Rescuing the Golden Age of Antibiotics:

Can Economics Help Avert the Looming Crisis?

by
Mukesh Eswaran and Nancy Gallini
Vancouver School of Economics
University of British Columbia
June 2016

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. Bolstered by scientific evidence, this result arises from a fundamental interplay between economic and biological externalities. We propose a patent-antitrust regime for achieving efficient drug research and usage that calls for a revised justification of the patent system.

JEL Classification Nos.: I11, I12, I13, O31, O38
words: antibiotic resistance, market competition, R&D incentives, patents

Email: mukesh.eswaran@ubc.ca, nancy.gallini@ubc.ca

Acknowledgements: We thank Colin Busby and Paul Grootendorst for helpful comments on an earlier draft of this paper, Bob Hancock, Kevin Davis, Bernadette Mah and Bhaven Sampat for informative discussions, and Kira Martin-Chan for careful research assistance. The input of seminar participants at the Indian School of Business, Gachibowli, Hyderabad, India, the Canadian Law and Economics Association Conference, and the Bates White Antitrust Conference is gratefully acknowledged.

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 is 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]

The puzzling reality is that, as global demand for antibiotics continues to grow at record rates, pharmaceutical companies are abandoning antibiotic research in favor of more lucrative lifestyle drugs or drugs for chronic diseases.[5] Why are antibiotics

[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 (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.(2004)].

[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] For example, 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), Massiolos, et. al. (2003)].

now considered to be less profitable than other pharmaceutical areas when the stakes are so high?[6] And what can be done to reverse this potentially devastating trend? These are the questionswe address in this paper.

We argue that an important aspect of the underinvestment (or low profitability) puzzle lies in the differences in the environment in which drugs for chronic diseases and those for infectious diseases operate. The former is static whereas the latter changes in ways that become increasingly hostile toward new drugs. This is facilitated by the natural selection of resistant bacteria and accelerated by overuse, 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 Layton (1996), Laxminarayan (2001), Herrmann and Gaudet (2009), Herrmann and Laxminarayan (2010)).[7] That is, natural selection and economic incentives conspire to limit the life of antibiotics, relative to those of chronic and life-style drugs. This is not because they are out-competed by better performing drugs, but because they are out-competed by the resistant bacteria that evolve from their own production as well as from production of antibiotics in the same or unrelated markets. In contrast, a drug for heart disease that was safe and effective 30 years ago will be safe and effective now, though it may lose market appeal if superseded by superior drugs.[8]

Indeed, this inherently self-destructive nature of antibiotics, coupled with a market failure in consumption, 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 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)]. Each time antibiotics are consumed, bacteria are given a chance to crack the codes that science has invented against them.

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 scientific discoveries for overcoming resistant bacteria. To be sure, other differences between drugs for chronic and infectious diseases contribute to firms' reluctance to engage in antibiotics research, such as prohibitive costs of discovering new ways to combatting increasingly complex bacteria and of attaining approval from a complex

[6]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)].

[7]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)].

[8]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.

regulatory regime [Spellberg (2010), Shlaes and Projan (2009)].[9] While these technological and institutional impediments are clearly important, our intention here is to understand the fundamental economic forces that contribute to the crisis: how the market allocates its scarce resources for antibiotics, why it fails, how it accelerates resistance, and what can be done to alter incentives for undertaking R&D.

In a simple framework, we highlight several novel features of this market that involve an important interplay between economic incentives and biological resistance. The first regards the nature of resistance, of which there are two kinds. First, a drug can be a victim of its own success when its overuse leads to resistance in the bacterium it targets (referred to here as own-resistance), and second, bacterial resistance to other drugs can be transferred to the targeted bacterium (referred to here as cross-resistance). While both are ultimately harmful in reducing the biological life of a drug, we show that the former is less of a deterrent to the entry of second-generation drugs. The reason is that own-resistance promotes the obsolescence of incumbent drugs and thereby confers a competitive advantage on the potential entrant. In contrast, cross-resistance asymmetrically imposes a negative externality on entrants and unambiguously weakens incentives to invest in new antibiotics. This finding suggests that the more conventional own-resistance — believed by scientists and policy makers to be at the core of the crisis — is not as compelling a reason for insufficient entry as is the biological externality of cross-resistance arising from incumbents' production.

This leads to a second important finding regarding imperfect competition between drugs that provide effective but alternative cures for a particular disease (in contrast to the above in which the second drug is an absolute improvement). Counterintuitively, competition can reduce accumulated resistance to a drug relative to monopoly, despite the fact that it increases total market output. An interplay between biological and economic forces is central to this result: if the business-stealing effect of a rival (the economic externality) overwhelms the cross-resistance effect (the biological externality), the decline in the pioneer's output will be sufficient to reduce overall resistance to that drug. In other words, competition between drugs can be "biologically efficient" in constraining resistance.

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 bolsters 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, competition 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

[9] Alternative constraints and strategies for counteracting them are discussed further in Section 5.

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.

Imperfect competition under this optimal patent-tax-antitrust nexus may, in general, not generate sufficient profits to motivate socially desirable R&D. In that case, we propose that patents not be used to increase innovation incentives. Rather, we recommend alternative forms of compensation that are independent of drug sales—such as subsidies, patent buyouts, prizes, and regulatory incentives (e.g., FDA expedited reviews)—for supplementing the returns from patents.

