Can Competition Extend the Golden Age of Antibiotics?*

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ABSTRACT

Countries world wide face an imminent global health crisis. As resistant bacteria render the current stock of antibiotics ineffective and the pipeline of back-up drugs runs dry, pharmaceutical companies are abandoning their research in antibiotics. In this paper we ask: Why are pharmaceutical companies closing antibiotic research labs when the stakes are so high? Implementing a simple dynamic framework, we show that the environment for new antibiotics is relatively hostile, compared to other medicines, due to market failures that result in excessive use and acceleration of natural selection. The analysis reveals, however, that increased competition between drugs can actually slow down the rate of resistance without, in some cases, diluting research incentives. This result, which is bolstered by scientific evidence, arises from a fundamental interplay between economic and biological externalities. We propose a patent-antitrust regime for aligning drug research and usage with those of the social planner, which implies an alternative justification of the patent system.

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1 Introduction

The accidental discovery of penicillin by Alexander Fleming in 1928 launched the "golden age" of antibiotics that revolutionized modern medicine. In its initial decades, success in the battle against infectious diseases such as pneumonia and tuberculosis was extraordinary, as were gains in overall health and economic welfare.[1] In addition to fighting infectious diseases, antibiotics dramatically lowered the risk of infection of many medical procedures that are considered routine today, including Caesarian sections, hip replacements and chemotherapy. Within a few decades, antibiotics became an essential staple of modern public health [Laxminarayan et al (2014)].

So great was the success of antibiotics that in 1968 the U.S. Surgeon General declared that "chronic diseases...now constitute the predominant health problem in this country."[2] However, since the 1980s, the tide began to turn: bacteria have become increasingly resistant to available drugs; approval of new antibiotics has reduced to a trickle;[3] and few alternatives are left in the pipeline. In an abrupt reversal, medicine began losing ground in its war against infectious diseases, and the collateral damage from continuing along this path could be the loss of many routine, life-saving medical achievements of the 20th century. Within the blink of an eye in human history, the "antibiotic miracle" has been replaced by the "antibiotic crisis".[4]

In this paper we ask: Why are pharmaceutical companies abandoning antibiotic research when the stakes are so high?[5] And what can be done to reverse this poten-

[1] In the United States alone the mortality rate from infectious diseases fell by 95% [Armstrong et al (1999)]. Between 1937 and 1943, with sulfa drugs – the first mass-produced antibiotics – maternal mortality fell by 24-36%, mortality from pneumonia by 17-32%, and that from scarlet fever by 52-67% [Jayachandran et al (2010)]. While Acemoglu and Johnson (2007) reported that life expectancy grew by 50% from 1940 to 1980, largely attributed to antibiotics and other health improvements, they estimated that any gains to growth per capita had been offset by a commensurate increase in population, whereas Venkataramani (2012) provided support that eradication of malaria led to long-term improvements in childhood health.

[2] Spellberg and Taylor-Blake (2013) notes that the Surgeon General never claimed that "the war on infectious diseases had been won", as urban myth had it, but that "maintenance of a vigilant effort will always be required."

[3] New antibacterial agents approved by the FDA declined by 56% over a 20 year period (between 1998-2002 vs.1983-1987). Moreover, in 2004, antibacterials constituted only 1.4% of the new products in development by the big pharmaceutical companies [Shlaes et. al.(2003)].

[4] At current rates of drug discovery and consumption, health and science experts predict the end of the golden age of antibiotics could be as soon as 2050, at a global cost of well over $100 trillion dollars (U.S.) and 300 million lives. See *Review on Antimicrobial Resistance* (*RAMR*) (2014), Smith and Coast (2013), Gandra *et al* (2014).

[5] The dramatic decline in the introduction of new antibiotics in the past few decades is well-documented [Spellberg (2010), Shlaes and Projan (2009), Projan (2003)]. Pfizer, Bristol-Myers Squibb, Johnson & Johnson, and Eli Lilly in the U.S., and Aventis (now Sanofi) in France have closed their research labs dedicated to antibiotics. Data on investment in drugs for chronic illnesses and lifestyle drugs reveal significantly higher rates of return than for antibiotics. For example, investment in cancer and neurological drugs is estimated to earn a rate of return that is, respectively, three and seven times greater that that for antibiotics [Projan (2003), Mossialos, et. al. (2014)].

tially devastating trend?

In order to understand why research in new antibiotics has been rapidly declining, we need to understand how the market for antibiotics operates; in particular, how economic incentives to sell a drug interact with the evolution of biological resistance. Fundamental to the economic-biology relationship is a tension: the greater a firm's incentive to increase sales of its drug, the more chances bacteria are given to crack the codes that science has invented against them, ultimately rendering the drug ineffective. That is, natural selection causes a successful antibiotic to self-destruct as its increased sales contribute to increased resistance. Moreover, the bacteria becomes more resistant to the drug from production of competing drugs [Iyer (2001), Laximinarayan (2002), Imamovic and Sommer (2013)].[6] That is, compounding *own resistance* from sales of a pioneer drug is *cross resistance* from sales of other drugs, which is beyond the control of a pioneer firm. Studies providing irrefutable evidence of the two causal links noted above between increased sales in the market and resistance are extensive.[7]

Accelerating the process of natural selection described above is a market failure stemming from consumers' myopia. This well-known market failure in antibiotics — a "tragedy of the commons" of sorts — arises when users fail to internalize the negative externality of their use on future drug efficiency [Tisdell (1982), Brown and Gruben (1997), Laxminarayan (2001), Herrmann and Gaudet (2009), Herrmann and Laxminarayan (2010)].[8] That is, natural selection and economic incentives conspire to limit the life of antibiotics, relative to those of chronic and life-style drugs. A drug for heart disease that was safe and effective 30 years ago will be safe and effective now, though it may be out-competed by superior drugs with greater market appeal.[9] In contrast, antibiotics are out-competed by resistant bacteria that evolve from their own and other drugs' production. That is, antibiotics lose market appeal because they simply stop working.

Indeed, the inherently self-destructive nature of antibiotics coupled with a market failure in consumption outlined above may be one of the major reasons for why R&D for new antibiotics has been declining over the past decades. Between 1987 and 2004, for example, penicillin-resistant *Streptococcus pneumoniae* increased from 0.02% to

[6] For example, beta-lactam antibiotics such as penicillin destroy bacteria by using the mechanism of targeting enzymes in the cell membrane. Mutations of resistant bacteria can extend to different antibiotics that use the same mechanism.

[7] See for example Tisdell (1982), Brownzwaer et. al. (2002), Laxminaryan (2001), Outterson (2005), Laximinaryan and Malani (2007), Mechoulan (2007), Jernigan and Kallen (2010),Hollis and Maybarduk (2015).

[8] The relationship between consumption of a drug and resistance is well-established [e.g. see Arason et al (1996), Bronzwaer et al (2002), Tacconelli et al (2008)]. In this sense, antibiotics are best understood as a non-renewable resource in which their efficacy declines with use and inevitably must be replaced [Laximayaran and Brown (2001); Hollis and Maybarduk (2015)].

[9] In this sense, a drug for a chronic disease is much like technological gadgets that are still functional, but become obsolete because far better ways of doing the job have been found.

over 50% in U.S. hospitals. Methicillin, responding to the growing ineffectiveness of penicillin, soon confronted the same fate as methicillin-resistant *Staphylococcus aureus* (MRSA) climbed from 2% to 50% [Herrmann and Laxminarayan (2010)]. Table 1 shows that, for various classes of antibiotics, resistance tends to set in even before the drug is commercialized.

While the process of natural selection cannot be stopped, economics can work with science to slow it down. In identifying policies that correct the market failure of excessive use, economics can help to prolong the lives of new antibiotics, complementing new scientific discoveries for overcoming resistant bacteria.

In a simple framework, we analyze the important interplay between economic incentives and biological resistance in identifying policies for arresting resistance and increasing incentives to research. The patent system is a mechanism proposed in the literature for controlling these two sources of resistance. The recommendation there is to extend patent protection through longer and broader patents.[10] Awarding the pioneer with a longer exclusivity period, it is argued, would provide greater incentives to internalize the consumption externality and cut back on production, knowing that it—rather than later generics— will reap future profits from preserving the drug's effectiveness [Horowitz and Moehring (2004)]. Indeed, that rationale lends support for the relatively new law in the United States that came into effect in 2012, *Generating Antibiotic Incentives Now* (GAIN), which extends the exclusivity period of a patented antibiotics treating serious infections by five years.

Furthermore, broadening breadth of the patent allows the pioneer to exclude or at least better manage the entry of related drugs, which are likely to generate cross-resistance that reduces the pioneer drug's effectiveness [Laxminarayan (2002)]. The attractive feature of this complementary pair of policies is that, if correct, improved design of the patent system would not only correct the market failure in consumption, but would also generate greater returns to innovation. That is, both problems—overuse and underinvestment at the heart of the crisis—could be mitigated.

While compelling, this reasoning is incomplete at best. Not only would those policies be politically difficult to implement, but they may not be the most effective. In stark contrast to these results, we show that, for a wide range of economic and biological environments, *limiting* rather than *extending* a pioneer's patent protection may be socially preferred. The reason for such divergent results lies in the interplay that arises between opposing economic and biological forces when competing drugs are admitted into the market. In a simple, dynamic framework, we show that, in addition to the usual social benefits from greater variety, imperfect competition contributes both a positive and negative externality that, respectively, increases and

[10]For example, see Brown and Gruben (1997), Laxminarayan (2001), Horowitz and Moehring (2004), Infectious Diseases Society of America (2004), Kades(2005), Laxminarayan and Malani (2007), Mechoulan (2007), Davies et. al. (2014)]. However, several disagree with this view. For example, see Outterson (2007, 2014) who argues that patents, or more generally sales-dependent awards, will not solve the antibiotic crisis.

decreases overall resistance to the pioneer drug. The negative externality arises when production of a new, competing drug can render the bacteria, also targeted by the pioneer's drug, resistant to it. A countervailing force reduces the pioneer drug's own-resistance by stealing some of its market share. We identify conditions under which the balance tips in favour of competition; that is, narrowing rather than broadening patents, as a mechanism for reducing overall resistance of the pioneer drug, and when it does not.

Barring a few notable exceptions (Laxminarayan (2002), Laxminarayan and Weitzman (2002)), this interplay between the benefits of drug variety and the costs of cross-resistance has not received much attention. The "business stealing" impact on resistance is analyzed in Laximinarayan and Weitzman (2002),however, for the case in which the biological externality of cross-resistance is absent. Therefore, competition between drugs of similar costs would always be optimal.[11] Also related is Laxminarayan (2002), where cross-resistance is analyzed for the case of homogeneous Cournot competition in which resistance evolving from a drug's own production and that of rivals are equally severe.[12] In that case, drug variety would always contribute to a pioneer drug's resistance, undermining the benefits of competition. Consistent with these polar cases, our framework more generally identifies an economic-biological tradeoff that ascertains when competition (or narrow patents) emerges as an effective policy for combatting resistance and when it does not. Furthermore, we derive conditions for when competition between current-generation drugs is also welfare-improving.

Recent scientific developments bolster the case for competition (more precisely, drug variety) as resistance-reducing. In particular, current evidence presented here reveals that exposure to some antibiotics can render the resistant bacteria more vulnerable to other antibiotics. By choosing appropriate combinations of drugs, the evolution of resistance can be arrested. This enhances the importance of having available a menu of drugs to choose from and experiment with.

In the light of these findings, we identify a combination of patents, antitrust policy and Pigouvian taxes for achieving efficient drug use. If cross resistance is high, then broad patents are efficient, followed by a tax on generic drugs. When cross resistance is expected to be low, then narrow patents are efficient, with patent duration adjusted to account for competition in the market. Moreover, a competition policy that allows rival firms to enter into limited cooperative agreements can internalize the biological externality of cross-resistance. Taxes on generic drugs moderate excessive production post-patent.

While this patent-tax-antitrust nexus achieves efficient consumption and moderates resistance of a pioneer drug, in general it may not provide sufficient incentives

[11] For example, if drugs have identical costs per effectiveness in their model, then spreading patients among different drugs will be beneficial for reducing resistance in any single drug. However, that may no longer be true if cross-resistance is strong.

[12] As will be discussed later, cross-resistance is equal to own-resistance in his model.

to generate socially desirable R&D. Rather than adjusting the patent component—for example, by extending lives or broadening scope—in order to increase innovation incentives, we recommend that alternative forms of compensation such as subsidies, patent buyouts, prizes, and regulatory incentives (e.g., FDA expedited reviews) be used to supplement returns from patents. And, in order to preserve efficient drug usage, this secondary or supplemental R&D award must be independent of drug sales.

This is the first paper, to our knowledge, that provides an economic framework for analyzing why patents should not be relied on for increasing the supply of new antibiotics. This is consistent with Outterson (2007, 2014) who argues that the patent system, or more generally an incentive mechanism based on sales-dependent awards is ineffective for solving the antibiotic crisis. While we agree that patents alone cannot solve the antibiotic crisis, our framework suggests that they are a critical component of any policy combination going forward. In fact, it is precisely that feature of the patent award—that it depends on sales—which makes it socially beneficial for moderating resistance and achieving efficient drug use, even at the cost of compromising incentives for research. In this sense, the analysis here turns the patent system on its head: rather than using intellectual property to encourage R&D at the cost of suboptimal use, we argue that it should be employed to encourage efficient drug use at the cost of optimal R&D.

Another significant contribution is our analysis of the impact of competition on resistance when antibiotics are plagued by cross-resistance from their rival drugs' production as well as from their own. The paper derives an intuitive policy rule for achieving efficient usage of antibiotics as the outcome of a simple dynamic framework. This rule informs antitrust and patent policy when to admit competing drugs of similar biological quality by setting relatively narrow patents. We then turn to the impact of that policy on innovation incentives between biologically similar in effectiveness but economically differentiated drugs and show that own- and cross-resistance have similar effects on R&D. Drawing out the implications from these results to next-generation antibiotics—biologically superior in overcoming resistant bacteria—we show that cross-resistance can play a central role in undermining R&D incentives. In fact, cross-resistance may be the primary culprit behind the decline in investment in antibiotics. Finally, we apply these results to data on strains of *E-Coli* to identify when competition of same-generation drugs may have prolonged or shortened the lives of these drugs, and the impact that they have had on later-generation drugs.

