \tag{19}$$

[4]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.

Consider now the case where antibiotic quality per unit cost is greater for antibiotic 1, *i.e.* $r_1/c_1 \geq r_2/c_2$ (or equivalently $r_2c_1 - r_1c_2 \leq 0$). In this situation, antibiotic 2 is dominated so that $f_2^\infty(t) = 0$ for all $t \geq 0$.[5] Using condition (17) along with (14), we get:

$$f_1^\infty(t) = \begin{cases} 1 - \frac{c_1}{w(t)r_1} & \text{if } w(t) > \frac{c_1}{r_1}; \\ 0 & \text{otherwise .} \end{cases} \tag{20}$$

The above results suggest three main conclusions, which will help us to characterize the equilibrium trajectories of antibiotic use under open access. First, the firms' treatment decisions are independent of the stock of infected individuals (the market size). This result is intuitive because firms under open access are benevolent (they do not gain any rent from production). Second, there exists a critical level of antibiotic efficacy, below which no antibiotic will be produced in the open-access equilibrium. The 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 other model parameters, there exist four possible regimes, denoted by D, F and $A_i, i = 1, 2$. In regime D, the two antibiotics are produced simultaneously, in regime F no individual buys an antibiotic and in regime A_i, only antibiotic i is produced. These findings will help us to fully characterize the open-access allocation.

3.1 The steady state in 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 (5) 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: $I^\infty = I^S$. Therefore, the steady state in the open-access equilibrium is

$$(f_1^{S\infty}, f_2^{S\infty}, I^\infty, w^\infty) = (0, 0, I^S, \min(w_0, c_1/r_1, c_2/r_2)), \tag{21}$$

where $w^\infty = w_0$ in the case where it is never economically viable to use any antibiotic because its initial level of antibiotic efficacy was insufficient.

[5] If antibiotic 2 where not dominated at date t, we would have $f_2^\infty(t) > 0$. This is not possible. Indeed, when $r_2c_1 - r_1c_2 \leq 0$ the interval $[\frac{c_2}{r_2}, \frac{c_1 - c_2}{\Delta r_f}]$ is empty. Hence, (19) indicates that $f_2^\infty(t)$ cannot be positive in such a case.

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 is decreasing and it has a limit which is its steady state. Also note that, having assumed $r_1 > r_2$, we always have

$$\frac{c_1 - c_2}{\Delta r_f} > \frac{r_2 c_1 - r_1 c_2}{r_2 \Delta r_f}. \tag{22}$$

As we will show, condition (22) and the particular structure of (18) and (19) suggest the existence of critical values of the initial efficacy level w_0 and other parameter values, which distinguish four possible cases for the dynamic behavior of the model.

The first case corresponds to the initial efficacy levels $w_0 > (c_1 - c_2)/\Delta r_f$ and $r_2/c_2 > r_1/c_1$. In this case, (18) and (19) indicate that initially regime D prevails over the interval of time $[0, t_1)$, where t_1 represents the length of time over which $w(t)$ lies above $(c_1 - c_2)/\Delta r_f$. Notice that t_1 is defined by $w(t_1) = (c_1 - c_2)/\Delta r_f$ and t_1 is finite. To see this, note that over the interval $(0, t_1)$, $f_1^\infty > 0$ and $f_2^\infty > 0$. Using (18) and (19) along with (15), we get $\dot{w} = (1 - w)(c_1 - r_1 w)$. Integration yields

$$w(t) = \frac{-c_1(1 - w_0) + (c_1 - r_1 w_0)e^{t(c_1 - r_1)}}{-r_1(1 - w_0) + (c_1 - r_1 w_0)e^{t(c_1 - r_1)}}, 0 \leq t \leq t_1. \tag{23}$$

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 $\lim_{t \to +\infty} h(t) = c_1/r_1 - (c_1 - c_2)/\Delta r_f < 0$.[6] Since w is monotone, so is h. Therefore, it exists a unique $t_1 \in (0, \infty)$ such that $w(t_1) = (c_1 - c_2)/\Delta r_f$. Equations (18)-(19) and (22) 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 $\dot{w} = -w(1 - w)r_2 f_2^\infty = -(1 - w)(r_2 - c_2 w)$, with the boundary condition $w(t_1) = (c_1 - c_2)/\Delta r_f$. Using a similar reasoning as for regime D, it can

[6] 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 $(0, +\infty)$.

be shown that A_2 has a finite length. Since we have $w(t_2) = c_2/r_2$, (18) and (19) show that regime F prevails from t_2 forever. Since in regime F, $f_1^\infty = f_2^\infty = 0$, the level of antibiotic efficacy remains constant $w(t) = c_2/r_2$ for all $t \geq t_2$. These results are illustrated in Figure 1. As antibiotic efficacy tends to decrease, patients switch from antibiotic 1 to antibiotic 2, which has greater relative grade $r_2/c_2 > r_1/c_1$. This pattern continues until antibiotic 1 becomes not economically viable. After this instant, the fraction of individuals using antibiotic 2 decreases up to a point where antibiotic efficacy (or quality) becomes very small leading to non economic viability of antibiotics. These results may be attribute to the fact that as antibiotic efficacy decreases (or equivalently resistance increases), antibiotic demands diminish. Moreover, for a given dose, (15) suggests that antibiotic 1 lowers antibiotic efficacy than antibiotic 2 does.