To our knowledge, this paper provides the first formal economic justification of the recommendation proposed in recent policy studies examining the crisis, that (at least part of) the R&D award should be independent of drug sales.[10] Our reason stems, however, from the virtues of patents in achieving allocative efficiency of drug use rather than in providing sufficient incentives for dynamic R&D efficiency. In this sense, the analysis turns the justification of the patent system on its head: rather than using intellectual property to encourage R&D at the cost of suboptimal consumption, we argue that it should be employed to encourage efficient drug consumption at the cost of suboptimal R&D.

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 (2016)], 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)].[11] 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 expand on this literature by examining the role of imperfect competition in slowing down or hastening consumption and biological resistance. Moreover, we analyze the impact of resistance in affecting incentives to innovate new drugs, and identify policy levers for achieving a second-best outcome of new drug development and drug usage.

The paper is organized as follows. In Section 2 we develop a framework for an antibiotic market and derive the equilibrium outcome, conditional on the drug already having been developed. We consider environments, characteristic of markets

[10] For example see Outterson (2014), Clift, et.al. (2015).

[11] 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)).

for antibiotics, of a protected monopoly and of imperfect competition with lagged generic entry, in which alternative drugs are available for combatting a particular disease. In Section 3, we turn to welfare analysis and examine conditions under which competition is socially desirable or not, focusing on the single objective of efficient drug consumption. Policy levers combining patents, competition policy and taxes are identified for aligning the social and private incentives. In Section 4 we build on this analysis to determine when those policies for efficient use also support adequate R&D incentives for new drugs. In this analysis, we introduce the idea of lagged entry, which typifies second-generation drugs, to examine the impact of the economic and biological environments on incentives to enter the market. Section 5 concludes, with a discussion identifying topics warranting urgent economic exploration, including the excessive use of drugs in agriculture and the dire distributional consequences of the antibiotic crisis.

We turn now to the economic analysis of the antibiotic crisis.

2 Market Competition and Antibacterial Resistance

In this section, we investigate how competitive forces negotiate the tension between economic incentives to sell a drug and the biological response to it; in a later section we examine the impact of these forces on incentives to innovate. The tension between the economics and biology in antibiotics markets arises because of natural selection: in destroying bacteria that are susceptible to the drug, antibiotics create a breeding ground for the resistance bacteria to flourish, thereby rendering the drug ineffective in the long run. We investigate this process with a model of a single antibiotic that is already available and designed to combat a particular bacterium, and investigate how competition interacts with resistance to influence profit-maximizing drug production. In Section 2.1, we consider the case of a drug producer with a limited-duration monopoly faced with lagged generic competition. Then, Section 2.2 introduces contemporaneous competition to investigate how competition interacts with resistance and drug effectiveness.

To begin, consider a model with 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. We set the discount factor at unity since discounting contributes little to the ideas developed here. 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.[12]

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

[12] 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 [Laxminarayan (2001)]. Under this interpretation, however, the period length will change depending on how quickly the stock of available dosages is depleted.

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.[13] If healthy, at time t the individual receives a utility valuation υ of her health that is distributed over the interval $[0,\overline{v}]$, according to uniform distribution $F(\upsilon)$. An unhealthy person without treatment receives utility 0 in that period but recovers in the same period. The probability of being re-infected in subsequent periods is independent of one's history of illness. By consuming a completely effective antibiotic, her health is restored to υ. However, if the antibiotic is compromised by resistance, then her health is restored to a level $\upsilon - \theta X_t$, where X_t is the cumulative output up to and including the period *prior* to t — that is, $X_t = \sum_{s=1}^{t-1} x_s$ — and the parameter $\theta > 0$ captures the marginal biological resistance for an increase in the cumulative consumption.

Let the marginal willingness to pay for an antibiotic (labelled X) be P_t^X in period $t = 1, 2..., T$ and x_t be the aggregate quantity of the drug consumed in period t. Then, the expected demand for the antibiotic at time t is then given as $x_t = \delta N(1 - F(P_t^X + \theta X_t))$ which, with reparameterization, yields the inverse demand function:

$$P^X(x_t, X_t) = \alpha - x_t - \theta X_t, \tag{1}$$

where $\alpha = \overline{v} > 0$ and $\overline{v} = \delta N$ is a normalization invoked to simplify notation**.** The parameter θ is positive and 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 aggregate utility function in period t that is consistent with this set-up, is given by:

$$u_t^m(x_t, X_t) = (\alpha - \theta X_t)x_t - \frac{1}{2}x_t^2, \tag{2}$$

We assume that consumers are myopic and maximize their single period utility, which is strictly concave in x_t**.** This analytically tractable framework captures most simply the empirical reality that antibiotic production today lowers its own future effectiveness [e.g. Bronzwaer et al (2002), Tacconelli(2008)].[14] We refer to this sort of

[13] 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 period 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 proportion of sick people at t who did not purchase the drug.

[14] 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.

resistance as *own-resistance*. On the production side, we assume the marginal cost of production is constant and set to zero.