In addition to those papers already mentioned, our analysis builds on several important papers that analyze antibiotic resistance in perfectly competitive and monopoly markets [Laxminarayan and Brown (2001), Mechoulan (2007), Philipson and Mechoulan (2006), Herrmann and Gaudet (2009)]; on the role of patents in mitigating resistance [Tisdell (1982), Brown and Gruben (1997), Laxminarayan (2002), Horowitz and Moehring (2004), Power (2006), Laxminarayan and Malani (2007), Mechoulan (2007), Herrmann (2010); Sampat (2015)], as well as other policies such

as taxes, state-dependent quotas/subsidies and tradeable permits [Smith and Coast (1998), Coast, Smith and Millar (1998), Rudholm (2002), Laxminarayan, Over, Smith (2006), Herrmann, et. al. (2013), Albert (2015)].[13] We also draw from the legal literature, especially work by Outterson (2005, 2007, 2010, 2014), as well as the vast science literature [e.g. Goulart et al (2013), Imamovic and Sommer (2013)], especially data regarding the relationship between consumption and resistance and scientific advances.

We turn now to a theoretical framework to illustrate these ideas. In the next section we first examine the case of a single drug, and derive the social and private consumption paths. In Section 3, competition is introduced and contrasted. Section 4 examines the welfare implications of competition and identifies optimal policies for achieving efficient consumption. We return to the question posed above in Section 5 to investigate the impact of these policies on innovation incentives for both current and future generation antibiotics. Discussions of the results and possible future extensions are presented in Section 6. Section 7 concludes.

2 The Single Drug Market and Antibacterial Resistance

2.1 Social Planner's Problem

Consider a model for a single antibiotic, $\mathbf{X}$, which lasts for T periods, where T is finite and exogenous. This might reflect a situation in which the disease is expected to be eradicated in T years due to a future vaccine program. An alternative approach that would yield similar results would be to assume that only a fixed number of *effective* dosages of the drug is available at the beginning of the period.[14]

In our model, N consumers are assumed to be in one of two states in each period—healthy or sick—and the probability of being sick, δ, is constant over time. In each period, an infected person has the option of staying ill for that period or relieving the illness immediately by consuming an antibiotic. We abstract from considerations of endogenous transmission of the disease, since this allows us to highlight the impact of resistance on incentives to innovate.[15] We also set the discount rate to zero since

[13] Several papers have attempted to examine the direct and indirect costs of resistance [Coast, Smith, Millar (1996), Cosgrove and Carmeli (2003), Smith, Yago, Millar, Coast (2005, 2006), Evans, *et. al.* (2007), Roberts, *et.al.* (2009), Reynolds, *et. al.* (2014)].

[14] The latter approach is useful in that it reflects the "exhaustible resource" nature of antibiotics that is induced by bacterial resistance, as noted in the literature [Tisdell (1982), Laxminarayan (2001)]. Under this interpretation, however, the period length will change depending on how quickly the stock of available dosages is depleted.

[15] In other words, we assume that the state of being sick does not depend on the probability of coming into contact with a sick person during that periood or on the proportion of sick people in the population. See Mechoulan (2007) for an analysis of endogenous infectiousness; there, the proportion of sick people at $t+1$ is determined by a transmission function that depends on the

discounting does not contribute qualitatively to the main results and has the virtue of isolating the effects of resistance without contamination from well-understood effects associated with discounting. Consumers are assumed to be myopic and maximize their single period utility. If healthy, at time t an individual receives a utility valuation v of her health. Consumers' valuations are distributed according $NF(v)$, where $F(v)$ is the cumulative distribution of v over the interval $[0, \overline{v}]$ with a continuous density function $f(v)$ and with $F'(v) > 0$ in the interior of the domain. Unhealthy individuals without treatment receive utility 0 in that period but recover by the end of the period. The probability of being re-infected in subsequent periods is independent of one's history of illness. By consuming a completely effective antitbiotic, their health is restored to v. However, if the antibiotic is compromised by resistance, then their health levels are restored to $v - \theta X(t)$, where $X(t)$ is the cumulative market output up to time t—that is, $X(t) = \int_0^t x(s)ds$, where $x(s)$ is the sales of the drug at time s—and the parameter $\theta > 0$ captures the marginal biological resistance for an increase in the cumulative consumption. We refer to this sort of resistance as *own-resistance*. We assume that the marginal cost of production is constant and set equal to zero. This framework captures most simply the empirical reality that antibiotic production today lowers its own future effectiveness [e.g. Bronzwaer et al (2002), Tacconelli(2008)].[16]

Let $c(t)$ be the value of good health to the marginal consumer, so that the proportion of consumers treated with the drug is given by $1 - F(c(t))$. The expected utility of unhealthy individuals consuming the drug at time $t, t \in [0, T]$ is given by:

$$u(c(t), X(t)) = \delta N \int_{c(t)}^{\overline{v}} (\upsilon - \theta X(t))\ dF(\upsilon).$$

Then, the social planner's problem is to maximize total surplus over the life of the drug given by:

$$\max_{\{c(t)\}} \ U = \int_0^T u(c(t), X(t))dt \quad s.t.\ dX/dt = x(t) \tag{1}$$

Note that x_t is the demand for drug $\mathbf{X}$ at time t, given by:

$$x(t) = \delta N(1 - F(c(t))). \tag{2}$$

proportion of sick people at t who did not purchase the drug.

[16]This representation of resistance in our model is through consumers' declining valuation of the drug as it becomes increasingly ineffective against the resistant bacteria. This contrasts with Mechoulan (2007) in which resistance increases by the proportion of non-resistant strains of bacteria that decline over time. That is, here resistance renders the drug ineffective when $\alpha - \theta X_t = 0$, whereas in Mechoulan, it occurs when the proportion of resistant bacteria approaches 1.

The Hamiltonian, H, of this problem is given below, after substituting the expression for $x\,(t))$ in (2):

$$H = \delta N\,[\int_{c(t)}^{\overline{v}} (v - \theta X(t))\; dF(v) + \lambda(1 - F(c(t))],$$

where λ is the user cost or shadow price associated with consumption.

Then, the control problem above is solved for $\{c(t)\}$. This yields the following result:

Proposition 1: The optimal value of good health above which the antibiotic is consumed that maximizes discounted social surplus is constant over the life of the drug, and therefore, the output path of drug consumption is also constant over time.

Proof: By the Maximum Principle, $c(t)$ must satisfy

$$c(t) - \theta X(t) + \lambda(t) = 0, \tag{3}$$

where the equation of motion for the shadow price, $\lambda(t)$, is given by:

$$\begin{aligned} \frac{d\lambda}{dt} &= -\frac{\partial H}{\partial X} \\ &= \theta\delta N(1 - F(c(t)). \end{aligned}$$

Taking the time derivative of (3) and substituting the above, gives $dc/dt = 0$; that is, the valuation of the marginal consumer, denoted by c^*, is invariant with respect to time over the entire horizon. Consequently, the corresponding consumption, denoted by $x_m^* \equiv \delta N(1 - F(c^*))$, will also be time invariant. Integrating the equation of motion for λ with respect to time and invoking the terminal condition that $\lambda(T) = 0$, we obtain its solution as $\lambda(t) = \theta x_m^*(T - t)$. Using equation (3), we can solve for the constant consumption path, x_m^*, as the solution to:

$$F^{-1}\left(1 - \frac{x_m^*}{\delta N}\right) = \theta T x_m^*. \tag{4}$$

Since the right-hand side of (4) is a constant that captures the full cost of producing a marginal unit of the drug, it follows that the planner's outputs will be identical in all periods.[17]■

Proposition 1 reveals an important feature of resistance. Although, resistance increases over time at a rate of $\theta(dX_t/dt)/X_t$, the social planner optimally manages

[17] A strong sufficient condition for the solution in (3) to be a maximum is for the density function $f(.)$ to be non-increasing in its argument. Here and throughout the paper we assume that the solution generated by the Maximum Principle is also globally optimal.

the drug by setting a constant output over the drug's life, denoted by output x_m^*. Note that suppressing economic discounting allows us to highlight the "biological discounting" that occurs endogenously through resistance. That is, even when the planner does not explicitly discount the future, she does so indirectly through current consumption of the drug. As Proposition 1 shows, the social planner takes this into account by internalizing this user cost from current consumption so as to smooth the path of consumption.[18]

2.2 The Pioneer's Solution

We now turn to a comparison of the planner's solution with that of the exclusive monopoly. Demand at t is given by (2). We assume consumers are myopic and do not consider the impact of their current consumption on future drug effectiveness. Therefore, the marginal consumer's willingness to pay for the drug can be obtained by inverting (2). If $P^{\mathbf{X}}(t)$ is the willingness to pay in period $t \in [0, T]$, the inverse demand for drug $\mathbf{X}$ at time t is given by:

$$F^{-1}\left(1 - \frac{x(t)}{\delta N}\right) - \theta X(t) = P^{\mathbf{X}}(t). \tag{5}$$

Again, the parameter θ captures the effect of antibiotic resistance: an increase in output by one unit in any period t lowers by θ the drug's effectiveness and thus the marginal willingness to pay in all subsequent periods. The efficacy of the antibiotic depends on the volume of antibiotic previously consumed; however, current price reflects only the consumers' marginal willingness to pay but not the user cost on future effectiveness inflicted by their consumption. In choosing the path or production, the monopolist is constrained to take the current demand curve as presented but can correct for the intertemporal externality by adjusting her current production to the extent that it is profitable.

To see this, suppose the monopolist's lead time (patent life) before generic entry is L, where $L \leq T$ or, alternatively, the monopolist is given a patent for a period L. After the patent expires, generics enter the market. For now, we assume that the generic output is subject to a Pigouvian tax that elicits the efficient post-patent output.[19] Let the profit, $\Pi^{\mathbf{X}}$, defined over the L periods, be given by the undiscounted sum $\Pi^{\mathbf{X}} = \int_0^L P^{\mathbf{X}}(t)x(c(t))dt$, where $P^{\mathbf{X}}(t)$ is given in (5). Mimicking the procedure followed for the planner's solution, we maximize $\Pi^{\mathbf{X}}$ with respect to $\{c(t)\}$, subject to the condition $dX/dt = x(t)$. It is straightforward to show that the valuation of the marginal consumer will be constant over the time horizon L, denoted by c_m.

[18] This, of course, would not be true for a positive discount rate in which case the consumption path of the drug would decline.

[19] The generic output path and the tax policy is developed further at the end of section 3.

Therefore, so too will be the monopoly consumption path at output denoted by $x_m \equiv \delta N(1 - F(c_m)$, given by:

$$F^{-1}\left(1 - \frac{x_m}{\delta N}\right) - \frac{x_m}{\delta N f(c_m)} \ = \theta L x_m, \qquad for\ t\ \epsilon\ [0, L]. \tag{6}$$

The monopolist's constant output, denoted by x_m, balances the cost of consumption in the current period as determined by past usage as well as the cost of the marginal current production on future willingness to pay. Denote the marginal consumer's value under the social planner's path by $c^* \equiv h(T, \theta)$, in terms of exogenous parameters. Then, comparison of x_m^* and x_m from (4) and (6) demonstrates the following.

Proposition 2: If $\theta(T - L)\delta N h(T, \theta) > 1$ *the monopolist overproduces; if* $\theta(T - L)\delta N h(T, \theta) < 1$ *the monopolist underproduces, relative to the social planner's output. Then there will exist an optimal patent life* $\widehat{L}$ *such that* $\theta(T - \widehat{L})\delta N h(T, \theta) = 1$, *in which case the monopolist replicates the social planner's output.*

Proof. Bringing the term on the right hand side in (6) to the left hand side and evaluating the resulting expression at the planner's optimal output x_m^* from (4) yields the expression $-x_m^*/(\delta N f(c_t)) + (T - L)\theta x_m^*$. This will be positive if $\theta(T - L)\delta N f(c_t^*) > 1$, implying that the monopolist overproduces relative to the social planner in this case. She will underproduce if the inequality is reversed. Given that $\theta(T - L)\delta N h(T, \theta) = 0$ when $L = T$, the existence of $\widehat{L}$ follows.■

In Proposition 2, $\widehat{L}$ is the socially optimal patent length for the monopolist. This proposition clarifies two widely accepted views in the literature. First is the view that sales-dependent mechanisms are not effective in addressing the antibiotic crisis because the reward for innovation involves selling the drug which causes resistance [Outterson (2007, 2014)]. Indeed, when a monopolist cannot perfectly price discriminate, sales-dependent awards such as patents may be inefficient. But Proposition 2 also suggests that it is the design of the patent, rather than mechanism itself, that is flawed. If adjusted appropriately, the firm can replicate the social planner's output. Second is the view that extending patent life will provide those correct incentives [Horowitz and Moehring (2004)]. As seen in Proposition 2, this may not always be true; in fact, extensions of the exclusivity period could lead to under-production and, therefore, a greater proportion of the population without access to the drug.[20]

[20]Note that a longer patent life would be efficient for a perfectly price-discriminating monopolist. Since the monopolist would appropriate the entire surplus from the consumers, she would replicate the social planner's solution in the absence of generic entry if $L = T$. If instead $L < T$, by Proposition 2, the perfectly price-discriminating monopolist would choose the output, $\widehat{x}_m > x_m^*$ in each period. That is, a perfect-price discriminating monopolist will follow the optimal path when $L = T$, but if given a shorter patent life (or lead time), she would overproduce relative to the social planner.

2.2.1 Uniform Distribution

To illustrate the relationship between the economic and biological parameters and to develop the analysis further, in the rest of the paper we adopt a uniform distribution over v. In that case, the proportion of consumers treated in period t will be $1-c(t)/\overline{v}$ and the number of drug dosages at time t given by $x(t) = \delta N(1 - c/\overline{v})$. Then, substituting these expressions into (1)-(3) and simplifying notation by setting $\alpha = \overline{v}$ and $\beta = \overline{v}/\delta N$, the surplus function at t can be shown to be

$$u(t) = [\alpha - \theta X(t)]x(t) - \beta[x(t)]^2/2. \tag{7}$$

And so the inverse demand becomes

$$P(t) = \alpha - \theta X(t) - \beta x(t),$$

where $\theta < \beta$, a sufficient condition for concavity of the monopolist's profits. Finally, it follows that the social planner's output path that maximizes total utility and the monopoly path that maximizes profits for periods $t \in [0, T]$ are respectively:

$$x_m^* = \frac{\alpha}{\beta + \theta T}. \tag{8}$$

$$x_m = \frac{\alpha}{2\beta + \theta L}. \tag{9}$$

Note that if θ is increasing both the planner and monopolist lower their output as the time horizon T or θ increase in order to conserve the drug. In this analysis and what follows we look for an interior solution for which $x(t) > 0$ for all t, requiring that $\alpha - \theta X(T) > 0$, where marginal revenue at t, $(\alpha - \theta X(t)) - 2\beta x(t)$, is set equal to the *marginal user cost* of future antibiotic resistance from current consumption. In the terminal period this user cost is zero. Comparison of x_m^* and x_m yields the following policy result.