The second case is for initial efficacy levels $(c_1 - c_2)/\Delta r_f \geq w_0 > c_2/r_2$, 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 $f_2^\infty > 0$, (15) indicates that 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 see that t_3 is finite. Since we have $w(t_3) = c_2/r_2$, (18) and (19) 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 ($f_2^\infty = 0$). So, (15) and (20) 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, (18), (19) and (20) show that in this case, the

two antibiotics are not economically viable ($f_1^\infty = f_2^\infty = 0$). So, (15) 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 $f_1 = f_2 = 0$, (16) indicates that $\dot{I} \gtreqless 0$, if and only if $I \lesseqgtr I^S$. Hence, when starting below the biological steady state I^S, the stock of infected individual rises monotonically and converges to I^S defined in (6). However, when starting above I^S, the stock of infected individual declines monotonically and converges to I^S.

The dynamics of the open-access equilibrium for the first case as described above is illustrated in space (I, w) in Figure 2.[7] When initially located to the left of the isocline $\dot{I} = 0$, the stock of infected individuals rises and converges to the biological steady state given in (6). However, when initially located to the right of the isocline $\dot{I} = 0$, the stock of infected individuals evolves non-monotonically: it initially falls below its steady-state level, before it starts to increase again up to convergence to its steady-state level. This pattern of "undershooting" in the level of infection is caused by epidemiology (see, for instance Wilen and Msangi, 2003), in particular the underlying assumption on disease transmission.

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

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. Its expression is given by

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

Integration yields

$$\begin{aligned} W(f_1, f_2, w, I) &= \frac{1}{2}(N - I) + \frac{1}{2} r I + I[\frac{1}{2} r_2 w(\tilde{\theta}_{12} + \tilde{\theta}_2) - p_2](\tilde{\theta}_{12} - \tilde{\theta}_2) \\ &\quad + I[\frac{1}{2} r_1 w(1 + \tilde{\theta}_{12}) - p_1](1 - \tilde{\theta}_{12}) + (p_1 - c_1) f_1 I + (p_2 - c_2) f_2 I \\ &= \frac{1}{2}(N - I) + \frac{1}{2} r I + \frac{I}{2} r_2 w(2 - 2 f_1 - f_2) f_2 \\ &\quad + \frac{I}{2} r_1 w(2 - f_1) f_1 - c_1 f_1 I - c_2 f_2 I, \end{aligned} \tag{24}$$

where the last equality follows by making use of inverse demand functions (12) and (13) in combination with (10) and (11). 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 (24) corresponds to the average, expected surplus of the healthy population, the second one corresponds to the expected surplus of infected individuals recovering naturally, 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

$$\int_0^{+\infty} e^{-\rho t} W(f_1(t), f_2(t), w(t), I(t)) dt, \tag{25}$$

subject to (15), (16), $w(0) = w_0$, $I(0) = I_0$, where $W(f_1, f_2, w, I)$ is defined by (24) and where ρ is the social discount rate. The Hamiltonian in current value for this optimization problem is

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

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 implicit value of antibiotic efficacy. This contrasts with μ, which represents the implicit cost of infection for society, and should be non-positive.[8]

Optimality conditions for (25) require for antibiotic $i = 1, 2$

$$\frac{\partial \mathcal{H}}{\partial f_i} \leq 0, \quad f_i \geq 0, \quad \frac{\partial \mathcal{H}}{\partial f_i} f_i = 0, \text{ or } \frac{\partial \mathcal{H}}{\partial f_i} \geq 0, \quad f_i \leq 1, \quad \frac{\partial \mathcal{H}}{\partial f_i}(1-f_i) = 0, \tag{26}$$

where

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

as well as

$$\dot{\lambda} - \rho\lambda = -\frac{I}{2}r_2(2-2f_1-f_2)f_2 - \frac{I}{2}r_1(2-f_1)f_1$$
$$+(f_1 r_1 + f_2 r_2)(\lambda(1-2w) + \mu I), \tag{27}$$
$$\dot{\mu} - \rho\mu = \frac{(1-r)}{2} - \frac{r_2}{2}w(2-2f_1-f_2)f_2 - \frac{r_1}{2}w(2-f_1)f_1$$
$$+c_1 f_1 + c_2 f_2 - \mu[\beta(N-2I) - r - w(f_1 r_1 + f_2 r_2)], \tag{28}$$
$$\lim_{t\to+\infty} e^{-rt}\lambda(t)w(t) = 0 \quad \text{and} \quad \lim_{t\to+\infty} e^{-rt}\mu(t)I(t) = 0, \tag{29}$$

Let f_1^* and f_2^* denote the socially optimal treatment rates. For an interior solution, static efficiency in (26) implies

$$w(1-f_1^*)r_1 - w r_2 f_2^* = c_1 + w r_1[\frac{\lambda}{I}(1-w) + \mu] \equiv \hat{c}_1, \tag{30}$$
$$w(1-f_1^*-f_2^*)r_2 = c_2 + w r_2[\frac{\lambda}{I}(1-w) + \mu] \equiv \hat{c}_2. \tag{31}$$

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

where $\hat{c}_i$ is defined as the augmented marginal cost of treatment with antibiotic i. The left-hand sides of (30) and (31) represent antibiotic 1's and 2's socially optimal price, respectively. Hence, conditions (30) and (31) state that when in use, antibiotic i's price should be equal to its augmented marginal cost of treatment. Note that the implicit value 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.