2.1 Limited Duration Monopoly and Antibiotic Resistance

2.1.1 Pioneer's Problem

In this subsection, we address the problem confronting a drug producer with a lead time (exclusivity period) before perfectly competitive entry (or generics) dissipates monopoly rents. As noted above, 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. She corrects for the intertemporal externality by adjusting her current production and shifts future demands to the extent it is profitable.

To begin, suppose the monopolist's lead time before generic entry is L periods, where $L \leq T$. Given the above framework, the monopolist's profit, π_t^X, in period t, is given by $\pi_t^X = P_t^X(x_t, X_t)x_t$, where $P_t^X(x_t, X_t)$ is given in (1). Then, total profit, Π^X, defined over the L periods, is given by the undiscounted sum $\Pi^X = \sum_{k=1}^{L} \pi_k^X$. It is straightforward to show that $\theta < 1$ is necessary and sufficient for joint strict concavity of Π^X in x_t. In maximizing Π^X, the monopolist chooses an output profile that satisfies the first-order conditions:

$$x_t : \quad (\alpha - \theta X_t) - 2x_t - \theta X_t^+ = 0, \text{ for } t = 1, ..., L, \tag{3}$$

where $X_t^+ \equiv \sum_{k=t+1}^{L} x_k$, with $X_L^+ = 0$. 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, $(\alpha - \theta X_t) - 2x_t$, is set equal to the *marginal user cost*, θX_t^+, of future antibiotic resistance from current consumption. In the terminal period this user cost is zero. By adding and subtracting the term θx_t in (3), we can rewrite these first order conditions as

$$\alpha - (2 - \theta)x_t = \theta \sum_{k=1}^{L} x_k, \quad t = 1, 2, ..., L.$$

The right hand sides, which are identical across all periods, reflect both the cost in the current period as determined by past usage as well as the cost of the marginal current production on future willingness to pay. It follows, therefore, that monopoly outputs will be identical in all periods. Denoting this common output by x_m, we see

that the monopolist's profit-maximizing output is given by:

$$x_m = \frac{\alpha}{2 + (L-1)\theta}. \tag{4}$$

Note that the non-discriminating monopolist reduces output when the lead time is longer and the resistance parameter θ is higher because she incorporates the externality of antibiotic resistance over a longer period.

2.1.2 Generic Entry

After L periods, 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 $L+1$ on generics will produce until the price in each period is driven down to marginal cost (zero). That is, if the generic output in period t is denoted by g_t, then in period $L+1$, the generic output, g_{L+1}, is given by

$$g_{L+1} = [\alpha - \theta L x_m],$$

where Lx_m is the monopolist's cumulative output over the patent's life. This implies:

Proposition 1: In the first period of generic production, the industry's output is necessarily higher than the monopolist's (constant) output.

The above result follows immediately by comparing the expression for g_{L+1} above with that of x_m in (4) and invoking the assumption that $\theta < 1$ in our model. So we know that, despite the 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 and including the period *prior* to t by G_t, that is, $G_t \equiv \sum_{k=L+1}^{t-1} g_k$, for $L+2 < t \leq T$, $G_{L+1} \equiv 0$, then generic output at t is given by:

$$g_t = [\alpha - \theta(Lx_m + G_t)], \quad t = L+1, ...T, \tag{5}$$

Given the initial condition $G_{L+1} = 0$, the above expression can be recursively applied to determine the generic output over time. Cumulative output is increasing over time, and by pulling down the demand curve due to own-resistance to the drug, reduces generic output. As sketched in Figure 1 (for continuous time), the output profile of the industry will be constant up until period L, increases discontinuously at $L+1$, and then declines monotonically after generic entry takes over.

2.2 Contemporaneous Competition and Resistance,

Now suppose an alternative antibiotic for combatting a particular infectious disease is available. In contrast to generic competition, 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). 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, there is a second, potentially powerful force, referred to as *cross-resistance* or *multiple-drug resistance.* 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)).[15]

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.[16] 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 developed and these now constitute the main lines of attack for the disease.

Given this effect, it would seem at first blush that introducing competition might appear to be counterproductive. Since the aggregate output of two drugs in a duopoly is greater than the monopoly output of a single drug, evolved resistance to antibiotics in a given period would seem to be greater in a duopoly, thereby appearing to compromise effectiveness of the pioneer drug. However, as we demonstrate below, this intuition may be incorrect: introducing a greater variety of antibiotics, surprisingly, can reduce resistance to each drug.

To see this, allow a second producer to enter the market with her drug, say Y, that is distinct but in competition with the pioneer. 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. Expanding on

[15] 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.