Proposition 1: For a uniform distribution over preferences, the exclusivity period (patent length), L_m, that aligns the monopolist's output path with the social planner's is given by:

$$L_m = T - \beta/\theta. \tag{10}$$

For shorter (longer) exclusivity periods, the monopolist will over- (under-)produce relative to the social planner.[21]

Proposition 2 establishes that if θ is high for a given L, a monopolist will overproduce relative to the social planner. Because the monopolist's time horizon is shorter than the planner's and falls in the interval $[0, T - \beta/\theta]$, she ignores at least part of the social cost of resistance and overproduces. Consequently, a longer patent life is

[21] Note that L_m is the value of $\widehat{L}$ in Proposition 1.

warranted in this scenario, especially at higher resistance strengths.[22] Tempering the incentive to overproduce, however, is a monopolist's incentive to conserve the antibiotic for reasons that have to do with profitability alone. This countervailing force moderates the tendency to overproduce, as Hotelling noted for an exhaustible resource.[23] It is also the reason why it is possible for the monopolist to *underproduce* during its protected period.

Limited data suggest that for some strains of bacteria, resistance did not become a problem until well after the generic phase began. For example, Laxminarayan and Malani (2007) show that resistance to methicillin from *Staphylcoccus aureus* infections from 1987-1997 grew from 20% in 1987 to 45% a decade later.[24] Further data reveal that it has grown to over 60% in 2003. The patent on methicillin was awarded for the period 1960-1977 and so the drug was available 27 years prior to the start of the data. When the data in Figure 1 are extrapolated to earlier years, it appears that resistance during patent life was negligible.[25] Nevertheless, as observed earlier in Table 1, resistance commonly appears within a few years after or even before commercialization. If the patentee expects the rate of resistance to increase over the life of the patent, then extending the period of exclusivity to pioneer drugs could be ideal in two regards: first, in correcting the market failure, which would increase total surplus and profits over the life of the drug, and second, in providing the pioneer with greater profits.

However, such an inference may be incorrect.[26] As we show below, allowing competing drugs (equivalently, narrowing patents) may be a superior mechanism for

[22] However, this is not true in general. A monopolist will *underproduce relative to the social planner* if patent life for antibiotics lies in the interval $[T - \beta/\theta, T]$; that is, patent life covers a significant proportion of the drug's life, the interval of which increases for lower resistance strengths.

[23] Hotelling's claim that "a monopolist is a conservationist's friend" is relevant here [Hotelling, 1931]. Extending patent life, therefore, may not be a socially desirable mechanism for reducing resistance in that it would compel the monopolist to cut back further on an already under-produced drug. Special cases of this model are perfect competition for all periods (i.e., $L = 0$) and monopoly with $L = T$. It is easy to see that the competitive production path will start higher than the social planner's, eventually crossing it and ending at T. In contrast, the monopolist of duration T always underproduces, relative to the social planner. Therefore, if the discount rate were positive, all three consumption paths would decline. The competitive path would start higher than the social planner's, but the life of the drug would be shorter, whereas the monopoly path would start lower than the social planner's but drug's life would be longer. It should be noted that the externality of infection transmission is not modelled here; nevertheless, underproduction implies that more people remain sick during the period, which reduces welfare even when sick individuals choosing not to take antibiotics do not affect the transmission of the illness.

[24] The data were collected from intensive care units participating in the National Nosocomial Infections Surveillance System of the Center for Disease Control.

[25] Similar results apply for vancomycin for which the patent expired in 1979.

[26] Under an alternative interpretation, this would be tantamount to prolonging the life of the drug. For example, instead of fixing the effective life T of the drug and allowing total consumption to change, we could fix the total number of effective dosages, and allow the effective life of the drug to change.

both reducing resistance to the pioneer drug and increasing welfare.

3 Imperfect Competition and Resistance

Now suppose an alternative to the pioneer's antibiotic is available for combatting a particular infectious disease. The substitute is differentiated either in its composition (e.g. uses a different molecule) or in its method for attacking the bacteria (e.g., breaking down the cell wall vs. inhibiting protein) but it is of similar biological quality in its effectiveness against the bacteria. We call these "same-generation" drugs to contrast with future generations of drugs discussed in Section 5. The question we ask is: Does the introduction of imperfect competition in the market for drugs reduce or increase bacterial resistance?

As already seen, a powerful biological force is a bacterium's resistance to a drug; the greater the cumulative usage of the drug the greater is the bacterium's resistance (*own-resistance*). With contemporaneous substitutes, a second, potentially powerful force, referred to as *cross-resistance* or *multiple-drug resistance* is at play. This occurs when a bacterium's resistance to one drug crosses over to another drug, that is, the resistant organism displays decreased sensitivity to other drugs [Pál, Papp and Lázár, (2015)].[27]

The medical evolution in the treatment of tuberculosis (TB), a disease from which 1.5 million people the world over died in 2013, exemplifies the impact of cross- or multi-drug resistance.[28] Antibiotic treatment of the disease started in the 1940s with streptomycin. But soon (*own-*)resistance developed largely due to inappropriate use and insufficient patient compliance, and other antibiotics like rifampicin, isoniazid were introduced and these now constitute the main lines of attack for the disease.

Given this effect, it may seem at first blush that introducing competition could be counterproductive. Since the aggregate output of two competing drugs is greater than the monopoly output of a single drug, resistance to antibiotics in a given period would seem to be greater under competition, thereby compromising effectiveness of the pioneer drug. As we demonstrate below, this intuition may be incorrect: introducing a variety of antibiotics, surprisingly, can reduce resistance to each drug.

[27] In a laboratory setting, Suzuki et al (2014) showed that when bacteria develop resistance to one antibiotic they also have a reasonable probability of exhibiting resistance to one or more of the other antibiotics.The bacteria can also become resistant to another drug through "horizontal gene transfer" by obtaining resistant genes from other bacteria, for example, through direct cell-to-cell contact or by acquiring genetic material from its environment. While the latter is an important mechanism for transmission, we do not model it in this paper.

[28] WHO (2014), *Global Tuberculosis Report*. Also, in 2013 alone, more than 50,000 Indian babies died due to multi-drug resistance. [See Harris, "Superbugs' Kill India's Babies and Pose an Overseas Threat," *New York Times*, Dec. 3, 2014.]

3.1 Competition in Two Drugs

To see this, allow the pioneer **X** to confront a biologically similar (in confronting resistant bacteria) but economically differentiated antibiotic, denoted by **Y**. For these same-generation drugs, we assume the second firm enters instantaneously. Let $x(t)$ and $y(t)$ be the period t outputs of drugs **X** and **Y**, respectively. Furthermore, let the parameter $\gamma > 0$ capture the extent to which the drugs are perceived to be imperfect substitutes in use and $\phi > 0$ capture biological cross-resistance, that is, the degree to which cumulative output of drug **X** undermines the effectiveness of drug **Y**, and vice versa.[29] To analyze this problem, we expand the quadratic utility for a single drug to two differentiated drugs with an adaptation of the quadratic utility function, $u^d(x(t), y(t))$ in Singh and Vives (1984) that allows for both own- and cross-resistance:

$$\begin{aligned} u^d(x(t), y(t)) &= \alpha(x(t) + y(t)) - \frac{\beta}{2}(x(t)^2 + y(t)^2) - \gamma x(t)y(t) \\ &\quad -\theta(x(t)X(t) + y(t)Y(t) - \phi(x(t))Y(t) + y(t)X(t)), \end{aligned} \tag{11}$$

where $X(t) = \int_0^t x(s)ds$ and $Y(t) = \int_0^t y(s)ds$, are cumulative outputs prior up to time t, with $X(0) = Y(0) = 0$.[30] A necessary condition for joint concavity in x_t and y_t is $\gamma \leqslant \beta$. As before, we assume that consumers ignore the future consequences of their antibiotic consumption and, by maximizing their current utility, generate the linear inverse demand curves below for drugs **X** and **Y** at time $t \in [0, T]$:[31]

[29] We assume that ϕ's are symmetric. In reality, cross-resistance rates may be asymmetric, but this does not qualitatively affect the main findings in this section.

[30] Note that when $\gamma = \beta$, $\theta = \phi$, the utility function in (11) collapses to the case of a single good, say Z, with output $z(t) \equiv x(t) + y(t)$. That is, for identical substitutes both economically and biologically, there is effectively only one drug available in the market.

[31] In terms of the primitives outlined for the single drug case, we can think of there being two groups of consumers of size N, each with a probability δ of falling ill. Each group is typically prescribed one of the drugs, in which case they are restored to good health of valuations $v_1(t)$ and $v_2(t)$, distributed with identical uniform distributions on support $[0, \overline{v}]$. Consider purchases of the **X** drug. If a consumer has valuation $v_1(t) > c_1(t)$, where $c_1(t)$ is the valuation of the marginal consumer, then she consumes the **X** drug. However, she faces an opportunity cost if $v_1(t)$ is also greater than $c_2(t)$, the valuation of the marginal consumer of drug **Y**, in which case she could take **Y** instead. However, because the value she would receive from **Y** is some relatively lower (fixed) value η, denoted by the expected utility of consuming drug of all X users is given by:

$$u_x(t) = \delta N \int_{c_1(t)}^{\overline{v}} [(v_x - \theta X(t) - \phi Y(t)) - \eta(1 - F(c_2(t)))]dF(v_x)$$

Substituting $y(t) = \delta N(1 - F(c_2(t)))$ from (2) and $F(c_2(t)) = c_2(t)/\overline{v}$ for a uniform distribution gives:

$$u_x(t) = \alpha x(t) - \theta X(t)x(t) - \phi Y(t)x(t) - \frac{\beta}{2}x(t)^2 - \frac{\gamma}{2}x(t)y(t),$$

$$
\begin{aligned}
P^{\mathbf{X}}(t) &= \alpha - \beta x(t) - \gamma y(t) - \theta X(t) - \phi Y(t), \\
P^{\mathbf{Y}}(t) &= \alpha - \beta y(t) - \gamma x(t) - \theta Y(t) - \phi X(t),
\end{aligned} \tag{12}
$$

where $P^{\mathbf{X}}(t)$ and $P^{\mathbf{Y}}(t)$, respectively, denote the marginal willingness to pay for drugs $\mathbf{X}$ and $\mathbf{Y}$ at time t.

Since the drugs are also imperfect substitutes from a biological perspective, we expect that $\phi < \theta$, an assumption we maintain throughout. Biological evidence for the latter assumption that the cross-effect in resistance is smaller than own-effect in resistance, is provided in Figure 2, which reproduces a heat map from a recent study by Imamovic and Sommer (2013) that measures the degree of resistance to a drug resulting from its own use and from consumption of another drug.[32] Each cell measures resistance to drug $\mathbf{X}$ (on the horizontal axis) when the bacteria is treated with drug $\mathbf{Y}$ (on the vertical axis). The greater the resistance, the darker is the orange color. Note that along the diagonal as more of the drug is used—for example, consider GEN (gentimicin)—the more own-resistance against that drug develops. And, while others also light up when GEN is used, they do so with a paler orange, consistent with our claim that $\phi < \theta$.[33] (The blue cells are discussed later.)

It is also worth noting here that ϕ and γ, respectively, are modeled as unrelated biological and economic cross-effects. However, it might seem that as the two drugs become closer *economic* substitutes, they should also become closer *biological* substitutes; that is, as γ approaches β, ϕ should approach θ. The extreme case in which both $\phi \to \theta$ and $\gamma \to \beta$ characterizes generics: perfect substitutes in which production of any one of them inflicts resistance on the others. However, while ϕ may change with changes in γ, that relationship may not be linear or even monotonic. The reason is that two drugs may have completely different molecular structures but could have similar effects on the illness; that is, even if γ is close to β, ϕ may be significantly lower than θ. In that sense, there is a discontinuity at the limit as γ approaches β: in replicating the original molecule, generics are perfect substitutes both from biological and economic points of view; whereas close economic substitutes may be biologically very different. The light orange sections of Figure 2 provide examples of drugs that combat the same disease (γ is high) but exhibit low cross-resistance (ϕ is low).[34].

where as in the one-drug case, $\alpha = \overline{v}$, $\beta = \overline{v}/\delta N$ and $\gamma = \eta/\delta N$. Note that since $\eta \leqslant \overline{v}$, it follows that $\gamma \leqslant \beta$. Then adding $u_x(t)$ to the symmetric utility for $u_y(t)$ gives the expression in (11).

[32] See also Hancock (2014).

[33] In this analysis, we assume that a second drug is developed by a different firm. Implications for relaxing the assumption are discussed later.

[34] For example, gentamicin (GEN) and ciproflaxin (CFX) are both used against *MRSA* but do not reduce effectiveness of the other drug by their respective production.The opposite may also be true: that is, the two drugs may be distant economic substitutes, but the cross-resistance may be found to be strong (close to own-resistance). An example of this are the medicines administered for malaria and HIV/AIDS. The respective drugs are not economic substitutes within each disease

To keep the analysis simple, we look for a Nash equilibrium under the assumption that each firm takes its rival's output path as given. Each drug producer will choose output to maximize her profits over the duration L, prior to generic entry. We presume that the firms are able to commit themselves to a time path for their outputs and we determine below the nature of this Nash equilibrium time path.[35] Firm $\mathbf{X}$ maximizes its total profit by choosing the time path $\{x(t)\}$, taking as given $\{y(t)\}$:

$$\max_{\{x(t)\}} \int_0^L P^{\mathbf{X}}(t)x(t)dt, \quad s.t. \;\; dX/dt = x(t), \tag{13}$$

and, likewise, Firm $\mathbf{Y}$ maximizes its total profit by choosing the time path $\{y(t)\}$, taking as given $\{x(t)\}$:

$$\max_{\{y(t)\}} \int_0^L P^{\mathbf{Y}}(t)y(t)dt, \quad s.t. \quad dY/dt = y(t), \tag{14}$$

where $P^{\mathbf{X}}(t)$ and $P^{\mathbf{Y}}(t)$ are given in (12).

The following proposition characterizes the time profile of the duopoly output path.

Proposition 3: If firms can precommit to an output path, equilibrium duopoly output will be constant over time if the cross-resistance is zero and declining exponentially if the cross-resistance is positive.

Proof.By the Maximum principle, the output, $x(t)$, $t \in [0, L]$, of Firm $\mathbf{X}$ must satisfy:

$$\alpha - 2\beta x(t) - \gamma y(t) - \phi Y(t) - \theta X(t) = \lambda^{\mathbf{X}}(t), \tag{15}$$

where the shadow cost, $\lambda^{\mathbf{X}}(t)$, of $X(t)$ satisfies the equation of motion

$$\frac{d\lambda^{\mathbf{X}}(t)}{dt} = -\theta x(t).$$

Analogous equations hold for $y(t)$ and the shadow cost, $\lambda^{\mathbf{X}}(t)$, of $Y(t)$. Invoking symmetry in equilibrium between the two firms the output path must satisfy:

$$\alpha - (2\beta + \gamma)x(t) - (\theta + \phi)X(t) = \lambda^{\mathbf{X}}(t).$$

Taking the time derivative of the above equation and using the equations of motion

but can transmit resistant DNA to each other [Iyer et al (2001), Malamba et al (2006), Laufer and Plowe (2006)].