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 (30) and (31) respectively by r_1 and r_2 results in two equations, which subtracting side by side yield

$$\frac{p_1}{r_1} - \frac{p_2}{r_2} = \frac{r_2 c_1 - r_1 c_2}{r_1 r_2},$$

which is negative as long as $r_2 c_1 - r_1 c_2 \leq 0$ (*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 defined by $\dot{\mu} = \dot{\lambda} = \dot{w} = \dot{I} = 0$. Since $w_0 \in (0, 1)$ and w is decreasing, the biological steady state where $w = 1$ as given in (8) is not sustainable. The

biological steady state where $w = 0$ as given in(7) is also unsustainable because treatment rates must fall to zero form the instant on, where antibiotic efficacy reaches its viability level, $\min(w_0, \hat{c}_1/r_1, \hat{c}_2/r_2)$. Denote by w^s the steady-state level of antibiotic efficacy. We then have: (i) $w^s \in (0, 1)$ and (ii) w^s is equal to the long run antibiotic efficacy viability level.

At the steady state, we have $\dot{w} = -w(1-w)(r_1 f_1 + r_2 f_2) = 0$, which implies that $f_1 = f_2 = 0$. Combining these results along with (26)-(29) yields the steady state for shadow prices: $\lambda^s = 0$ and $\mu^s = -(1-r)/2(\rho + N\beta - r)$. Using the fact that w^s is equal to the long run viability level of antibiotic use, it can be shown that

$$w^s = \min\left(w_0, \quad \frac{2c_1(\rho + N\beta - r)/r_1}{2(N\beta + \rho - r) + (1-r)}, \frac{2c_2(\rho + N\beta - r)/r_2}{2(N\beta + \rho - r) + (1-r)}\right). \tag{32}$$

Hence, the steady-state level of the social optimum is

$$(f_1^s, f_2^s, I^s, w^s) = (0, 0, I^S, w^s), \tag{33}$$

where w^s and I^S are defined by (6) and (32), respectively.

Condition (33) suggests that no antibiotic is used in the social optimum when the initial level of antibiotic efficacy falls below the socially optimal levels of economic viability, in which case the level of antibiotic efficacy remains constant over time at w_0. The more interesting case arises when at least one antibiotic should be used initially. In such a case, $w^s < w_0$ and it can be shown that an increase in the discounted rate ρ or the transmission rate of infections β tends to increase w^s.

4.2 The socially optimal dynamics

Given the complexity of the static and dynamic efficiency conditions (26)-(28), 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 $T = 100$.[9] Note that the finite horizon impacts on the dynamics of all variables. However, for a sufficiently long time horizon, dynamics exhibit the turnpike pattern, which allows a good characterization of the infinite horizon problem. In particular, we observe numerical convergence to the steady state as defined in (33), while shadow values 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 $I_0 = 0.8$.[10] Treatment fractions f_1^* and f_2^* are shown in Figure 6 (ignore, for now, the trajectories corresponding to the open access). Initially, antibiotic 1 should be used more intensively as compared to antibiotic 2, as is 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. More importance is given to the antibiotic which diminishes antibiotic efficacy less and is also less costly. The socially optimal level of economic viability is reached first for antibiotic 1, and later on for antibiotic 2. When $I_0 = 0.5$ (graph not shown), more intensive use is made of antibiotics, in particular of antibiotic 1. The qualitative evolution with respect to the treatment rates is similar.

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. Overall, such an increase of β leads to an intensive exploitation of antibiotic efficacy

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

[10] Given these parameter values, we have $r_2/c_2 > r_1/c_1$. Our previous analysis hence suggests that antibiotic 2 is not dominated.

as illustrated in Figure 4.

We have also investigated the evolution of the shadow values, 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, 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 levels 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 implicit 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 implicit value 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 implicit value of antibiotic efficacy. In particular, we also find that the higher the initial level of infection, the higher will be the implicit value 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 interesting case in steady states (21) and (33) where w_0 is sufficiently high to warrant antibiotic production in the open-access and socially optimal allocation. It can be shown by comparing (21) and (33) that the steady-state level of antibiotic efficacy under open access is always greater than in the social optimum. This occurs, because a more intensive use of antibiotics must have been made in the social optimum while antibiotics are used, a point which we address in what follows. The steady-state level of antibiotic efficacy corresponds to the respective level of economic viability. When w_0 lies below the respective level of economic viability, no antibiotic will be used under both allocations. This implies that the steady-state antibiotic treatment rates necessarily coincide in the socially optimal and open-access allocation. Note that this also implies the steady-state levels of infection to 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 (30) and (31), 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 8.

The numerical results described here are robust for a large range of parameter values when both antibiotics are produced initially. After that, 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, whereas the opposite tends to hold later on as can be seen in Figure 6.