[16] 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.]

the single-drug case to the two-drug scenario, we posit the following linear inverse demand curves for goods X and Y at time $t = 1$ and $t = 1, ..., T$**:**

$$P_t^X = \alpha - x_t - \gamma y_t - \theta X_t - \phi Y_t; \quad P_t^Y = \alpha - y_t - \gamma x_t - \theta Y_t - \phi X_t; \quad t = 1, ..., T, \tag{6}$$

where $X_t = \sum_{k=1}^{t-1} x_k$ and $Y_t = \sum_{k=1}^{t-1} y_k$, are cumulative outputs prior to period t, with $X_1 = Y_1 = 0$.[17]

The preferences underlying the demand curves can be represented by an adaptation of the quadratic utility function, $u_t^d(x_t, y_t)$, as in Singh and Vives (1984):

$$u_t^d(x_t, y_t) = \alpha(x_t + y_t) - \frac{1}{2}(x_t^2 + y_t^2) - \gamma x_t y_t - \theta(x_t X_t + y_t Y_t) - \phi(x_t Y_t + y_t X_t), \tag{7}$$

where $\gamma < 1$ ensures strict joint concavity in x_t and y_t. As before, we assume that consumers ignore the future consequences of their antibiotic consumption and, by maximizing their current utility, generate the above linear inverse demand curves for goods X and Y.[18] 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 shown 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.[19] The x- and y-axes measure 'Resistance to Drug X' and 'Resistance to Drug Y', respectively. 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 $\phi < \theta$.[20]

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 1, ϕ should approach θ. The extreme case in which both $\phi \to \theta$ and $\gamma \to 1$ characterizes generics: perfect substitutes in which production

[17] Note that the utility function in (7) collapses to the single good case for some good Z in (2), when $\gamma = 1$, $\theta = \phi$, and $z_t = x_t + y_t$.

[18] The second order sufficient conditions for a maximum are satisfied for $\gamma < 1$.

[19] See also Hancock (2014).

[20] In this analysis, we assume that a second drug is developed by a different firm. An extension could allow the pioneer to develop both drugs and may have the incentive to do so if having a variety of drugs could capture a larger population of customers that respond differently to effectiveness, to side effects, to the delivery of drugs, etc. If the duopolists can internalize the cross-resistance externality (as we assume in a later section), then it can be shown that drugs will be used more efficiently when separate firms rather than when a single researcher develops the two drugs.

of any one of them inflicts resistance on the others. However, we argue that, 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 1, ϕ may be significantly lower than θ. In that sense, there is a discontinuity at the limit as γ approaches 1: in replicating the original molecule, generics are perfect substitutes both from biological and economic points of view; whereas close economic substitutes may be biologically 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).[21]

To keep the analysis simple, we look for a Nash equilibrium under the assumption that each firm takes its rival's entire output path as given. Each drug producer will choose output to maximize their 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.[22]

In maximizing its total profit $\sum_{t=1}^{L} P_t^X x_t$, where P_t^X is given in (7), firm X chooses its period t output, x_t, $t = 1, ..., L$, to satisfy:

$$\alpha - 2x_t - \gamma y_t - \theta X_t - \phi Y_t - \theta X_t^+ = 0,$$

where $Y_t^+ \equiv \sum_{s=t+1}^{L} y_s$, with $Y_L^+ = 0$.[23]

Invoking symmetry in equilibrium across the two firms and denoting the common output of the two firms by $x_t, t = 1, 2, ...L$, the above equations can be rewritten:

$$\alpha - (2 + \gamma)x_t - (\theta + \phi)X_t - \theta X_t^+ = 0. \tag{8}$$

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

Proposition 2: If firms can precommit to an output path, equilibrium duopoly output will be constant over time if the cross-resistance is zero and declining in a geometrical ratio if the cross-resistance is positive.

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

[22] 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 yields very complicated expressions from which little insight can be gained.

[23] The second order conditions are satisfied under our assumption that $\theta < 1$. The objective function is strictly concave in $x_t, t = 1, 2, ..., L$, which ensures that the solution to the first order conditions is also the unique maximum.

Proof. The case of $\phi = 0$ follows directly from (8) and algebraic manipulations; as in the monopoly case to get the constant output level:

$$x_d = \frac{\alpha}{2 + \gamma + (L-1)\theta}. \tag{9}$$

When $\phi > 0$, the output profile is time-dependent. It is readily verified that the solution to the system of L linear equations in (8) can be written in the form:

$$x_t = \frac{\alpha}{\Delta}(2 + \gamma - \theta)^{L-t}(2 + \gamma - \theta - \phi)^{t-1}, \quad t = 1, 2, ..., L, \tag{10}$$

where $\Delta > 0$ is a function of exogenous parameters α, γ, θ, ϕ and L. It follows that for $t = 1, 2, ..., L-1$, the ratio of successive period outputs is given by:

$$\frac{x_{t+1}}{x_t} = \frac{2 + \gamma - \theta - \phi}{2 + \gamma - \theta}.$$

We see that the ratio $(x_{t+1}/x_t) < 1$ if $\phi > 0$ and equals 1 if $\phi = 0$. □

As stated in Proposition 2, 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, when generic production begins in period $L+1$, the demand curve has shifted 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

$$R_m = \theta L x_m \ , \tag{11}$$

where x_m is given in (4). 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 $R_d = \theta \sum_{t=1}^{L} x_t + \phi \sum_{t=1}^{L} y_t$, where x_t and y_t (by symmetry) are given by (10). Furthermore, by symmetry, we can rewrite R_d as:

$$R_d = (\theta + \phi) \sum_{t=1}^{L} x_t. \tag{12}$$

Inspection of (11) and (12) 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 duopoly given in (9) is constant and clearly less than the monopoly output x_m in (4); therefore, R_d in (12) will be less than R_m in (11). By continuity of R_d in ϕ, that 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) by the cross-resistance externality. If cross-resistance is sufficiently small, it can be shown that for a given L, the lower duopoly output slows down the pace at which resistance accumulates to a drug.[24]

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 relative to own marginal utility (as captured by γ). Intuitively, the economic externality can reduce resistance because of the "business stealing" effect and, if that effect overcomes the biological externality of cross-resistance, then overall resistance to each drug can be reduced.