[35] The assumption of commitment corresponds to an open-loop resolution of the competition and obviates the need to work backwards that the subgame perfect equilibrium requires. While the latter equilibrium concept may be more desirable, it adds complexity without the benefits of new insights.

for $X(t)$ and $\lambda^{\mathbf{X}}(t)$, we obtain the differential equation

$$(2\beta + \gamma)\frac{dx(t)}{dt} = -\phi x(t),$$

which yields the common solution to $\{x(t)\}$ and $\{y(t)\}$:

$$x(t) = y(t) = C\exp[-\phi t/(2\beta + \gamma)]. \tag{16}$$

The constant C (> 0), which is the initial output of the firms, can be determined by (15) and the terminal condition $\lambda^{\mathbf{X}}(L) = \lambda^{\mathbf{Y}}(L) = 0$. ■

As stated in Proposition 3, when cross-resistance is present, each firm's demand curve shifts down over time in a manner that it cannot control; and so output declines over time. We can use this information to compare the accumulated resistance under duopoly with that under monopoly over L periods.

First note that in the case of the limited-duration monopoly model of the previous section, by the end of the patent period L, the demand curve has shifted in by $\theta L x_m$, and so the decline in the marginal willingness to pay, R_m, due to a loss in drug effectiveness is given by

$$R_m = \theta L x_m \ , \tag{17}$$

where x_m is given in (9). That is, R_m captures the damage from the drug resistance that evolved during the pioneer's exclusivity period. Under duopoly total resistance to a drug prior to generic entry is given by $R_d = \theta \int_0^L x(t)dt + \phi \int_0^L y(t)dt$, where x_t and y_t (by symmetry) are given by the solution to (13). Furthermore, by symmetry, we can rewrite R_d as:

$$R_d = (\theta + \phi)\int_0^L x(t)dt. \tag{18}$$

Inspection of R_m and R_d reveals that, for a common lead-time L, resistance to any single drug will develop more slowly when there are two imperfect substitute drugs than when there is a protected pioneer drug if cross-resistance is sufficiently small (i.e., $\phi \backsimeq 0$). This observation follows immediately from the fact that, at $\phi = 0$, each firm's output in (14) not surprisingly will be less than the monopoly output x_m; therefore, R_d will be less than R_m. By continuity of R_d in ϕ, the above shows that the relationship will be preserved for ϕ sufficiently small.

While straightforward, this observation identifies a powerful result that, counter-intuitively, imperfect competition can be more effective than monopoly in moderating the negative impact of consumption on drug effectiveness. When $\phi > 0$, R_d can be lower than R_m since each duopolist will produce less output than a protected pioneer, even though the per unit resistance weight under duopoly $(\theta + \phi)$ is greater than

that of monopoly (θ). So, for a given L, the lower duopoly output can offset the cross-resistance to slow down the pace at which resistance accumulates to a drug.[36]

The result that duopoly can generate less resistance than monopoly is particularly instructive in revealing how the interaction between biological and economic forces affects the relationship between the two drugs. In particular, the two drugs are related biologically through the resistance they transfer to each other (as captured by ϕ) and economically through the substitutability between the two drugs (as captured by γ). The precise condition under which resistance falls with competition is derived in the welfare analysis of the next section. But first, we complete the positive analysis with a derivation of the post-patent generic equilibrium.

3.2 Generic Entry

In the previous sections, we derived the efficient monopoly and duopoly paths, under the assumption that generic production was efficient. Generally, generic production will be socially excessive and a Pigouvian tax will be needed to curb production. To see this, recall that after time L, generic entry occurs. We assume this phase plays out in a perfectly competitive environment because of free entry. Generic firms take the market demand as given but, from the vantage point of resistance, there is no longer the redeeming feature of a restricted output of a non-discriminating monopolist. In terms of antibiotic resistance, it is theoretically possible that the generic industry may be more problematic than the preceding monopoly since from period L on generics will produce until the price in each period is driven down to marginal cost (zero). That is, if the generic output at time t is denoted by $g(t)$, then at time L, the generic output, g_L, is given by

$$g(L) = [\alpha - \theta L x_m]/\beta,$$

where Lx_m is the monopolist's cumulative output over the patent's life. This implies that the industry's output at time L is necessarily above the monopolist's (constant) output.[37] So we know that, despite the tempering effect of antibiotic resistance on future output, the industry's output necessarily expands at least initially after generic entry.

If we denote the cumulative generic output up to time t by $G(t)$, that is, $G(t) \equiv \int_L^t g(s)ds$, for $L < t \leq T$, $G(L) \equiv 0$, then generic output at t is given by

$$g(t) = [\alpha - \theta(Lx_m + G(t))]/\beta, \quad t \in [L, T], \tag{19}$$

Given the initial condition $G(L) = 0$, the above expression can be recursively applied to determine the entire generic output over time. Cumulative output is increasing over time, and by pulling down the demand curve due to own-resistance

[36] In a subsequent section of this paper, we derive the precise condition under which this is true.

[37] This follows immediately by comparing the expression for g_L above with that of x_m in (10) and invoking the assumption that $\theta < \beta$ in our model.

to the drug, reduces generic output. As sketched in the Figure 3 (for continuous time), the output profile of the industry will be constant up until period L, increases discontinuously at L, and then declines monotonically after generic entry takes over.

In contrast to the patentee, generics always have a tendency to overproduce relative to the planner for a given stock of cumulative resistance, because they completely ignore the resistance externality. This is illustrated in the figure for the scenario in which the monopolist is shown to underproduce relative to the social optimum. The generics compensate for this to some extent by overproducing in the initial post-patent period but eventually, the cumulative buildup of resistance may force the generic industry to produce below the social planner's output.

While generics temper the high prices patentees can charge, they also pay no attention to the evolution of resistance. One way to delay the onset of generic overproduction is to extend optimal patent life, but a more efficient way is to impose a Pigouvian tax on the competitively produced output to realign private and social efficient levels [Pigou (1920), Baumol (1972)]. Such a tax would be an addition to the price of every unit of antibiotic consumed, taking account of the user cost of the antibiotic in a dynamic scenario. By forcing otherwise short-sighted consumers to recognize the future resistance consequences of their current consumption, the Pigouvian tax would depress current demand for antibiotics, and thereby improve welfare.[38]

Since the output of the generic industry is time-dependent, the planner will adjust the tax over time so that the generic output coincides with the planner's (constant) output, x_m^*. Observe that at any time $L+s, s \in [0, T-L]$, when the generic is produced, the output in each of the preceding instants is x_m^* and the cumulative output is $(L+s)x_m^*$. Thus the tax rate, $\tau^g(L+s)$, at time $L+s$, $s \in [0, T-L]$, must equate the generic output in (19), adjusted for a tax, to the social planner's output in (8):

$$[\alpha - \tau^g(L+s) - \theta(L+s)x_m^*]/\beta = x_m^*,$$

The solution to this equation, after substituting for x_m^* from (8), yields optimal Pigouvian taxes:

$$\tau^g(L+s) = \frac{\alpha\theta(T-L-s)}{\beta+\theta T}, \quad s \in [0, T-L]. \tag{20}$$

When $L < T$ the above tax rate is always strictly positive; the planner never subsidizes the generic for efficiency ends. Note that at a constant output, the mar-

[38] Similar to the generics, a tax could be placed on an overproducing monopolist. This could be an equally effective alternative to patent life extension. The per-unit tax would be constant over time, equal to that which would ensure the monopolist's (constant) output coincides with the planner's (constant) output. It is straightforward to show that the tax rate, τ_m, is given by $\tau_m = \frac{\alpha[\theta(T-L)-\beta]}{\beta+\theta T}$. Note that if the monopolist overproduces, the required tax rate needs to be larger for shorter patent lives. If $L = L_m$, naturally the tax rate would be zero.

ginal willingness to pay declines over time as own-resistance accumulates.[39] And so, successively lower taxes are needed over time in order to bring the generic output in alignment with the planner's, mimicking the profile of the industry output shown in Figure 3.

4 When *More is Less* under Competition: Welfare Implications and Policy

Given the results on the evolution of resistance to a pioneer drug when competition is introduced, we can now analyze whether a protected monopoly or a narrow patent that admits competition is more effective at addressing the antibiotic crisis. We do so in two steps: First we identify the set of policies that can best achieve efficient consumption when only the pioneer drug is available, and then when a competing drug can also also be used to combat the targeted bacteria. Second, we find conditions under which admitting a second drug into the market with narrow patents is preferred to awarding the pioneer a monopoly in the market.

Starting with the monopoly, we note from the previous section that if $L < L_m$ overproduction by a monopolist can be a problem. In that case extending patent life to L_m and setting a Pigouvian tax on generics can align social and private incentives. However, our observation following Proposition 3 on the effect of competition on resistance suggests that competition could alternatively moderate resistance. That is, rather than *increasing* patent protection with longer life, the planner could *reduce* protection by allowing competition through a narrower patent breadth. We explore this alternative below.

We begin by solving the social planner's problem given the surplus function $\int_0^T u^d(x(t), y(t))dt$, where $u^d(x(t), y(t))$ is given in (11) for two drugs. When multiple drugs are available, the social planner accounts for the economic substitutability between the drugs in the market, as represented by γ, as well as their impact on future resistance, as represented by ϕ in addition to θ, which was relevant in the single drug case. Following the analysis in Section 3.1, it is easily shown that the planner's optimal (time-independent) and symmetric output, x_d^*, of a drug in a duopoly is given by:

$$x_d^* = \frac{\alpha}{\beta + \gamma + (\theta + \phi)T}. \tag{21}$$

Note that $x_d^* < x_m^*$. That is, when two drugs are available, the social planner reduces output of each drug, relative to the single-drug case in (8), to account for economic substitutability (γ) and the biological cross-externality (ϕ). As in the

[39] If $L = T$, generics do not produce. Therefore, the tax on generics is zero.

monopoly case, the planner will want to find a mechanism that aligns the efficient output in (21) with the private firms' outputs in (15), which declines over time since firms do not internalize the biological externality of $\phi > 0$ that they inflict on their rivals.

4.1 Allowing for Coordination

If the firms were allowed to coordinate on the externality of cross-resistance, effectively internalizing the cost imposed on their rival while continuing to compete in the market, duopoly output in (14) would be constant over time at the common value, $x_d^\dagger$, given by:[40]

$$x_d^\dagger = \frac{\alpha}{2\beta + \gamma + (\theta + \phi)L}. \tag{22}$$

While this strategy is appealing from a social point of view, a policy that allows coordination on technological externalities while maintaining competition with pecuniary externalities could facilitate anti-competitive price collusion that would be difficult to separate from welfare-increasing biological coordination. One approach would be to define a "safe harbor", a price ceiling, above which antitrust action would be initiated. That ceiling, which is readily computed as the price that obtains when the socially optimal output in (21) is substituted into the inverse demand functions in (12), is given by:

$$\overline{P}^d(t) = \frac{\alpha(1 + (L - t)(\theta + \phi))}{(2\beta + \gamma + (\theta + \phi)L)}. \tag{23}$$

Such an expedient would enable firms to partially collude up to the point where the cross-resistance is internalized, but no further. Note that the price cap in (23) declines over time since the marginal willingness to pay for the drug declines due to resistance.

The policy in (23) allows firms to coordinate on output so as to internalize the negative externality of biological resistance but not go so far as to eliminate competition in the market. This is consistent with recent antitrust practices that have recognized the social value of partial cooperation and have allowed a variety of joint ventures for coordinating non-price instruments such as R&D, capital facilities, patents, standards and other assets between competitors, while strictly prohibiting price collusion. The challenge with the policy in (23), however, is that there is only one instrument—output reduction—which could be implemented for efficient reasons, such as reducing resistance, but also for anticompetitive reasons, such as raising prices. That said, it should be noted that even when coordination occurs only on non-price instruments, it will depend on prices and, in that sense, disentangling efficient from collusive behav-

[40] This is found by rewriting the integrand of Firm $\mathbf{X}$'s profit in (13) as $P^X(t)x(t) - \phi X(t)y(t)$ to force it to internalize the user cost of its own drug to its rival's drug. The integrand of Firm $\mathbf{Y}$'s profit is also changed analogously.

iour would still be difficult. So, the policy proposed here does not introduce a new, insurmountable problem. Antitrust authorities are well-equipped to evaluate such agreements, given the framework laid out in the *Joint FTC and DOJ Antitrust Guidelines for Collaborations Among Competitors* (2000) for facilitating welfare-improving collaborations, a framework that could be applied directly to the cooperative agreements in antibiotics markets described above.

An alternative to price regulation would be to impose a form of compulsory licensing in which drug producers would be required to pay a per unit royalty on their output. To achieve the output in (22), given the first-order condition in (13), the regulated per unit royalty, ρ_t, paid by firm $\mathbf{X}$ at time t to its rival firm $\mathbf{Y}$ would be $\rho(t) = \phi Y^+(t)$, where $Y^+(t) = \int_t^L y_s ds$. Given symmetry between firms $\mathbf{X}$ and $\mathbf{Y}$, it is straightforward to show that the royalty rate in equilibrium, ρ_t^*, declines over time and is given by:[41]

$$\rho^*(t) = \phi(L-t)x_d^\dagger. \tag{24}$$

Then, under the royalty levy in (24) or antitrust rules in (23), the equilibrium duopoly output will be given by (22), the output allowing for coordination of only the biological externality. The analysis that follows assumes that such policies are implementable.

Assuming at least one of the policies is implementable that allows efficient coordination on resistance but not prices, we can find the optimal period of exclusivity under imperfect competition, L_d, by comparing the equilibrium duopoly output in (22) with the planner's duopoly output in (21):

$$L_d = T - \beta/(\theta + \phi). \tag{25}$$

Therefore, it is possible to reduce both forms of resistance further by increasing patent life. Comparison of L_d in (25) with L_m in (10) reveals that *the socially efficient patent life for duopoly is higher than optimal patent life when only the pioneer's drug is available.* Duopolists are given a longer patent life than a monopolist to encourage competing firms to lower output further to economize on own-resistance and also cross-resistance to their rival. So, efficient usage of a drug, given profits are sufficient to bring about its development, is to either award a broad patent (ensuring a monopoly) with duration L_m or a relatively narrow patent (accommodating a duopoly) with longer duration L_d.