6 Addressing strategic effects in the pharmaceutical industry

Having modeled antibiotic producers as having open access to the common pool of antibiotic efficacy represents an interesting benchmark, particularly for generic producers, as the biological formulae has become common knowledge. However, this abstracts from strategic interaction between producers, to which we now turn. In particular, we make the assumption that each antibiotic is produced by a single firm, such that the market consists of a duopoly. Each firm acts non-myopically in the sense that it takes into account the effects of its current treatment decision on future levels of antibiotic efficacy and infection. Firm i chooses the treatment path $0 \leq f_i(t) \leq 1$ that maximizes its discounted profit, considering as given the treatment strategy of the other firm, j. Current profit of firm i at time t is given by $\pi_i(t) = [p_i(f_1(t), f_2(t)) - c_i] f_i(t) I(t)$. Taking f_j as given, the intertemporal problem of firm i then becomes

$$\max_{0 \leq f_i \leq 1} \int_0^{+\infty} e^{-\rho t} \pi_i(t) dt, \tag{34}$$

subject to (15), (16), $w(0) = w_0$ and $I(0) = I_0$.

The current-value Hamiltonian at date t for optimal control problems (34) are, respectively

$$H_i = \pi_i - \lambda_i w(1-w)(f_1 r_1 + f_2 r_2) + \mu_i[(\beta(N-I) - r_r)I - wI(f_1 r_1 + f_2 r_2)], i = 1, 2,$$

where λ_i and μ_i represent the shadow price associated respectively to the level of antibiotic efficacy and to the stock of infected population. We have

$$\frac{\partial H_1}{\partial f_1} = [w(1-2f_1)r_1 - w f_2 r_2 - c_1]I - w r_1[\lambda_1(1-w) + \mu_1 I],$$
$$\frac{\partial H_2}{\partial f_2} = [w r_2(1 - f_1 - 2f_2) - c_2]I - w r_2[\lambda_2(1-w) + \mu_2 I].$$

The optimality conditions for (34) require for $i = 1, 2$

$$\frac{\partial H_i}{\partial f_i} \leq 0, f_i \geq 0, \frac{\partial H_i}{\partial f_i} f_i = 0, \text{ or } \frac{\partial H_i}{\partial f_i} \geq 0, f_i \leq 1, \frac{\partial H_i}{\partial f_i}(1 - f_i) = 0, \tag{35}$$

$$\dot{\lambda}_i - \rho\lambda_i = -\frac{\partial H_i}{\partial w}, \tag{36}$$

$$\dot{\mu}_i - \rho\mu_i = -\frac{\partial H_i}{\partial I}, \tag{37}$$

$$\lim_{t\to+\infty} e^{-\rho t}\lambda_i(t)w(t) = 0; \lim_{t\to+\infty} e^{-\rho t}\mu_i(t)I(t) = 0. \tag{38}$$

Conditions in (35) represent the static efficiency conditions while (36) and (37) are the arbitrage equations, which describe the optimal path for $\lambda_i(t)$ and $\mu_i(t)$, respectively. Equations in (38) are transversality conditions.

For an interior solution, we have $0 < f_i < 1, i = 1, 2$, so that (35) can be rewritten as:

$$\begin{aligned} w(1-2f_1)r_1 - w r_2 f_2 &= c_1 + w r_1[\frac{\lambda_1}{I}(1-w) + \mu_1], \\ w(1 - f_1 - 2f_2)r_2 &= c_2 + w r_2[\frac{\lambda_2}{I}(1-w) + \mu_2]. \end{aligned}$$

Define $\tilde{c}_i = c_i + w r_i[\frac{\lambda_i}{I}(1-w) + \mu_i], i = 1, 2$ as the augmented marginal cost for firm i. These conditions then state that it is profit maximizing for each firm to produce at a rate such that its marginal revenue equals its augmented marginal cost.

Using a similar method as for the social optimum, we derive the steady-state treatment rates and stock of infected individuals

$$(f_1^{Sm}, f_2^{Sm}, I^m) = (0, 0, I^S). \tag{39}$$

The steady-state level of antibiotic efficacy level is

$$w^m = \min\left(w_0, \quad \frac{2c_1(\rho_1 + N\beta - r)}{r_1(-1 - r + 2(\rho + N\beta))}, \quad \frac{2c_2(\rho_2 + N\beta - r)}{r_2(-1 - r + 2(\rho + N\beta)}\right). \tag{40}$$

We assume that $\rho + N\beta > (1 + r)/2$ in order to warrant the positiveness of the steady-state level of antibiotic efficacy w^m. It can be shown that $w^m \geq w^o \geq w^s$, *i.e.* the exploitation of antibiotics by the duopolistic firms leads to a steady-state level of antibiotic efficacy greater than that obtained under the open-access equilibrium, which in turn is greater than that of the social optimum. In addition, this order is strict when at least one antibiotic is used within these approaches.

We have run numerical simulations with parameter values $\rho = 0.04; r_1 = 0.17; r_2 = 0.154; N = 1; \beta = 0.7; r = 0.2; w_0 = 0.8;\ c_1 = c_2 = 0.004$, and $I_0 = 0.8$. Calculating the antibiotic quality/price ratio (r_i/p_i), we have verified that $r_2/p_2 > r_1/p_1$, *i.e.* that antibiotic 2 is not dominated in a duopolistic market setting. However, antibiotic 2 would be dominated if the market were to be served by firms having open access to the common pool resource of antibiotic efficacy, due to the fact that given the parameters considered, we have $r_1/c_1 \geq r_2/c_2$. This result implies that the duopolistic firm 2 adjusts its price in order for its product not to be dominated. Both antibiotics are produced over the complete time horizon as can be seen in Figure 9.