For the antibiotic crisis, a central goal would appear to be reduction of antibiotic resistance. As we show below, while reducing resistance is neither necessary nor sufficient for maximizing welfare, it is nevertheless fundamental to identifying the best way forward for tackling the antibiotic crisis, where our focus is on the degree of competition to admit into antibiotic markets. We turn now to the welfare analysis of competition in two parts, first on efficient consumption of antibiotics, and second on efficient innovation.

3 Welfare Analysis of Antibiotic Consumption

In this section, we compare the welfare implications of competition in antibiotic markets and identify policies that can best align private and social incentives. We first address the question of how the social planner would best provide for usage of a single antibiotic over its life.

3.1 Optimal Usage of a Pioneer Drug

Social surplus, generated by the antibiotic in period t, is given by the utility function in (2); therefore total surplus over the life of the drug is the undiscounted sum $\sum_{t=1}^{T} u_t^m$. As with the monopolist, $\theta < 1$ ensures strict joint concavity of $\sum_{t=1}^{T} u_t^m$ in x_t. The

[24] Proof is available from authors.

social planner maximizes this by choosing an output path satisfying the first order conditions for periods $t = 1, 2, ..., T$, given by:

$$x_t : \quad (\alpha - \theta X_t) - x_t - \theta X_t^+ = 0. \tag{13}$$

By adding and subtracting the term θx_t in the above expression, the first order conditions become:

$$\alpha - (1 - \theta)x_t = \theta \sum_{k=1}^{T} x_k, \quad t = 1, 2, ..., T.$$

As in the monopoly case, the right hand sides are identical across all periods and capture the full cost of producing a marginal unit of the drug. It follows that the planner's outputs, too, will be identical in all periods. Denoting this common optimal output by x_m^*, we immediately obtain

$$x_m^* = \frac{\alpha}{1 + (T - 1)\theta}. \tag{14}$$

If $\theta > 0$ the planner lowers this output as the time horizon T increases in order to conserve the drug. The same is true when present output inflicts a greater cost on future consumers through higher own-resistance.

We turn now to a comparison of the planner's solution with that of the exclusive monopoly.

3.1.1 Optimal Patent Life for a Pioneer Drug

Consider first the case of a perfectly price-discriminating monopolist. We begin with the analysis of a limited-duration monopoly, where the lead time before generic entry is assumed to be supported by a broad patent. The framework in Section 2 is instructive in addressing a disagreement in the literature. Researchers suggest that patent extensions could mitigate the resistance problem [Laxminarayan (2001), Horowitz and Moehring (2004), Infectious Diseases Society of America (2004), Kades (2005), Laxminarayan and Malani (2007), Davies (2013)], claiming that a finite patent life creates incentives for the monopolist to produce as much as possible prior to patent expiration. That is, a pioneer drug producer with a limited-duration patent will fail to internalize the long term impact of her production. Other researchers are skeptical that extension of patent length is warranted and have furnished various arguments for their view [Outterson (2005), Outterson et al (2007)]. We show that, while the argument for patent extension may hold for the particular case of a perfectly price-discriminating monopolist, it does not hold in general.

To see this, note that a perfectly price-discriminating monopolist appropriates the entire surplus from the consumers, and so would replicate the social planner's solution in the absence of generic entry, that is, if $L = T$. If instead $L < T$, by using the same

procedure as above we see that the perfectly price-discriminating monopolist would choose the output, $\widehat{x}_m$, in each period as

$$\widehat{x}_m = \frac{\alpha}{1 + (L-1)\theta}. \tag{15}$$

Thus, comparison of (14) and (15) imply that when $L < T$ the perfectly price-discriminating monopolist would overproduce relative to the social planner, thereby supporting results in the literature that argue for a longer effective patent life to minimize resistance.

While perfect price discrimination may be a useful benchmark, it overstates the tendency to overproduce for $L < T$ in the more realistic scenario of a non-discriminating monopolist who sets a single price for all consumers.[25] Comparing (4) and (14), we readily obtain the following result that captures the role of own-resistance on the non-discriminating monopolist's incentive to over- or under-produce.

Proposition 3: Relative to the social planner, the non-discriminating monopolist of a drug with a market exclusivity period of L overproduces or underproduces the antibiotic according as $\theta(T-L) \gtrless 1$. The monopolist reproduces the social planner's output when $\theta(T-L) = 1$, that is when:

$$L = T - 1/\theta \equiv L_m. \tag{16}$$

Proposition 3 establishes that if $\theta(T-L) > 1$, a non-discriminating monopolist too will overproduce relative to the social planner. Because the monopolist's time horizon is shorter than the planner's and falls in the interval $[1, T-1/\theta]$, she ignores at least part of the social cost of resistance and overproduces. Consequently, a longer patent life is warranted in this scenario, especially at higher resistance strengths.