On the face of it, this relationship between patent life and breadth may not seem so surprising, given results in the conventional literature, in which these two patent instruments typically are traded off to preserve the size of the award and, therefore, innovation incentives [Gilbert and Shapiro (1990), Gallini (1992)]. But here, innovation is not at play: the drug is already available and so only *ex post* efficiency is considered. What seems like a familiar trade-off arises here for a very different

[41] This is similar to a cross-licensing scheme that facilitates tact collusion [Eswaran, 1994]. Here, the tax imposed on each other's output is efficient in moderating cross-resistance.

reason: to provide *ex post* incentives to mitigate the costs of resistance. By extending the period of exclusivity, patentees will be compelled to directly internalize their own-resistance externality (captured by θ) and also the cross-resistance externality (captured by ϕ).

The above results are gathered in Proposition 4 below.

Proposition 4: If post-patent generic production is efficient (for example, through a Pigouvian tax), then conditional on the socially optimal number of drugs, the policy that will achieve first-best output will be either a broad patent of length L_m or a relatively na*rrow patent with duration L_d, complemented by antitrust rules allowing cooperation subject to a 'safe harbor' on prices or compulsory licensing.*

4.2 Welfare Analysis: Efficient Consumption

Given Proposition 4, the question that remains then, is: What is the optimal degree of competition, a protected monopoly or duopoly made feasible by a narrow patent? Let K be the cost of research to identify a new drug, then imperfect competition will dominate monopoly if[42]

$$\mathbf{V}^d(x_d^*) - \mathbf{V}^m(x_m^*) \geq K, \tag{26}$$

where $\mathbf{V}^d(x_d^*) = \int_0^T u^d(x_d^*, x_d^*)dt$, that is, the present value of utility in (11) evaluated at the symmetric x_d^*. Similarly, $\mathbf{V}^m(x_m^*) = \int_0^t u^m(x_m^*)dt$ is the present value of utility shown in (7) evaluated at x_m^*.[43]

If (26) holds, duopoly is at least as good as a protected monopoly; otherwise, the pioneer drug should receive a broad patent for L_m periods.[44] We can determine conditions under which (26) is satisfied, adopting the policies in Proposition 4, that is, when competition in the antibiotics market is socially efficient. First, we identify an important relationship between the economics of competition and the biology of resistance.

Proposition 5: If socially efficient outputs are achieved under both competition and monopoly (or equivalently, patent durations are set optimally), then competition will generate less resistance than monopoly over the protected period L_m if and only

[42] For simplicity, we have assumed the cost of research is the same for all (γ, ϕ) combinations. More realistically, developing a substitute that is very different as perceived by consumers (low γ) or that does not exert an externality (low ϕ) may be costlier to develop. In that case, the condition would be more difficult to satisfy for low-valued (γ, ϕ) pairs.

[43] Condition (26) allows for transfers or subsidies if total surplus from competition is positive to compensate for potentially negative duopoly profits, net of R&D.

[44] See (A2) in the Appendix for condition (26) in terms of exogenous variables.

if

$$\phi/\theta < \gamma/\beta. \tag{27}$$

If the duopolists face the same patent life as a monopolist, the condition for *the multi-firm setting to generate less resistance over any period L is*

$$\phi/\theta < \gamma/2\beta. \tag{28}$$

The expressions in (27) and (28) can be shown to be invariant with respect to the number of (symmetric) firms in the industry. The condition in (27) is easily derived starting with the following inequality: resistance accumulated over an arbitrary number of L periods under duopoly is less than that under monopoly if

$$(\theta + \phi)Lx_d^* < \theta Lx_m^*.$$

Substitution of optimal output for duopoly (with cross-resistance internalized) and monopoly in (21) and (8), respectively, gives the result in Proposition 5. Condition (28) follows similarly, but with a fixed rather than optimal L. This condition is more stringent than (27) because the firms in this case are not granted a longer patent to economize on resistance.

The expressions of Proposition 5 provides a remarkably simple and fundamental statement of how economics and biology interact in reducing resistance. When the social planner adds a second drug, it contributes to the cross-resistance faced by the pioneer, which depends on ϕ. But she also reduces the output of the pioneer's drug, depending on the substitutability between the two drugs. This, in turn, lowers own-resistance, the magnitude of which is determined by γ/β and θ. The relationship in (27), for example, states that when the cross-resistance effect is smaller than the own-resistance effect or "business-stealing" effect, then competition will slow down a bacterium's overal resistance to the pioneer's drug. In essence, when the economic forces are stronger than the biological forces between two drugs, allowing for a competing patent can slow down a bacterium's resistance to the drug.

However, a reduction in resistance does not necessarily imply that competition is welfare improving. Combining the results in Propositions 4 and 5, we can identify when competition in antibiotics dominates a protected monopoly. (Proof in the Appendix.)

Proposition 6. If competition reduces resistance (that is, (27) holds), then there exists a $\overline{\gamma}$ such that when

$$\phi/\theta < \gamma/\beta < \overline{\gamma}/\beta \tag{29}$$

competition is also welfare increasing. Conversely, when competition is welfare-improving, the measure of $(\gamma/\beta, \phi/\theta)$ pairs for which resistance is lower is at least as large as the measure for which resistance is higher.

Propositions 5 and 6, which are the main results of the paper, characterize the

economics-biology interaction in the antibiotics market that drives resistance and welfare. The first part of Proposition 6 is expected in that when resistance falls with competition, welfare necessarily increases for the standard reason, provided the two goods are not too close economically to justify the additional R&D costs. This result, nevertheless, is interesting from a policy point of view. The result in (29) suggests that the breadth of a patent has two dimensions: one economic, one biological. The economic one, given by the second inequality, is conventional: the competing drug cannot too close in product space. The biological breadth, given by the first inequality, restricts the drug from being too close in biological space in the sense of inflicting excessive cross resistance.[45]

The converse result, stated in the second part of Proposition 6, indicates that when competition increases welfare, it is more likely than not that resistance will also be lower. This idea is illustrated in Figure 4. The 45° line OA is where $\gamma/\beta = \phi/\theta$, and so combinations of $(\gamma/\beta,\ \phi/\theta)$ that fall above OA satisfy (27) and those that fall below satisfy its converse.The "iso-benefit" curves from competition between γ/β and ϕ/θ, derived from (26) are negatively sloped and linear in $(\gamma/\beta,\ \phi/\theta)$ space. An iso-benefit line in Figure 4 has a slope smaller than -1 because a small increase in ϕ/θ has a cumulative effect on surplus that must be offset by a more than proportionate decline in the degree of substitutability. The iso-benefit line BC is the one for which the net benefit is equal to K. As shown, all the $(\gamma/\beta,\ \phi/\theta)$ combinations in the shaded triangle ODB, where (27) is satisfied, is larger than the area of the triangle OCD for which resistance under competition is higher, as stated in Proposition 6.

Propositions 5 and 6 can be used to explain the result in Laxminarayan (2002) calling for broad patents. There, he analyzes cross-resistance for a symmetric n-firm oligopoly in a two-period ($L = T = 2$) model for parameter values (using the above notion) $\beta = \gamma$ and $\theta = \phi$.[46] This case of homogeneous Cournot competition is a special case of the above analysis. Since patent life is constrained to be the same for all n in his model, the relevant condition under which competition reduces resistance is given by (28). Note that when $\beta = \gamma$ and $\theta = \phi$, condition (28) is not satisfied; therefore, resistance under an n-firm oligopoly is greater than that under monopoly. Moreover, under the converse of (28), it can be shown that as the number of symmetric competitors increases beyond $n > 1$, resistance and therefore effectiveness of the pioneer drug monotonically worsens.[47]

In contrast to this polar case, Propositions 5 and 6 identify a wide range of economic and biological conditions satisfying (28) in which competition reduces resistance and increases effectiveness of the pioneer drug. And, when that condition

[45] This biological dimension of the patent would presumably fall under the purview of the FDA.

[46] Although the equilbrium in his two-period model is sub-game perfect, the framework developed in this paper can be used to provide intuition for his result.

[47] To see this, note that the accumulated resistance at any time t is given by $R_t^n = t[\theta+(n-1)\phi]x(n)$, where $x(n)$ is the equilibrium oligopoly output for a firm facing $n-1$ symmetric competitors is similar to (22) but where $n-1$ multiples both γ and ϕ. It is straightforward to show that R_t^n decreases (increases) in n if (28) holds (does not hold).

holds, increasing n beyond $n > 1$ reduces resistance further. In that case, optimal patent breadth, as defined by the number of competing drugs, will be relatively narrow. When (28) holds, competition (narrow patents) increases gross surplus, not only because competition generates the usual economic benefits from lower-prices and differentiated products, but also because it reduces the biological impact of resistance. Therefore, R&D costs dictate patent breadth; that is, patent breadth will be narrowed until the surplus gain from additional variety equals R&D costs. In contrast, if (28) is not satisfied, as in Laxminarayan (2002), then increasing n beyond $n > 1$ increases resistance, thereby warranting a relatively broad patent breadth that balances the economic benefits from competition with the biological cost of increased resistance.

4.3 The Biology of Competition

The result in Proposition 6 delivers an important insight: competition can be a mechanism for reducing resistance and increasing welfare. These results are predicated on the assumption that competing drugs are biological substitutes in the sense that one drug crowds out the other. However, scientific studies have shown that drugs that are *economic substitutes* can be *biological complements*. This makes the case for competition even stronger than argued above.

The direction of the inequality in (27) depends on the values of the economic and biological parameters. While precise estimates of these parameters are not available, there is considerable evidence in the science literature suggesting that economic substitutes can be valuable in slowing down the accumulation of resistance. For example, the practice of 'mixing' or 'heterogeneity' requires multiple differentiated products. Under that practice, heterogeneity in patients with the same bacterial illness at a given point in time are prescribed different antibiotics, either because it is unknown which one works best for the patient or because they react differently to drug characteristics (e.g., active ingredients, coating, delivery method, etc.). Consistent with predictions of the above model, tests in clinical settings have shown that "mixing" has been successful in curbing the growth of resistance [Laxminarayan and Weitzman (2002), Sandiumenge et al (2006), Masterton (2010)].

Beyond the benefits from variety, allowing substitute drugs also facilitates research and experimentation toward identifying effective treatments for diseases that can arrest the onslaught of bacterial resistance. A notable example centers around the debate between broad-and narrow-spectrum antibiotics. Broad-spectrum antibiotics are used when the precise bacterium causing the illness has not yet been isolated before action needs to be taken. These antibiotics tend to target a commonly held characteristic of many bacteria and therefore have a high probability that the bacterium causing the illness will likely be attacked. While having the virtue of dealing with a wide range of bacterial infections, the downside of such antibiotics is that they address many other bacteria that are not causing the illness. Evidence suggests that this contributes to an increase in resistance [Neuhauser et al (2003)]. By providing

a gratuitous environment for evolutionary selection, these bacteria are inadvertently given an opportunity to evolve resistance to the antibiotic.[48]

For example, in a study conducted at a children's hospital in the Netherlands, de Man et al (2000) compared the resistance that developed to broad-based antibiotics (an amoxillin-ceforaxime combination) to that which developed against narrow-based antibiotics (a penicillin-tobramycin combination). The study found that the colonization by resistant strains of bacteria was 18 times more likely with the use of broad-based antibiotics. While a more recent study found no statistically discernible differences in the health outcomes[49] for children with pneumonia in which nearly 90% of the children were given broad-spectrum antibiotics, the scope for reducing antibiotic resistance by switching to narrow-spectrum antibiotics would be considerable. In our framework, broad-spectrum drugs would be characterized by a higher ϕ relative to narrow-spectrum. However, the effectiveness of introducing narrow-spectrum drugs would depend on improvements in diagnostic testing so as to identify the precise bacterium that is causing the illness in an individual.

A third approach using multiple drugs is combination therapy. Under this approach, multiple antibiotic agents are used synergistically to attack different aspects of the pathogen (cell wall synthesis, bacterial enzymes, protein translation), all of which must be counteracted in order to successfully resist and prosper in the environment. This approach has been shown to be a powerful mechanism for resisting bacteria and recommended for community-associated *Staphylococcus aureus* (MRSA) that is resistant to methicillin,[50] and is standard treatment for tuberculosis and HIV. This approach would not necessarily reduce resistance directly, but would do so indirectly by increasing effectiveness of the drug and lowering demand for the drugs.

Finally, different antibiotics for the same disease are needed to slow down the development of resistance under antibiotic *cycling*. Antibiotic cycling refers to the practice of using an antibiotic for a given period in a hospital ward, then withdrawing it and replacing it with another antibiotic, then withdrawing the latter after a period and replacing it with different one (possibly the original one), and so on. While simulated models and clinical evidence to date suggest that antibiotic cycling does not work or the benefits are small or the results are mixed,[51]more recent attempts at cycling

[48]For example, the extended-spectrum cephalosporins have fostered the development of the serious methicillin resistant *staphylococcus aureus* (MRSA), a bacterium that is resistant to many antibiotics and causes anywhere from about half to about two-thirds of the health-care related infections in the U.S. [Jernigan and Kallen (2010)]. Problems such as these could conceivably be addressed by the use of multiple, narrow-spectrum antibiotics with more precise targets, tempering the growth of resistance.

[49]The study was on broad-spectrum vs. narrow-spectrum antibiotics to treat pneumonia in children. The data came from 43 U.S. hospitals over the period 2005 to 2011 [Williams et al (2014)].

[50] For viral diseases, the multiple antiretroviral drug cocktails have been known to be far superior to AZT, the first drug treatment against HIV infection. See [Leekha et al. (2011)] for discussion of combination therapy.

[51]See Warren et al (2004), Bergstrom et al (2004), Kollef (2006), Masterton (2010). After resistance to an antibiotic has evolved in a bacterium, it does not die out if removal of the antibiotic

involving a phenomenon called collateral sensitivity are proving to be more promising. Goulart et al (2013) attempted cycling with antibiotics having a *similar structure*, that is, belonging to the same class using similar mechanisms. By judiciously choosing the antibiotics and their order in the cycling, the authors show theoretically and empirically that, in forcing the bacterium to chase a constantly changing target, it can be forced to cycle back to *its original position*. In a laboratory setting, Imamovic and Sommer (2013) demonstrated that if two drugs showing such collateral sensitivity (basically strong complementarity in undermining resistance) are cycled, resistance can be stymied.[52] The collateral sensitivity identified from their study is highlighted by the blue cells in the heat map of Figure 2. This important breakthrough can easily be incorporated into our framework by setting $\phi < 0$ in (27).

The discovery and execution of cycling and other practices described above require the availability of many antibiotics to experiment with and draw from. Given that the science is continually evolving at the time of this writing, it appears that patent law may have a role to play in alleviating the problem of resistance. The indications are that patent breadths may need to be narrowed if resistance is to be held at bay.