Finally, we want to address which market structure is socially more desirable, *i.e.* represents a second best outcome. While antibiotic producers having open access cannot account for any intertemporal effect of their current antibiotic use on antibiotic efficacy and infection, duopolistic firms can. However, infection represents a desirable resource for duopolistic firms, which attribute a positive implicit value. Recall that in the social optimum the implicit value is negative and represents the social cost of infection. We find numerical evidence that the discounted social welfare as defined in (25) evaluated along the different market equilibria is lower in the open-access setting as compared to the duopolistic setting when the discount rate is relatively small.

7 Conclusion

This paper has addressed the management of antibiotics belonging to a given class of antibiotics 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, the open access leads to a long-run level of antibiotic efficacy, which is greater than the socially optimal level. 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.

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 classes), 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 an antibiotic. After observing his production level, a follower chooses its treatment path. 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 $\theta \geq p_2/wr_2 \equiv \tilde{\theta}_2$.

• **Discrete time numerical analysis**

In a discrete time framework with a finite horizon T, given I_0 and w_0, optimality conditions for (25) require

$$\frac{\partial \mathcal{H}}{\partial f_1} \leq 0, f_1 \geq 0, \frac{\partial \mathcal{H}}{\partial f_1} f_1 = 0, \text{ or } \frac{\partial \mathcal{H}}{\partial f_1} \geq 0, f_1 \leq 1, \frac{\partial \mathcal{H}}{\partial f_1}(1 - f_1) = 0,$$

$$\Delta\lambda - \rho\lambda = -\frac{I}{2} r_2(2 - 2f_1 - f_2) f_2 - \frac{I}{2} r_1(2 - f_1) f_1 + (f_1 r_1 + f_2 r_2)(\lambda(1 - 2w) + \mu I),$$

$$\Delta\mu - \rho\mu = \frac{(1 - r)}{2} - \frac{r_2}{2} w(2 - 2f_1 - f_2) f_2 - \frac{r_1}{2} w(2 - f_1) f_1 + c_1 f_1 + c_2 f_2$$

$$- \mu[\beta(N - 2I) - r - w(f_1 r_1 + f_2 r_2)],$$

$$\Delta w = -w(1 - w)(f_1 r_1 + f_2 r_2),$$

$$\Delta I = [\beta(N - I) - r - w(f_1 r_1 + f_2 r_2)] I,$$

$$\lambda(T) = 0; \quad \mu(T) = 0.$$

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 $t = 0, 1, ...T - 1$.

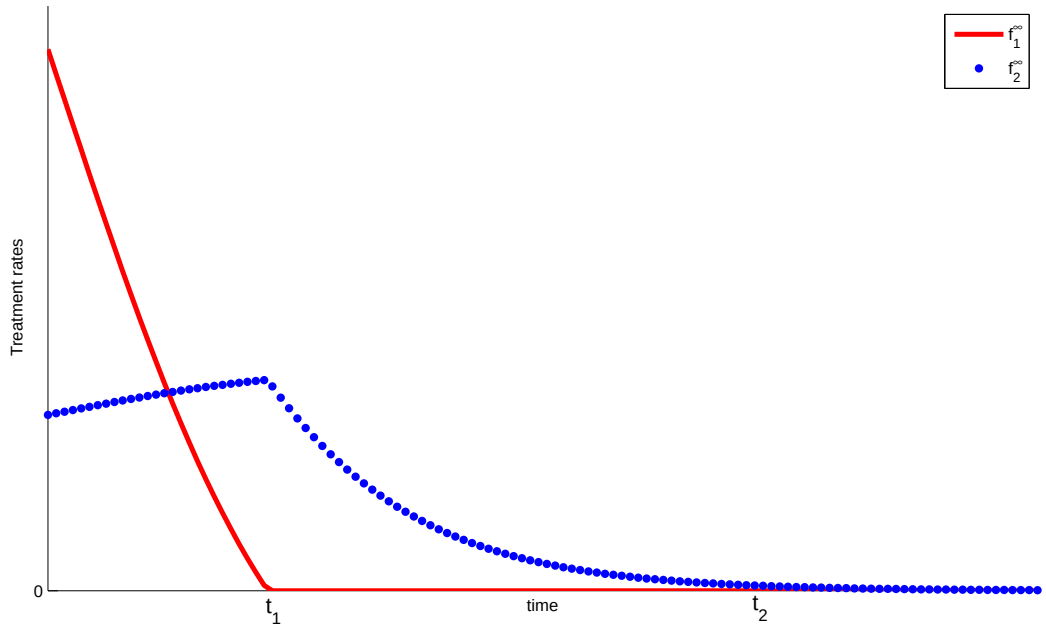

Figure 1: Treatment rates in open access when $w_0 > (c_1 - c_2)/\Delta r_f$ and $r_2/c_2 > r_1/c_1$.