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 $[T-1/\theta, T]$; that is, patent life covers a significant proportion of the drug's life, the interval of which increases for lower resistance strengths. This is a countervailing force that tempers the tendency to overproduce, in contrast to the perfectly price-discriminating patentee, who always overproduces for patent lives in this range (except when $L = T$). While the non-discriminating monopolist incorporates the same concern for antibiotic resistance as the planner does, she has an incentive to conserve the antibiotic for reasons that have to do with profitability alone. Hotelling's adage for an exhaustible resource that "A monopolist is a conservationist's friend" is relevant here (Hotelling, 1931).[26] Therefore, extending patent life may not be a socially desirable mechanism

[25] Moreover, drug companies are not likely to have the sort of information necessary to perfectly price discriminate, or to costlessly prevent arbitrage across consumers who are charged different prices.

[26] Special cases of this model are perfect competition for all periods (i.e., $L = 0$) and monopoly with $L = T$. It follows directly from equations (4) and (5) that the competitive production path

for reducing resistance in that it would compel the monopolist to cut back further on an already under-produced drug.[27]

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 Figure 1 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 monopolists 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 beyond L_m, but a more efficient way is to impose a Pigouvian tax on the competitive produced output [Pigou (1920), Baumol (1972)] to realign private and social efficient levels. 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 therefore will improve welfare.[28]

Since the output of the generic industry is time-dependent, the planner will adjust the tax in each period so that the generic output coincides with the planner's (constant) output, x_m^*. Observe that in any period $L+s, s = 1, 2, ...T-L$, when the generic is produced, the output in each of the preceding periods is x_m^* and the cumulative output of these periods is $(L+s-1)x_m^*$. Thus the tax rate, τ_{L+s}^g, in period $L+s$, $s = 1, 2, ..T-L$, must equate the generic output in (5), adjusted for a tax, to the social planner's output in (14):

$$[\alpha - \tau_{L+s}^g - \theta(L+s-1)x_m^*] = x_m^*,$$

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.

[27] 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.

[28] Similar to the generics, a tax could be placed on an overproducing monopolist. This could be an equally effective alternative to patent life adjustment would be a tax on the monopolist's product. 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 $\tau_m = \frac{\alpha[\theta(T-L)-1]}{1+\theta(T-1)}$. Note that if the monopolist overproduces, the required tax rate is larger the smaller the patent length; if $L = L_m$, the tax rate is zero because the shorter the monopolist's horizon, the more she ignores the externality.

The solution to this equation, after substituting for x_m^* from (14), yields optimal Pigouvian taxes:

$$\tau_{L+s}^g = \frac{\alpha\theta(T-L-s)}{1+(T-1)\theta}, \quad s = 1, 2, ...T-L. \tag{17}$$

When $L < T-1$ the above tax rate is always strictly positive; the planner will never subsidize the generic for efficiency ends. Note that at a constant output, the marginal willingness to pay declines over time as own-resistance accumulates.[29] And so, successively lower taxes are needed over time in order to bring the generic output in alignment with the planner's. The time profile of the tax rate imposed on the industry would somewhat mimic the profile of the industry output shown in Figure 1.

The above analysis reveals that theoretically, while generics always overproduce, a pioneer with a finite patent can go either way, producing too much or too little prior to generic entry. The direction of inefficiency, therefore, becomes an empirical question. Although data are limited, biological evidence suggests that resistance for some important drugs may not become a problem until well after the generic phase begins.[30] Figure 3 provides such an example: resistance to methicillin from *Staphylcoccus aureus* infections from 1987-1997. From the data, collected from intensive care units participating in the National Nosocomial Infections Surveillance System of the Center for Disease Control, resistance is shown to have grown from 20% in 1987 to 45% a decade later; further data reveals that it has grown to over 60% in 2003 [Laxminarayan, et. al. (2007)]. The patent on methicillin was awarded in 1960 and so the drug was available 27 years prior to the start of the data. Extrapolating to the earlier period, it appears that resistance during patent life, which ended in 1977, was negligible.[31] Even if the relationship were not linear toward the end of the patent period, it nevertheless seems reasonable to conclude that the patented monopolist was already conserving the drug, and so extending the patent further would have reduced output further, and also resulting in an increase in infections (not modelled here).

[29] If $L = T-1$, the generic is produced for only one period at the end of the planner horizon and their production has no external effects that concern the planner. In this case, the tax on generics is zero.

[30] Mechoulan (2007) proposes two phases of patent rights: an initial patent phase to encourage development of the drug, followed by a period of generic competition, and finally as second patent phase when the resistance problem becomes severe.

[31] To see this, let κ_t be the proportion of the x_t infected individuals who are resistent to methicillin. Then, given the time 17 years in the sample period that ranges from $\kappa_{1987} = 0.20$ to $\kappa_{2003} = 0.60$, then $\kappa_t = 0.20 + 0.40t/17$. Linearly extrapolating to the time t_0 in which the $\tau_0 = 0$ and assuming the rate of resistance was zero for all periods before that time, then $t_0 = 19873.4/0.4 = 1978$; that is resistance was neglible during throughout the life of the patent until its expiration in 1977. Similar results apply for vancomycin for which the patent expired in 1979.