In summary, our analysis finds that (limited) competition between drugs can lead to efficient usage of antibiotics, reduce bacterial resistance, and support scientific methods for extending the lives of existent antibiotics, especially if the economic impact of competition overshadows the negative biological externality.[53] However, while competition may in some circumstances be beneficial for correcting the market failure of usage, given that the drugs have already been developed, the impact of competition on R&D incentives is not likely to be inconsequential. We now turn to the issue of innovation.

5 Cross Resistance and the Incentives to Innovate

Thus far our focus has been on optimal policies for ensuring efficient usage of antibiotics. Since resistance is an inevitable outcome of natural selection, it cannot be eliminated; however, it can be tricked into slowing down by altering economic incentives through carefully designed policies. While doing so corrects the market failure of socially excessive consumption, it also can affect innovation incentives, potentially adversely. In this section, we bring together the results of the previous sections to

does not inflict significant cost on the organism. And so, when the original antibiotic is reintroduced, the evolution of resistance simply picks up from where it left off—or, at least from not far behind. In that case, cycling largely fails to deliver its expected benefits.

[52] In particular, they allowed *E. coli* bacteria to evolve in response to 23 different antibiotics that are used clinically. Interestingly, the authors found that bacteria that evolved resistance to one antibiotic often showed *greater sensitivity* to another.

[53] As noted by Laxminarayan (2001), narrow patents could bias the choice of technologies toward "me-too" drugs that have relatively low-cost and less risk, and that compete "inefficiently for the same pool of effectiveness embodied in a class of antibiotics."

answer the questions posed in the Introduction: Why are antibiotics considered to be less profitable than other pharmaceutical drugs when the stakes are so high? And what can be done to reverse this potentially devastating trend?

To be sure, many features of antibiotics markets could make research in this area less attractive than research in drugs for treating chronic diseases, for example. Included in this set are prohibitive costs of discovering new ways of combatting increasingly complex bacteria and of attaining approval from a complex regulatory regime [Spellberg (2010), Shlaes and Projan (2009)]. Indeed, costs of bringing an antimicrobial to market is high, estimated at close to $1 billion with a lag time of over 10 years from the time the new antibacterial agent is discovered to when it can be launched in the market [Power (2006)].

While these technological and institutional impediments are clearly important, our focus has been on understanding the impact of the market failures in accelerating resistance and the impact it has on the profitability of antibiotic research. The analysis in the previous sections provides insights into the former by highlighting two characteristic features of antibiotic markets: (I) market failure in consumption of a drug $\mathbf{X}$ interacting with the evolution of own-resistance θ to drug $\mathbf{X}$; and (II) market failure in production of a drug $\mathbf{Y}$ interacting with the evolution of cross-resistance ϕ to drug $\mathbf{X}$. Propositions 4 - 6 identify policies that correct these two market failures toward an efficient usage of antibiotics currently available in the market. But how do they impact incentives to develop them in the first place, and importantly, incentives to replenish the pipeline with future-generation drugs?

5.1 Incentives to Innovate: Same-Generation Drugs

In this subsection we analyze the impact of optimal policies regarding the *ex post* use of current antibiotics on *ex ante* incentives to bring them market. First consider the case in which $\mathbf{V}^d(x_d^*) - \mathbf{V}^m(x_m^*) < K$; that is, a protected monopoly is socially preferred to duopoly. By Proposition 3, a broad patent of length $L = L_m$ will result in efficient drug usage with a monopoly. So, if we start out in an environment in which $L < L_m$, the social optimum could be achieved by imposing the tax in (20) on generic output, coupled with: (a) a tax on monopoly output to correct for overproduction or (b) an increase in the exclusivity period to $L = L_m$.

The policies in (a) and (b) both lead to identical consumption paths but, even if the entire tax is redistributed back in lump sum to the pioneer, increasing patent life will provide greater profits and therefore *ex ante* incentives for the pioneer to develop the drug in the first place. This observation is consistent with a point made by Philipson and Mechoulan (2006), who caution that Piguovian taxes to correct for externalities can be dynamically inefficient in diluting R&D incentives. In conventional innovation markets there is typically a tension between efficient usage of a new product and incentives to innovate [Nordhaus (1969)]. Here, however, a policy of extending patent life has the attractive feature of improving both usage of the drug by encouraging the

patentee to internalize the market failure and providing innovation incentives.

Extending patent life may not always be efficient, however, as we have seen. If $L > L_m$, the pioneer underproduces the drug, which leads to an inefficiently high proportion of sick people (and spread of the disease, which we do not model here). For efficient usage, patent life should be shortened, although doing so could reduce innovation incentives. And so, for sufficiently long patent lives, the familiar usage-innovation trade-off reemerges: to encourage R&D, patent life is extended but at the cost of dead-weight loss in consumption.

We turn now to environments in which $\mathbf{V}^d(x_d^*) - \mathbf{V}^m(x_m^*) > K$; that is, imperfect competition socially dominates a broad patent monopoly. As noted in the previous section, if the firms are allowed to internalize the cross-resistance externality, then patent life, L_d, will be longer than under a protected monopoly. In addition to providing greater total surplus, adding a competing drug has the extra benefit of reducing resistance if $\phi/\theta < \gamma/\beta$. Again, we examine how this efficient usage aligns with the firms' *ex ante* incentives to develop the drugs.

Since greater competition typically reduces the pioneer's profits, it could stifle incentives to innovate. However, under optimal patent and antitrust policies in Propositions 4 - 6, this need not happen. Since $L_d \geq L_m$ it may be that even if the per period profit of a duopolist is necessarily less than that of a monopolist, the present value profits generated over the patent life to a duopolist firm can be greater.[54]

This claim is straightforward to verify in the extreme case in which the two drugs are independent economically and biologically; that is, $\phi = \gamma = 0$. Let Π_m and Π_d denote the equilibrium present-value profits excluding R&D costs in monopoly and a duopolist, respectively. If a pioneer with a broad patent of duration L_m strictly prefers to perform R&D (that is, $\Pi_m > K$) , then so will a duopolist with patents of duration L_d (that is, $\Pi_d > K$). Then, by continuity of Π_d in both ϕ and γ, the duopolist's profits will exceed that of the monopolist for sufficiently small ϕ such that both the pioneer and competitor could be better off in a duopoly. This follows from the fact that optimal patent life under duopoly increases with ϕ, since $L_d = T - \beta/(\phi + \theta)$. However, countering this positive effect on a duopolist's profits is the decline in the output in each period due to added cross-resistance. Denoting average per period profits of a firm by π_d so that $\Pi_d = L_d\pi_d$, the change in Π_d with respect to ϕ is given by: $(\pi_d \partial L_d/\partial\phi|_{\phi=0} + L_d \partial\pi_d/\partial\phi|_{\phi=0})$, where the first term is positive and the second

[54] As noted earlier, the pioneer is assumed not to have the capacity to develop more than a single drug. If that assumption were relaxed, a narrow patent may still be desirable. It can be shown that if patent life on the two drugs were the same whether the drugs were produced by a single or different firms, social welfare would be higher under competition that internalized the cross-resistance externality. Moreover, a narrow patent may be required to induce the patentee of the pioneer drugs to develop the second competing drug if research incentives of a protected monopoly were not sufficiently strong.

is negative. The net effect can be shown to be positive, when evaluated at $\phi = 0$.[55] On the other hand, even small increases in γ will reduce a duopolist's profits without extending patent life. Nevertheless, continuity suggests that for small γ, it will still be the case that $\Pi_d > K$.

The following discrete-time example illustrates that this result can hold even for nontrivial ϕ and moderate γ. Consider an antibiotic market with the following parameters: $T = 4$, $\gamma = 1/2, \theta = 1/3, \phi = 1/6$, parameters which conveniently give optimal patent lives for the monopoly and duopoly of $L_m = 1$ and $L_d = 2$, respectively. The upper bound on K for profitable entry can be easily calculated to be $K \leq \Pi_m = \alpha^2/4$. Finally, given the above parameters, each duopolist in a symmetric equilibrium earns $\Pi_d = 5\alpha^2/18 > K$ and so $\Pi_d > \Pi_m$. Therefore, if it is profitable to perform R&D under monopoly, it will be profitable to develop both drugs under duopoly. Moreover, it can also be shown that developing a second drug is socially efficient.[56]

The above discussion establishes that environments can be found in which patents internalize the true user cost of consumption, while also providing adequate incentives for research. But this may not always be true. If the drug sales generated from patents—whether broad or narrow—do not provide a sufficient return on investment in antibiotics R&D, then we recommend supplementing profits with a less distortionary award, independent of sales, such as prizes, regulatory cost reductions, or patent buyouts[Outterson (2014)][57]. The main message here is that while patents cannot be relied on to solve the antibiotic crisis, they nevertheless can play a central role in extending the effective use of any new antibiotic. This recommendation implies a stark reversal of the traditional objective of a patent system. Here, the conventional social cost of patents becomes a virtue in correcting the market failure

[55] The profit functions for monopoly and a duopolist are easily derived to be:

$$\begin{aligned} \Pi_m &= \frac{\alpha^2 L_m[2\beta + L_m\theta]}{2[2\beta + L_m\theta]^2}, \\ \Pi_d &= \frac{\alpha^2 L_d[2\beta + L_d(\theta+\phi)]}{2[2\beta + \gamma + L_d(\theta+\phi)]^2}. \end{aligned}$$

To prove the result claimed, set $\gamma = 0$ in Π_d. Then $\partial\Pi_d/\partial\phi$ is given by:

$$\partial\Pi_d/\partial\phi = \alpha^2 \frac{\beta^2 + 2T\beta(\theta+\phi) - T^2(\theta+\phi)^2}{2(\theta+\phi)^2(\beta + T(\theta+\phi))^2},$$

which, when evaluated at $\phi = 0$ gives the result for small θ. Then, since $\Pi_d = \Pi_m$ for $\phi = \gamma = 0$, and Π_m does not change with ϕ, it follows that for ϕ sufficiently small, $\Pi_d > \Pi_m$.

[56] This follows from the expression (A2) in the Appendix.

[57] In an ongoing study on the antibiotic crisis, Outterson (2014, *Chatham Report*) presents alternative business approaches toward encouraging antibiotic research. Of course, awards that are delinked from sales are not without implementation challenges. (See, for example, Gallini and Scotchmer (2004) for a general discussion and Kremer (1998) and Hopenhayn, et. al. (2006) for an analysis of patent buyouts.) Nevertheless, we agree that they are superior to compromising the important role that patents can play in achieving efficient usage.

and, therefore, weakening the growth of bacterial resistance, even if at the potential cost of suboptimal innovation.

5.2 Incentives to Innovate: Next-Generation Drugs

The above subsection examined innovation incentives for competing drugs under efficient usage policies in Proposition 4 - 6. Here, we ask whether those results extend to "next-generation" drugs that appear after the current, incumbent drugs are rendered ineffective by the resistant bacteria. For example, the next-generation of drugs can be thought of as moving up a "quality-ladder" of antibiotics, where each successful set of drugs is of biologically higher quality in being more successful at countering resistant bacteria. While an inter-generational framework is not modeled explicitly here, it is straightforward to see how our earlier results can generate predictions about future innovation.

First consider the case in which the next generation of drugs implement an entirely new mechanism for destroying bacteria that can overcome all bacterial resistance in the environment. In that case, the next generation is independent of the previous one and all the results on competition in the paper are preserved.

Next consider a more realistic case in which the next generation drugs are imperfect in overcoming existing resistance. In that case, both economic-biological features in (I) and (II) defined above are relevant but the two externalities have different effects. This contrasts with drugs that are biologically similar in effectiveness but economically diffentiated (that is, same-generation drugs), where θ and ϕ enter firms' decisions symmetrically. Regarding (I)—the interaction between the market failure of consumer myopia and own-resistance θ—an increase in θ can increase incentives to innovate for an entrant who would be in competition with an incumbent. Although own-resistance will eventually set in against the entrant's drug, at least initially it gives the new antibiotic a competitive edge over incumbent drugs, already weakened by the accumulation of resistance. The net effect of own-resistance on an entrant's innovation incentives can be positive, in contrast to the case of competing drugs of the same generation.

The cross-resistance externality, ϕ, in (II) has the opposite inter-generational effect, potentially impacting more harshly on future generations than earlier ones. To see this, consider two generations of drugs. Suppose that the second-generation generation version of $\mathbf{X}$, denoted by $\mathbf{X}'$, is an improvement that uses the same mechanism for destroying bacteria; $\mathbf{Y}$ is assumed to use a different mechanism. In a symmetric first-generation duopoly, the total bacteria resistance to drug $\mathbf{X}$ over the life the drug T will be $(\theta + \phi)Tx_d^*$, since in equilibrium $y_d^* = x_d^*$, given in (21). Turning to the second generation, let κ be the proportion of this total resistance that transfers to $\mathbf{X}'$, and let σ be the proportion of resistance from $\mathbf{Y}$. It is reasonable to assume that $\kappa > \sigma$ since bacteria that mutate against a mechanism implemented by one drug will likely develop resistance to another in that same class. Then, for monopoly output x_m^*

in (8), the condition under which bacterial resistance faced by the second-generation drug will be less under first-generation competition than monopoly is given by:

$$\kappa(\theta+\phi)x_d^* + \sigma(\theta+\phi)x_d^* < \kappa\theta x_m^*.$$

Note that if $\sigma = 0$, the above inequality collapses to the condition in (27): not surprisingly, if the source of resistance toward the next-generation drug is the output only from one of the drugs, then competition will reduce resistance relative to monopoly under (27), and increase R&D incentives for second-generation drugs.

However, the more interesting case is when $\sigma > 0$, the benefits from competition can be muted. Substituting the expressions for x_d^* and x_m^* yield the set of environments in which competition transfers less resistance than monopoly to second-generation drugs:

$$\frac{\gamma}{\beta} - \frac{\phi}{\theta} > \frac{\sigma}{\kappa}(1+\frac{\theta}{\beta}T)(1+\frac{\phi}{\theta}). \tag{30}$$

Note that the right hand side is increasing in three resistance ratios: $\frac{\sigma}{\kappa}, \frac{\theta}{\beta}and\frac{\phi}{\theta}$. The greater the resistance from earlier-stage drugs due to cross-resistance, the more damaging competition will be to the next generation relative to monopoly for higher spillover rates σ/κ**.** Therefore, the inequality in (30) is a stricter condition than (27)—that is, reducing resistance for same-generation drugs is a necessary condition for (30) and for competition (narrow patents) to reduce resistance for next-generation drugs. If (27) is satisfied, then for sufficiently low cross-resistance ϕ/θ between drugs of the same generation, as well as between drugs from different generations σ/κ the positive benefits from competition can be preserved.