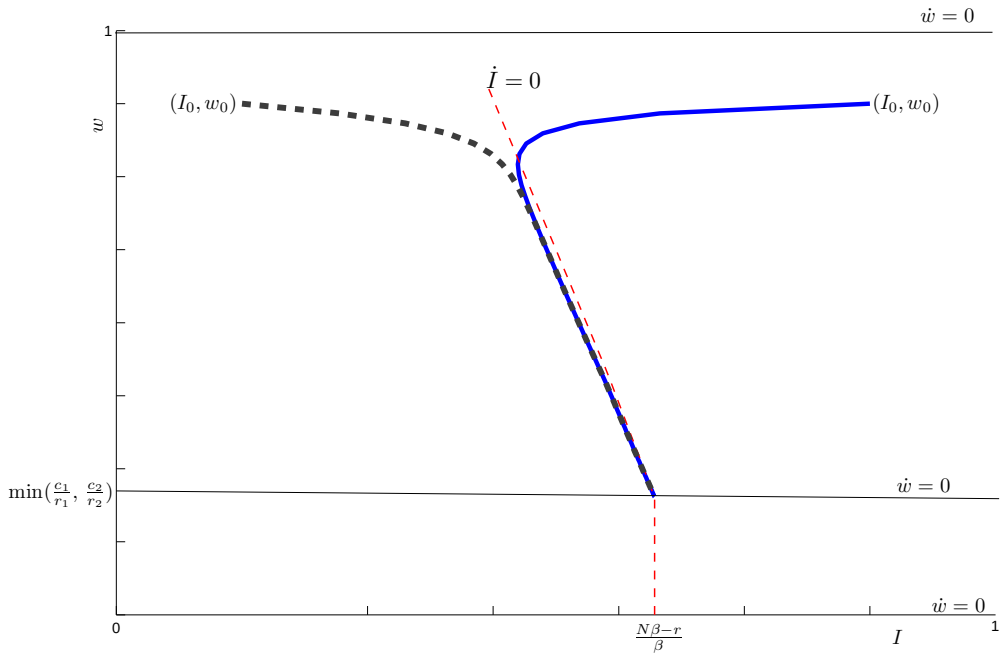

Figure 2: Phase diagram representing (I, w)-space in open access.