3.2 When *More is Less* under Competition

Although the previous section supports the intuition that generics categorically contribute to the resistance problem, the incentives to conserve by a pioneer patentee are less conclusive. While this does suggest that policy makers should not be quick to extend patent protection, it is important that we understand what policies should be undertaken when, in fact, production is excessive throughout the life of the drug. After all, rising resistance rates have been central to the grave concerns expressed by scientists over the antibiotic crisis. So, in this section, we focus on the case of overproduction by a patented pioneer, and ask if the resistance problem worsens or improves when competition is introduced.

As noted in the previous section, if $L < L_m$, overproduction by a monopolist can be a problem, in which 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 2 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 entry through a narrower patent breadth. We explore this alternative below.

We begin by solving the social planner's problem given the surplus function $\sum_{t=1}^{T} u_t^d(x_t, y_t)$, where $u_t^d(x_t, y_t)$ is given in (7) for two drugs. When multiple drugs are available, the social planner accounts for the economic substitutability between the drugs in the market — represented by γ — as well as their impact on future resistance — represented by ϕ in addition to θ, which was relevant in the single drug case. For $T = 2$, we are able to show that strict joint concavity in x_t and y_t is assured if $\theta + \phi + \gamma < 1$, that is, if the direct effect of a marginal increase in output on the price exceeds the total indirect effect through externalities. However, for $T \geq 3$, the conditions quickly become cumbersome, so we invoke the assumption that $\gamma + \theta + \phi << 1$, which guarantees strict joint concavity of the surplus function.[32] Two observations about these seemingly restrictive conditions on the parameters are noteworthy: First, they are sufficient, not necessary. Second, even very small resistance parameters are consistent with conditions giving rise to the antibiotic crisis: although the marginal effect of a unit of antibiotic consumption has a relatively weak effect on resistance, the build-up of cumulative resistance $\theta X_t + \phi Y_t$ can nevertheless be severe. 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:

$$x_d^* = \frac{\alpha}{1 + \gamma + (T-1)(\theta + \phi)}. \tag{18}$$

[32] Under this assumption, the determinant, D_k, of the leading principal minors of order k of the Hessian matrix is of the form $D_k = (-1)^k \beta^k$ plus terms that are of second and higher order in the parameters, γ, θ, and ϕ. So these determinants alternate in sign as k increases, ensuring that the Hessian is negative definite.

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 (14), to account for economic substitutability (γ) and the biological cross-externality (ϕ). As in the monopoly case, the planner will want to find a mechanism that aligns the private firms' outputs in (10) with the efficient output in (18). Recall from Proposition 2 that the duopolist's output profile declines over time because the firms do not internalize the biological externality (cross-resistance) they inflict on their rivals. However, if the firms were allowed to coordinate on that externality, effectively internalizing the cost imposed on their rival while continuing to compete in the market, the duopoly output in (10) would be constant at the common output, $x_d^\dagger$, given by:[33]

$$x_d^\dagger = \frac{\alpha}{2+\gamma+(L-1)(\theta+\phi)}. \tag{19}$$

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 be difficult to implement since this "partial" coordination could be used as a screen for more anticompetitive collusion. However, antitrust authorities could define a "safe harbor" given by the duopoly price in (19) below as the limit to which prices would be allowed to rise before antitrust action would be initiated. That ceiling, which is readily computed as the price that obtains when the socially optimal duopoly output in (19) is substituted into the inverse demand functions in (7), is given by:

$$\overline{P}_{d,t} = \frac{\alpha(1+(L-t)(\theta+\phi))}{(2+\gamma+(L-1)(\theta+\phi))}. \tag{20}$$

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 (20) declines over time since the marginal willingness to pay for the drug declines due to resistance.

A policy that 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 may appear to be too challenging to implement. However, antitrust authorities have recognized the social value of partial cooperation, especially over the past two decades, and have allowed a variety of joint ventures for coordinating R&D, capital facilities, patents, standards and other assets between competitors, while strictly prohibiting price collusion. In contrast to the antibiotics problem, these agreements typically allow coordination only on non-price instruments (e.g., R&D investment, production assets, marketing); nevertheless their interdependence with price muddies the waters between beneficial and welfare-reducing outcomes, similar

[33] This is found by rewriting the first-order conditions in (8) to allow firms to internalize the user cost of reduced efficiency for their own drug but also of that for their rival's drug. In effect, under symmetry this adds the cross-resistance term ϕX_t^+ to the left hand side of (8).

to the cooperative agreements suggested here. But antitrust authorities are well-equipped to evaluate such agreements, given the framework laid out in the *Joint DOJ and FTC 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.[34]

Setting a ceiling above which prices cannot rise is one way to ensure the firms are not using collaboration as a screen for anti-competitive behavior. Another approach would be to impose a type of compulsory licensing regulation in which drug producers would be required to pay a per unit royalty on their output. To achieve the output in (19), given the first-order condition in (8), the regulated per unit royalty, ρ_t, paid by firm X at time t to its rival firm Y would be $\rho_t = \phi Y_t^+$, where recall $Y_t^+ = y_{t+1} + ... + y_L$. Given symmetry between firms X and Y in (8), it is straightforward to show that the royalty rate in equilibrium, ρ_t^*, declines over time and is given by:[35]

$$\rho_t^* = \phi(L - t)x_d^\dagger. \tag{21}$$

Then, under the royalty levy in (21) or antitrust rules in (20), the equilibrium duopoly output will be given by (19). The analysis that follows assumes that such policies are implementable.