These benefits are threefold. First, by increasing the effectiveness of current drugs and slowing down resistance, the research period to develop new drugs is lengthened. This, in turn, can lower the costs of developing new drugs and therefore, increase incentives to research. Second, if policies promote efficient use of the drug, then innovators can anticipate higher profits when their drug is commercialized. Third, if (30) is satisfied, entrants with improved drugs will face less cross-resistance. The well-known "tragedy of the commons" interacting with biological resistance described in (I) above clearly affects research incentives. But, a more damaging effect to innovation incentives, as this analysis reveals, may be the cross-resistance externality in (II). In creating a hostile environment for new entrants, cross-resistance transferred between generations can blunt incentives to develop the much needed new drugs to avert the antibiotic crisis.[58] However, as discussed above, judicious design of patent and competition policy can mitigate the negative effects of these inter-generational externalities.

[58]This notion of inter-generation cross-resistance is further corroborated by the time-line in Table 1 shich shows resistance setting in for new drugs before large-scale commercialization begins.

6 An Application and Future Extensions

The results in this paper can be illustrated using the data in Figure 2. The Figure shows cross-resistance and collateral sensitivity for drugs that are used to attack various strains of *E-Coli*. In particular, we consider a subset of the E-Coli-resistant drugs that are taken for urinary tract infections (UTI). These drugs are shown in Figure 5, on both the horizontal and vertical axes, with the "resistance" (orange) or "sensitivity" (blue) shading transferred from Figure 2. Using the *Merck Manual of Diagnosis and Therapy* (2011, 19th edition), we identified the drugs most commonly used. The different shades of green indicating substitutability between drugs, with darker shades denoting stronger substitutes.

The drugs commonly used for simple uncomplicated UTI that arrived roughly at the same time are TRI (trimethoprim), NIT (Nitrofurantoin), FOS (Fosfomycin). Note that they have very low cross-resistance and are strong substitutes. Also available at that time is GEN(Gentamycin). While this latter drug is reserved for more serious conditions and, therefore, a poorer substitute to the others, it also has favourable biological interactions with two of the core drugs through positive collateral sensitivity, shown by the blue cells. In other words, these "same generation" drugs are consistent with (27): that is, competition among them would have had the effect of reducing resistance to each drug.

The next two drugs are also good substitutes but they arrived later with CFX (Cefuroxime) and CFP (Cefepime) being different generations (2nd and 4th, respectively) in the same cephalosporins class. Note that CFX entered the market facing low cross-resistance from the other drugs, as predicted by the condition in (30), and imparted positive collateral sensitivity to FOS, an incumbent drug. However, CFP, a later generation drug, inflicted high cross-resistance on CFX and, in doing so, also compromised FOS.[59] While CFP may have been introduced early for valuable medical uses, it came at the cost of reducing effectiveness of earlier generation drugs: CFX and FOS.

More problematic is the last pair, CIP (Ciprofloxacin)and LEV (Levofloxacin), both strong substitutes to each other in the quinolone class, and also showing strong cross-resistance against each other. While the environment in which they entered was not too hostile (as shown in the last two columns of Figure 5), they inflicted considerable harm on first generation drugs. Moreover, because they are weak substitutes with the earlier UTI drugs, the condition in (27) is likely to be violated.[60] The introduction of LEV reduced the effectiveness, not only of the previous generation CIP, but also the core drug TRI as well as CFX, and therefore, FOS (through collateral sensitivity).

[59] Moreover, note that the cross-resistance appears to be more intense between generations of the same class, relative to drugs from different classes; that is $\kappa > \sigma$ in (30).

[60] These drugs are reserved for more serious UTI conditions and are known to have greater side effects.

While this discussion is impressionistic, it illustrates the type of data that would be required to assess the value of new drugs entering the market. Based on the limited economic-biological data provided here, a case could be made that CFP and LEV should have been delayed in order to prolong the lives of the other drugs. This is not to suggest that such a delay would be optimal if, for example, they are serving populations with no other recourse for serious UTI conditions. That is, this economic-biological interaction is only one component in the calculus of evaluating which drugs should be admitted. However, it is an important one for preserving effectiveness of drugs currently in use.

Also deserving further investigation is the interaction between animal and human consumption of antibiotics. In analyzing the market failure from use of all antibiotics, we have not separated these two types of consumption, but it is important to note that a substantial amount of antibiotics is used in agriculture for nontherapeutic uses to promote animal growth. Non-therapeutic use in the U.S. has been estimated to exceed antibiotic consumption for humans by a factor of eight [Mellon et. al. (2001)] and evidence indicates that cross-resistance transferred from that animal use to human antibiotics is severe [Marshall and Levy (2011), Wegener (2012)]. Some countries, notably Denmark and others in the European Union, have banned use of antibiotics in farm animals for non-therapeutic purposes. Others, including the U.S., Canada, Japan and Australia, are engaged in rigorous surveillance programs to monitor the use of antibiotics and impact on resistance [WHO, *Antimicrobial Resistance* (2014)].

Related to the use of antibiotics for animals is the problem of antibiotic misuse by humans, estimated to be as high as 50% of total consumption [CDC, 2017]. Again, this feature of consumption is not explicitly modelled, for example, when consumers do not take the full course of the antibiotics, physicians diagnose the illness incorrectly, or the drug is used for non-therapeutic purposes. Allowing "conservation" policies for addressing improved antibiotic usage—better diagnostics tools, stricter standards on cleanliness in hospitals, and bans on non-therapeutic use of antibiotics for farm animals—would complement the analysis derived here and not qualitatively alter the main findings.[61] Furthermore, the role of vaccines for prevening illnesses versus antibiotics that treat already prevalent infections remains for future research.[62]

Our focus has been on the demand side in encouraging innovation, in contrast to the supply-side policies undertaken in the U.S. and U.K. For example, the U.S. and U.K. announced multi-million dollar prizes for diagnostic tools and discovery of new antibiotics. There have also been proposals for reducing delays and high costs of the FDA regulatory process, such as the Wildcat proposal that would give accelerated approval for a firm's most profitable drug if it developed an antibiotic

[61] An ongoing policy study focuses on this issue along with finding better diagnostics and surveilance as well as finding non-patent mechanisms for ramping up research around the world. See *Review of Antimicrobial Resistance, http://amr-review.org.*

[62] For research on vaccines see, for example, Kremer (2001), Finkelstein (2004), Kremer and Synder (2015).

[Spellberg et. al., 2007]. GAIN (Generating Antibiotics Incentives Now) is another program, not without controversy, signed into law in 2012 that extends the exclusivity period for five years and, importantly, fast-tracks FDA approval. While this policy appears to have increased the number new drugs approved by the FDA, as shown in Figure 6, the new drugs are simply modifications of existing drug classes. Moreover, it appears that the expedited FDA approval provided at the beginning of the drug's life was greater motivation than the additional years of patent life tacked on at the end. Other strategies include cost-sharing of research and development by industry, governments and academia toward discovery of new medicines. While these other incentive mechanisms may be necessary, as we also suggest, without attention to the demand-side those new drugs will suffer the same destructive fate as its predecessors. An extended model that integrates both types of policies would be a useful direction for future research.

Finally, an important consideration not examined here regards the serious distributional implications of the analysis need further investigation. We recognize that in a globalized world with fluid mobility between countries, the policies recommended here will have limited bite if they are not adopted across the world [Carlet et.al. (2012), Laximinarayan et.al. (2014)]. But this fact brings into stark focus a troubling reality arising from the policy of increasing the prices of antibiotics through patents and taxes: such policies can worsen an already grave global health problem in making antibiotics too expensive for the poor. The burden of infectious diseases, at 31% of all diseases worldwide [WHO (2004)], is significantly higher in developing and emerging economies, as are the costs of antibacterial resistance.[63] [64]Better access to antibiotics will constrain the spread of infectious diseases, as well as reduce incentives to misuse the drug.[65] Therefore, providing antibiotic access is not only an ethical mandate, it is an absolute necessity for solving the antibiotic crisis.

How then can governments reconcile the need to correct the problem of excess use examined here with the need to improve access of antibiotics to the poor? Insurance for antibiotic coverage is one possibility to address the adverse distributional consequences of higher prices. While the challenges of insurance markets are well-known, this policy warrants investigation in future research, especially if conservation policies noted above (for lowering demand from animal use) were put in place. This question remains as an important piece of the puzzle, complementary to the analysis developed here, that is necessary to avert the impending global health crisis.

[63]For example, in a recent paper Laxminarayan et al (2015, p.171) have estimated in their analysis of 101 countries that, of the 590,000 children under 5 who die of pneumonia, 445,000 could be saved if there was universal access to antibiotics. See also Jayachandra and Lleras-Muney (2009) on the impact of maternal mortality in Sri Lanka on education and literacy between 1946 and 1963 due to the introduction of sulfa drugs, penicillin and blood transfusions.

[64]See Amabile-Cuevas (2010) for an overview of the problems confronting developing countries.

[65]Without access, consumers may be more inclined to shorten the course of the drug when they are feeling better and hoard the remainder for future use.

7 Conclusions

The discovery of antibiotics, arguably, marked the most remarkable public health transformation in the history of medicine. Yet, in less than an average person's lifetime, we have witnessed its tremendous rise in strength against infectious diseases as well as its precipitous decline in effectiveness against resistant bacteria. This is, in part, due to a classic market failure in which users myopically consume antibiotics at prices below their true social cost, as well as to a cross-resistance externality which producers fail to internalize. And now the arsenal of defense against evolving bacteria has nearly become empty while pharmaceutical companies continue to exit antibiotics research in search of more lucrative medicines. Consequently, countries around the world are facing the grave threat of returning to pre-penicillin days unless action is taken to avert the impending crisis.

In this paper, we focus on an issue central to the crisis—the two market failures in antibiotics—and the role that competition and patents can play in stemming the tide of resistance. We consider biologically equivalent but economically differentiated drugs for combatting a particular disease and identify conditions that trade-off economic and biological forces under which competition (or narrow patents) can slow down resistance to a pioneer's drug. Under these conditions, increasing competition can be a more effective remedy for the current antibiotic crisis than increasing incentives through patents, as suggested in the literature and implemented in the United States. We demonstrate that, in addition to the usual benefits of increased variety and lower prices, competition can slow down the evolution of resistance. This result is further corroborated by evidence from recent scientific studies showing that drug variety can facilitate novel methods of stymying resistance and prolonging the life of important drugs. This can have the effect of providing variety in same-generation drugs as well as providing incentives for developing next generation drugs that can replenish the pipeline.

This result has further implications for policy. One is that there are gains from antitrust policy permitting contracts between competing firms so as to internalize the externality from cross-resistance imposed on each other. Complementing this is patent policy. By allowing patent life to increase with drug variety, each firm has the incentive to better internalize the resistance generated by its own production. Furthermore, we show that patent breadth should be two-dimensional, so that competing drugs not be too close either in economic or biological space.

A central concern in the policy arena is that the possibility of correcting the overconsumption problem could conflict with the goal of increasing incentives for R&D. Our analysis suggests that this logic is incomplete at best. By improving drug usage, the increased surplus generated from drug consumption can be redirected to the researcher through prizes and costs sharing schemes. In fact, if antitrust and patent policies provide incentives for competitors to internalize the biological resistance, a pioneer's incentive to pursue research can be greater under competition (or narrow

patents) than under broader monopoly protection for a wide range of market and biological environments.

If, on the other hand, competition achieves efficient drug usage but dilutes incentives for research, we argue that the patent design which corrects the market failure, should not be distorted to improve R&D incentives. In contrast to the conventional view, the message here is that patents should be used to achieve allocative efficiency (better drug usage) even at the cost of dynamic inefficiency (more R&D for drugs). Improving effectiveness of current drugs can bolster research incentives for next-generation drugs, which is necessary to avert the impending crisis.

8 APPENDIX

Proof of Proposition 6:

Substitution of the optimal output levels into the utilities in (7) and (11), integrated over the interval [0,T], yields social surplus for the monopoly and duopoly cases:

$$\begin{aligned} \mathbf{V}^m(x_m^*) &= \frac{T\alpha^2}{2\beta(1+\omega T)}, \\ \mathbf{V}^d(x_d^*) &= \frac{T\alpha^2}{\beta(1+\nu+\omega(1+\mu)T)}. \end{aligned} \tag{A1}$$

where $\mu = \phi/\theta, \upsilon = \gamma/\beta$ and $\omega = \theta/\beta$. Then, using the expressions in (A1), (26) can be written in terms of exogenous variables as:

$$Z \equiv \frac{T\alpha^2[(1-\upsilon)+\omega(1-\mu)T]}{2\beta[1+\omega T][1+\upsilon+\omega(1+\mu)T]} \geq K. \tag{A2}$$

The first part of the Proposition is found by noting that an upper bound, $\overline{\upsilon}$, of υ is given by the solution to:

$$\frac{T\alpha^2[(1-\overline{\upsilon})+\omega(1-\mu)T]}{2\beta[1+\omega T][1+\overline{\upsilon}+\omega(1+\mu)T]} = K,$$

since for any $\upsilon < \overline{\upsilon}$, (A2) will be satisfied.

The second part of the Proposition is found by noting that the iso-benefit curves are negatively sloped; in particular the slope of the iso-benefit curves are:

$$\frac{d\upsilon}{d\mu} = -\omega T, \tag{A3}$$

holding constant ω and T, and that lower iso-benefit curves yield larger values of Z. To complete the proof, we need to show that when (27) in the text is satisfied, then (A2) will be as well for a larger measure of (μ, υ) combinations. Recall that by (10) L_m is defined by $\omega(T - L_m) = 1$. But since that holds by definition of x_m^* in (A1), then ωT in (A3) must be greater than 1. Therefore, the slope of the iso-benefit curves in (A3) is greater than 1 in absolute value, implying that the range of (μ, υ) to the left the 45° line — where (A2) is satisfied — is greater than to the right of the 45° line line where resistance under duopoly increases.