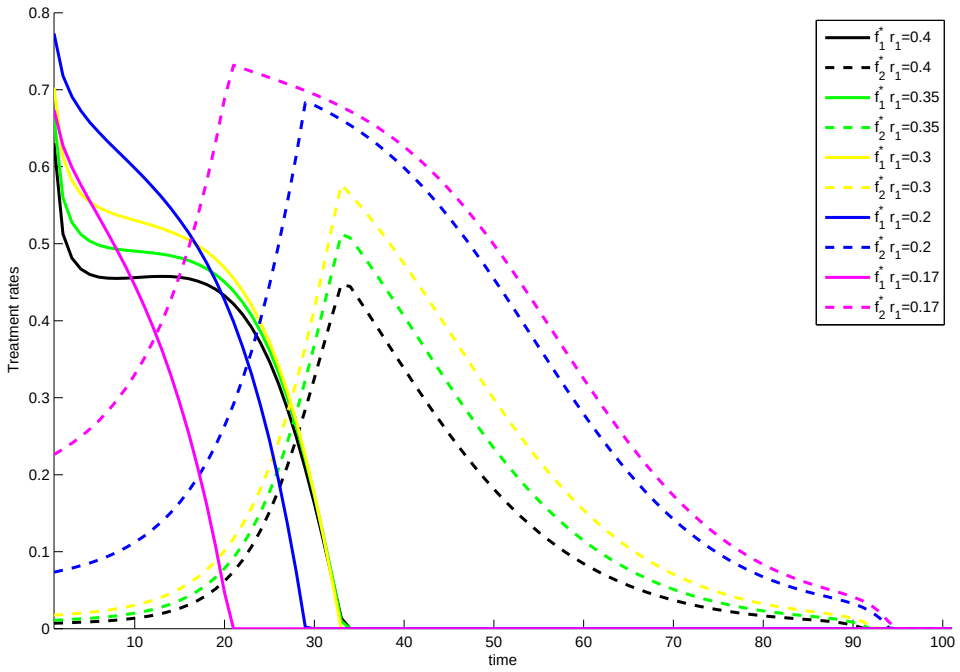

Figure 3: Effects of varying r_1 on the socially-optimal treatment rates

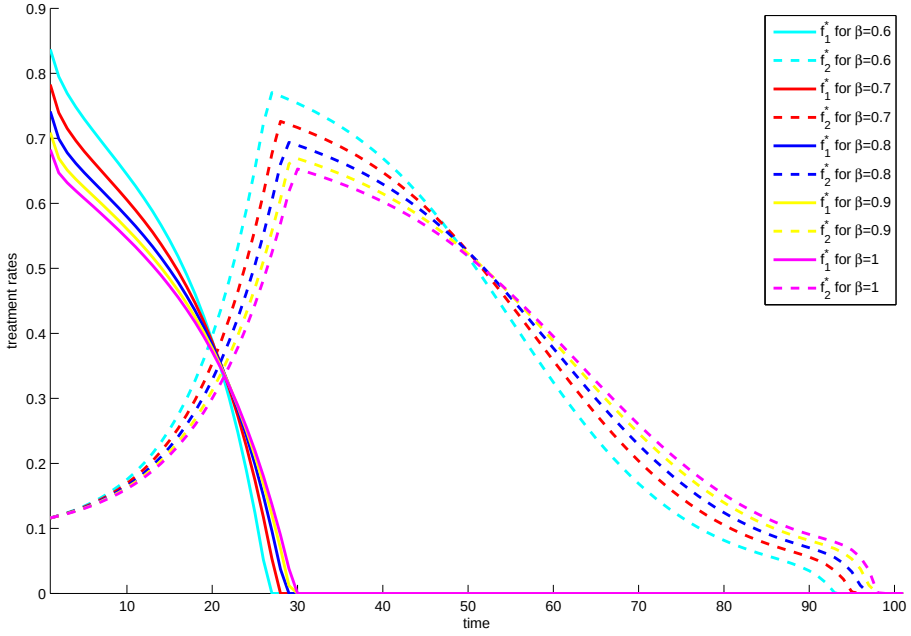

Figure 4: Effects of varying β on the socially-optimal treatment rates

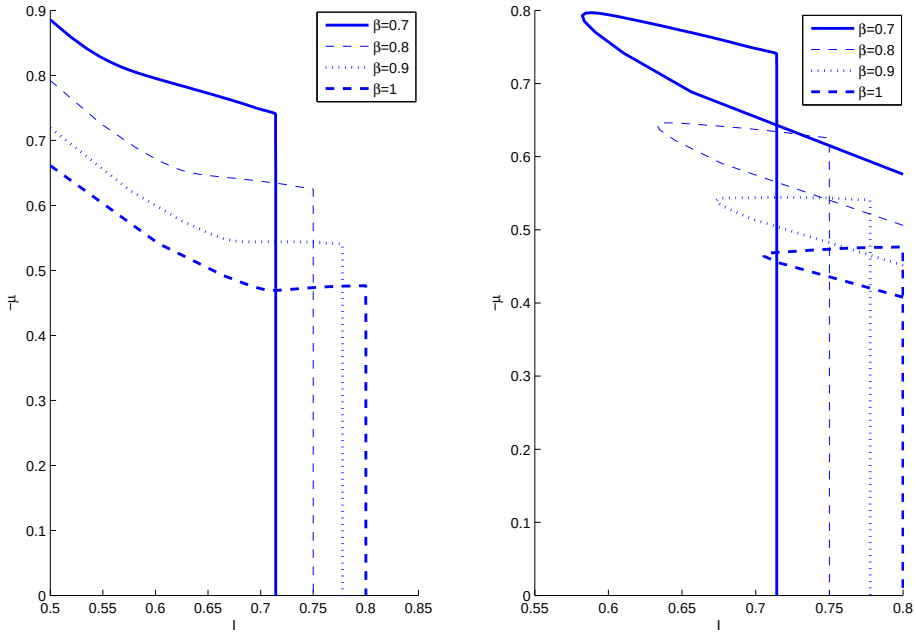

Figure 5: Effects of varying β on the evolution of $(I, -\mu)$.

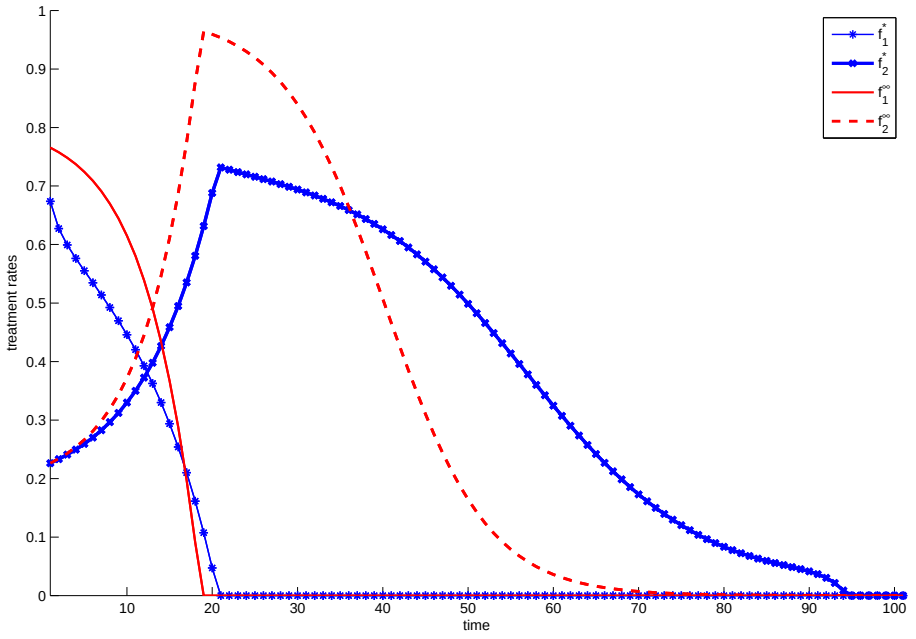

Figure 6: Comparing socially optimal and open-access treatment rates for $I_0 = 0.8$.