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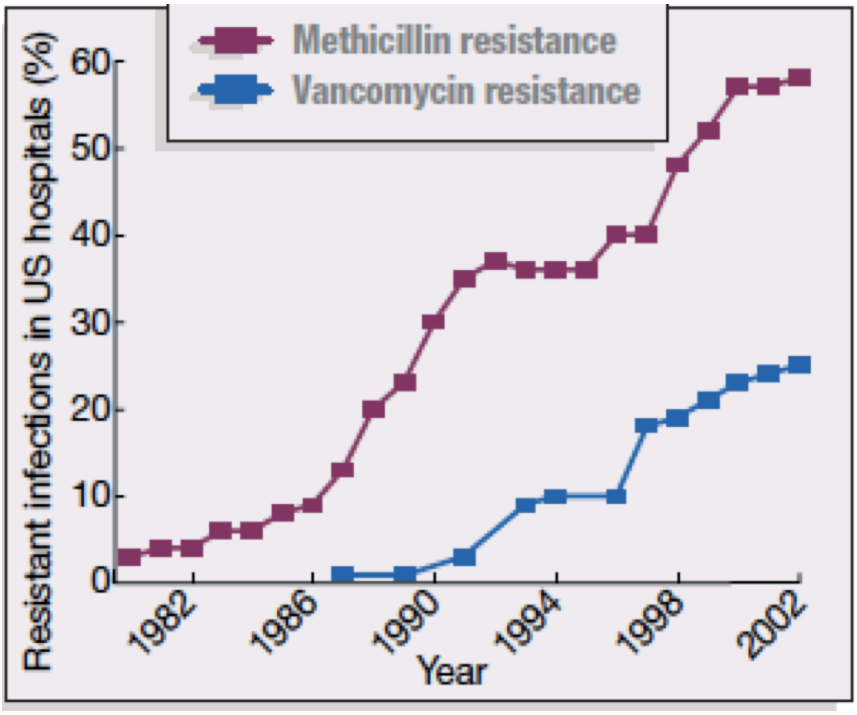
Table 1
Antibiotics Discovery Timeline

Antibiotic class; example	Year of discovery	Year of introduction	Year resistance observed
β-lactams; penicillin	1928	1938 (1943*)	1945 (1940*)
Sulfadrugs; prontosil	1932	1936	1942
Aminoglycosides; streptomycin	1943	1946	1946
Tetracyclines; chlortetracycline	1944	1952	1950
Chloramphenicols; chloramphenicol	1946	1948	1950
Macrolides; erythromycin	1948	1951	1955
Fidaxomicin (targeting *Clostridium difficile*)	1948	2011	1977
Glycopeptides; vancomycin	1953	1958	1960
Oxazolidinones; linezolid	1955	2000	2001
Rifamycins; rifampicin	1957	1958	1962
Quinolones; ciprofloxacin	1961	1968	1968
Streptogramins; streptogramin B	1963	1998	1964
Lipopetides; daptomycin	1986	2003	1987
Diarylquinolines; bedaquiline	1997	2012	2006

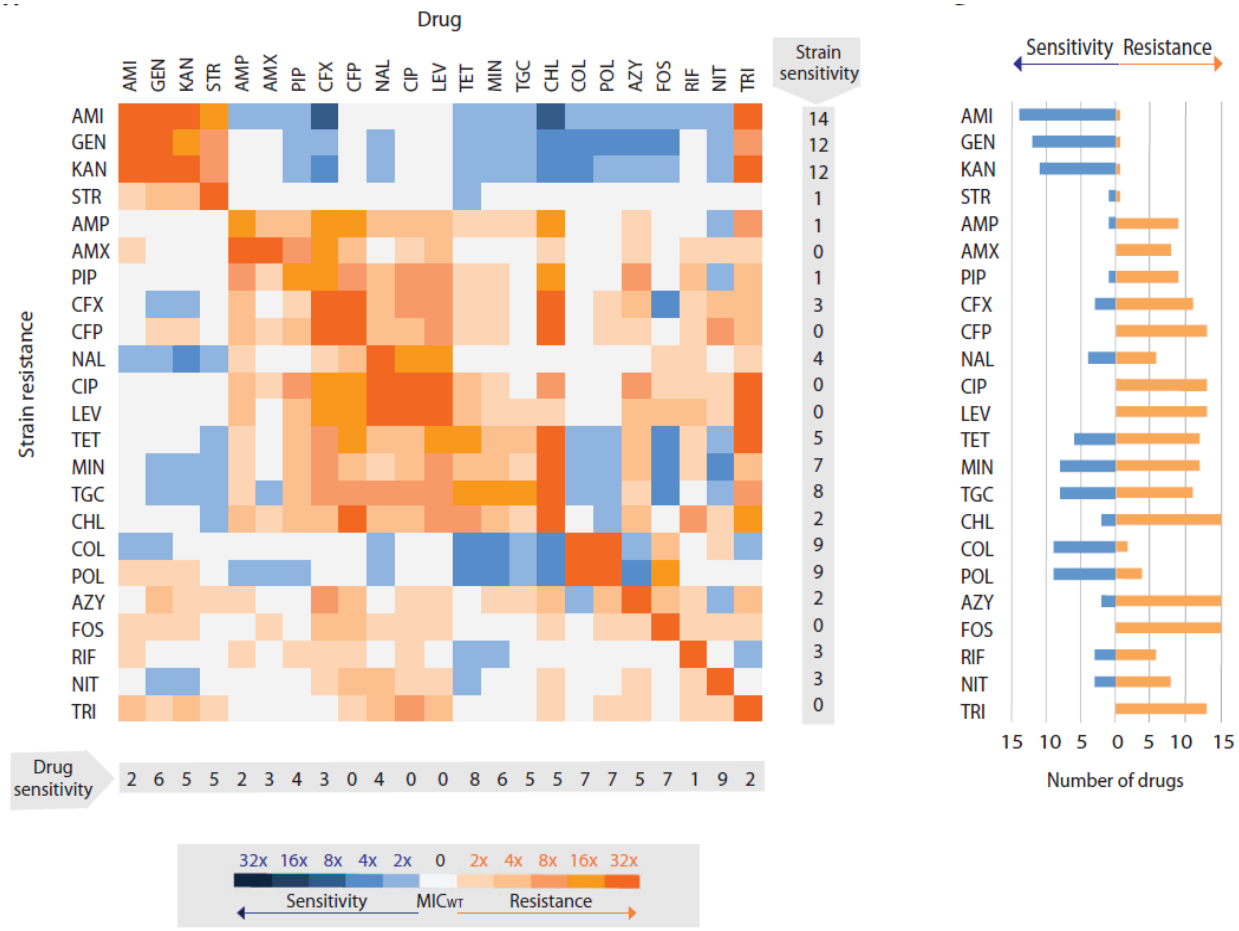
Source: http://www.nature.com/nrd/journal/v12/n5/fig_tab/nrd3975_T1.html
* https://www.cdc.gov/drugresistance/about.html

Figure 1
Rates of *Methicillin-Resistance* and *Vancomycin- Resistant Staphylcococcus Aureus*



Source: Data from Center for Disease Control.
Graph from https://www.nature.com/nature/journal/v431/n7011/full/431892a.html

Figure 2
Cross-Resistance and Collateral Sensitivity for *E-Coli* Resistant Drugs



Source: Imamovic and Sommer (2013). Table shows cross- (and own) resistance to drugs on horizontal axis when *E-coli* bacteria are treated with drug on vertical axis. Orange denotes resistance; blue denotes collateral sensitivity, with darker colours showing greater intensity.

Figure 3
Output Profile of Industry Over Life of Drug

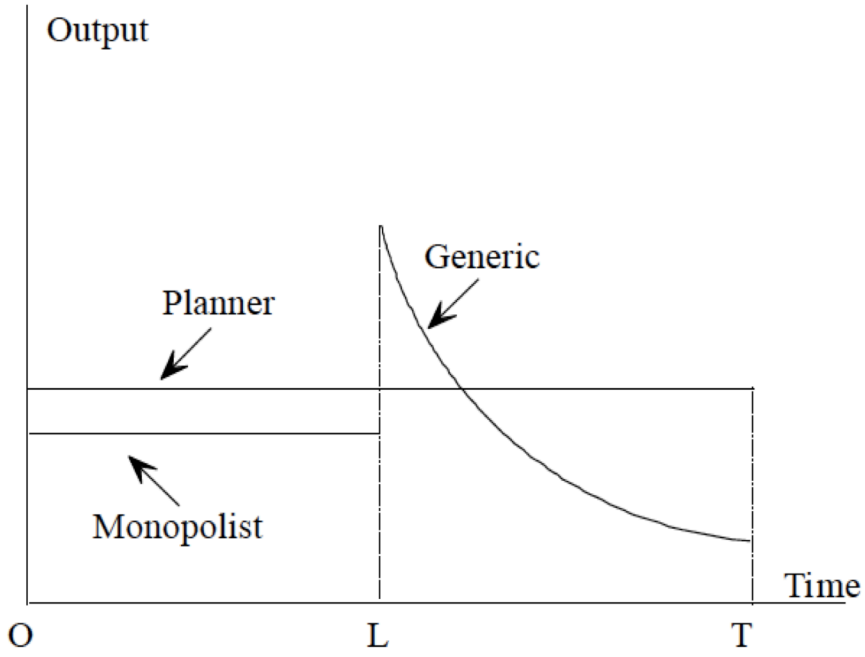
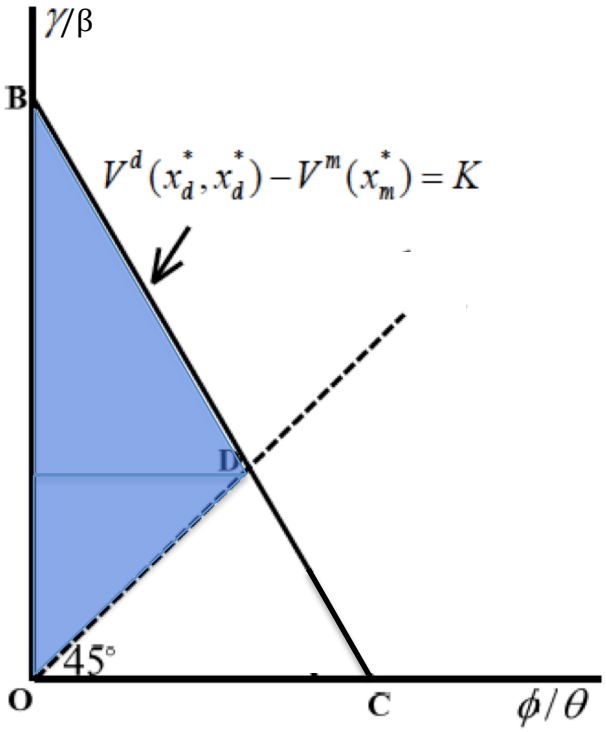
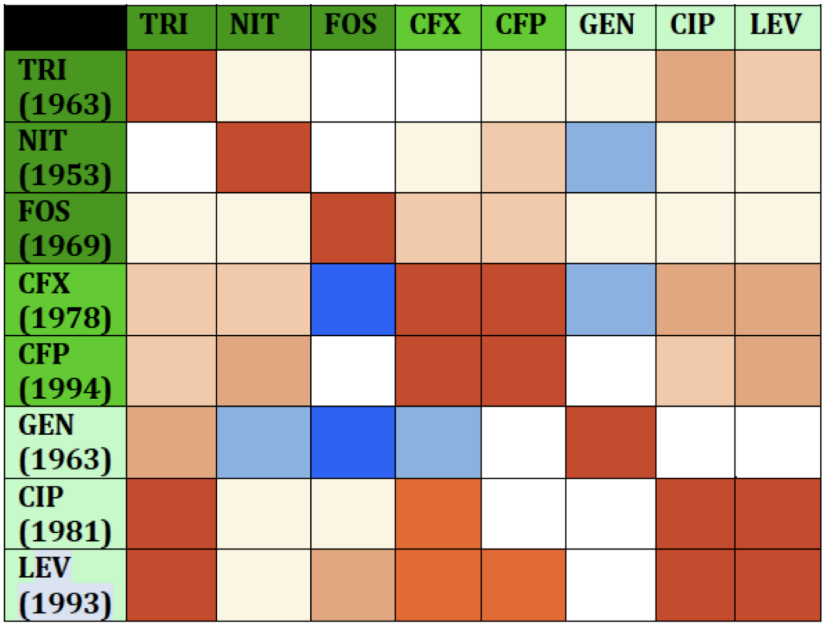


Figure 4
Competition that is biologically and economically efficient



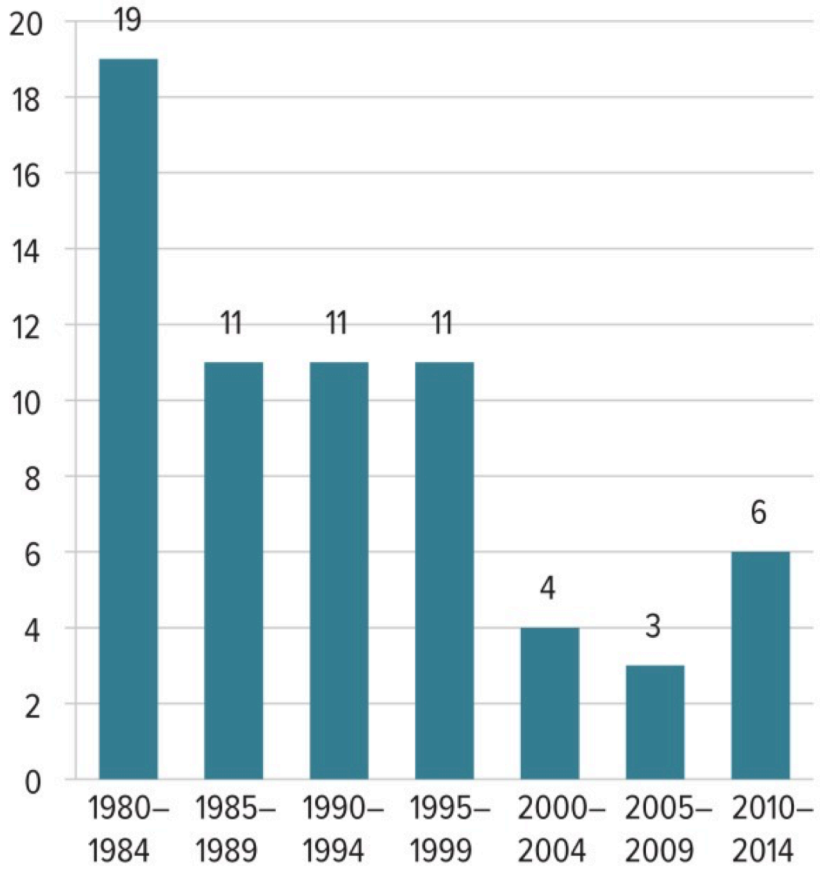
Note: Above the diagonal line, competition reduces resistance to the pioneer drug. Below the solid line BC, competition is welfare-improving. In the shaded region both conditions in expression (29) are satisfied.

Figure 5
Example of Efficient Competition:
Case of *E-Coli* Resistant Drugs for Urinary Tract Infections



Source: Imamovic and Sommer (2013). Table shows cross- (and own) resistance to drugs on horizontal axis when *E-coli* bacteria are treated with drug on vertical axis. Orange denotes resistance; blue denotes collateral sensitivity, with darker colours showing greater intensity. The year in which the drug was introduced is given in parentheses. Darker green denotes stronger economic substitutes.

Figure 6
Antibacterial New Drug Application Approvals in 5-year intervals
(1980-2014)



From Ventola, C.L., *Pharmacy and Therapeutics* (2015) 40(4): 277–283. Drugs are limited to systemic agents. Data are from CDC and the FDA Center for Drug Evaluation and Research.