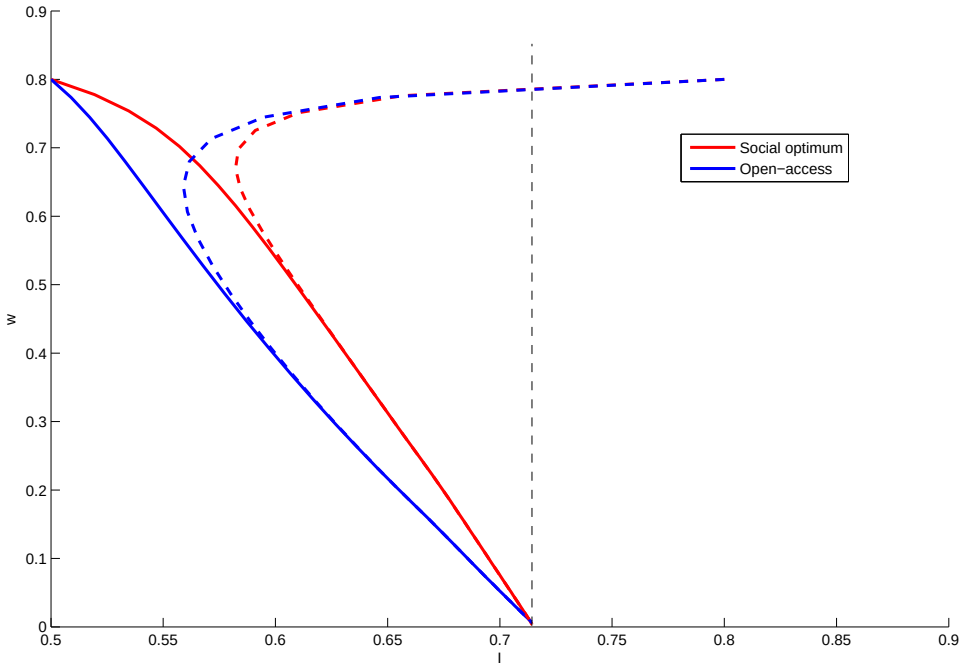

Figure 7: Comparing socially optimal and open-access evolution of (I, w).

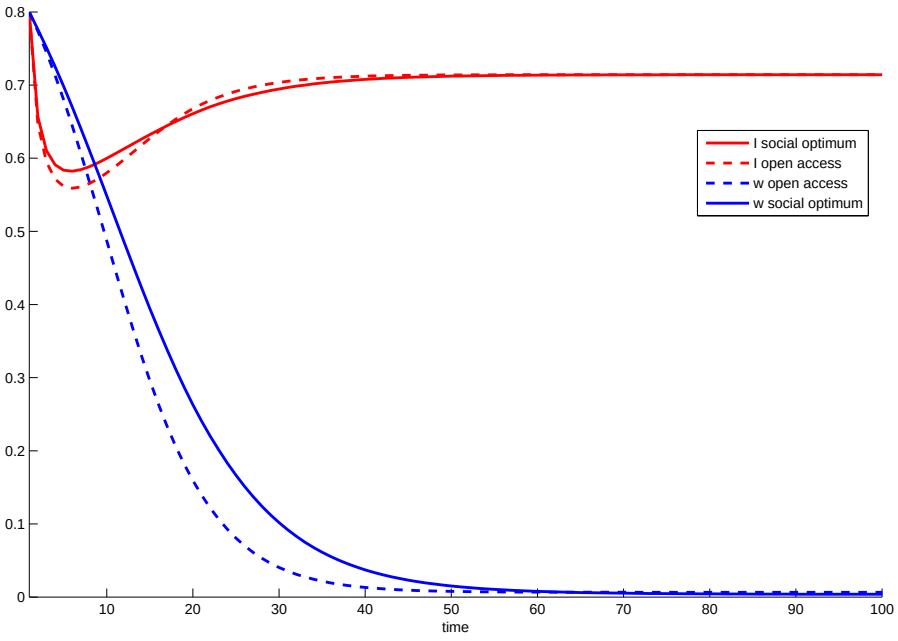

Figure 8: Evolution of the stock of infected individuals and antibiotic efficacy under open access and social optimum for $I_0 = 0.8$.

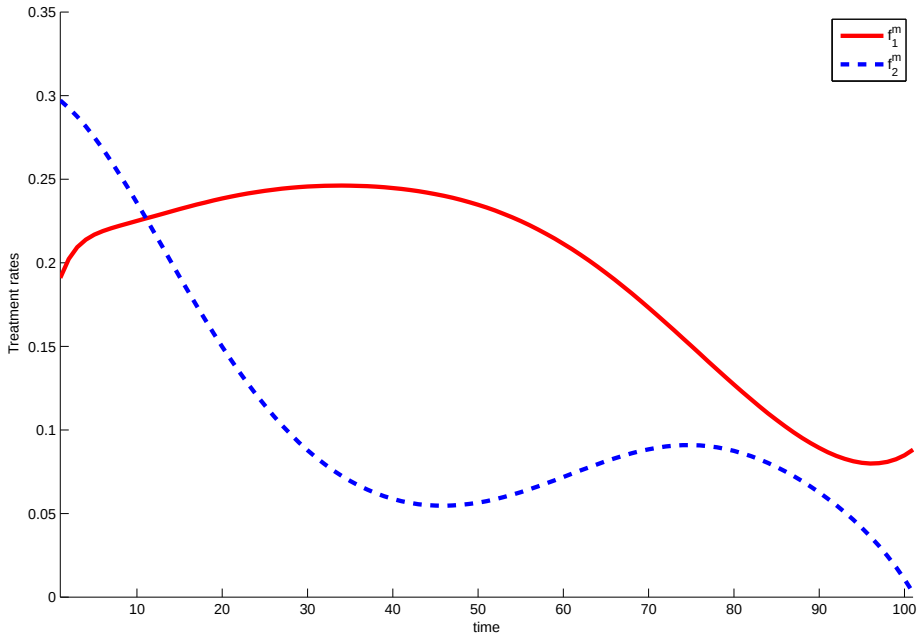

Figure 9: Equilibrium dynamics within the strategic behavior

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