We compare the equilibrium duopoly output in (19) with the planner's duopoly output, to determine the optimal patent life, L_d, under competition:

$$L_d = T - 1/(\theta + \phi). \tag{22}$$

Therefore, it is possible to reduce both forms of resistance further by increasing patent life. Comparison of L_d in (22) with L_m in (16) reveals the following result.

Proposition 4: The socially efficient patent life for duopoly is higher than optimal patent life when only the pioneer's drug is available.

The reason that duopolists are given a longer patent life than a monopolist is to encourage the competing firms to lower output further to economize on own-resistance and, in doing so, indirectly reduce 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.[36]

[34] The difficulty in the antibiotics problem is that the same strategy — reducing output — is used to reduce resistance and to raise prices. However, even if firms were allowed to cooperate only on an instrument distinct from price, such as R&D investment, identifying good from bad collaborations would still be challenging. For example, sharing R&D can reduce risks so the joint venture may undertake riskier and costlier projects that will increase the price of the final product. So, even in cases that are familiar to antitrust authorities, the task of disentangling beneficial R&D from anticompetitive collusion can be challenging.

[35] 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.

[36] Here, we assumed that only the entrant can produce the second drug. If the pioneer is capable

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)]. But here, innovation is not at play: the drug is already available and so only *ex post* efficiency is considered. The familiar trade-off arises here 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 (θ), thereby indirectly reducing the cross-resistance externality (ϕ). Of course, profits to the researcher, and therefore the incentives to innovate, indeed will be affected by introducing competition, as examined in the next section.

Before turning to the innovation problem, we complete the analysis of competition on efficient use. We do so in two steps: First we identify the set of policies that can best achieve efficient consumption of a protected monopoly drug and under imperfect competition. Second, we find conditions under which competition is socially preferred. The former results are gathered in Proposition 5 below:

Proposition 5: The first-best consumption can be achieved in one of two ways. First, with (a) a broad patent of length L_m and (b) optimal Pigouvian taxes on generic firms post-patent. Second, it can be achieved also with (b) and simultaneously with (c) a relatively narrow patent that admits a second drug of duration L_d, and (d) antitrust rules that allow cooperation with a 'safe harbor' on prices or per unit royalties.

So which is better for achieving a more efficient use of antibiotics: a protected monopoly or a relatively narrow patent that allows competitive entry? If K is the cost of research, then the answer depends on the validity of the following inequality:[37]

$$\mathbf{V}^d(x_d^*) - \mathbf{V}^m(x_m^*) \geq K, \tag{23}$$

where $\mathbf{V}^d(x_d^*) = \sum u_t^d(x_d^*, x_d^*)$, that is, the sum over all $t = 1, ...T$ of utility in (7) evaluated at the symmetric x_d^*. Similarly, $\mathbf{V}^m(x_m^*) = \sum u_t^m(x_m^*)$ is the sum over all $t = 1, ...T$, of utility in (2) evaluated at x_m^*.

If (23) holds, competition is at least as good as a protected monopoly; otherwise, the pioneer drug should receive a broad patent for L_m periods.[38] We can determine conditions under which (23) is satisfied, adopting the policies in Proposition 5, that is, when competition in the antibiotics market is socially efficient. First, we identify an important relationship between economic competition and biological resistance:

Proposition 6. If socially efficient outputs are achieved under both competition

of developing both drugs, then it is straightforward to show that the patent life would be shorter than L_d because the monopolist would internalize the cost of both own- and cross-resistance.

[37] 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.

[38] See (A2) in the Appendix for condition (23) in terms of exogenous variables.

and monopoly, then competition will generate less resistance than monopoly over the protected period L_m if and only if:

$$\phi < \gamma\theta, \tag{24}$$

The above condition is easily derived starting with the following inequality: resistance accumulated over L periods under duopoly is less than that under monopoly if

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

Substitution of optimal outputs for duopoly and monopoly in (14) and (18), respectively, gives the result in the Proposition.

The expression in (24) of Proposition 6 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 $\boldsymbol{\gamma}$ and θ**.** The relationship in (24), therefore, 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.[39]

Finally, the results in Propositions 5 and 6 can be combined to identify when competition in antibiotics dominates a protected monopoly:

Proposition 7: Under the policies in Proposition 5 that ensure antibiotic usage is efficient when either monopoly or competition dominates for a given K, the measure of $(\gamma, \phi/\theta)$ pairs for which duopoly is socially preferred to monopoly is greater when (24) is satisfied than when it is violated.

Proof. In the Appendix.

Propositions 6 and 7 are at the core of the interplay between the economics and biology in the market for antibiotics. The message here is that, if we assume (for now) that the profits generated are sufficient to encourage R&D, the usual benefits of competition from lower prices will be reinforced by an increase in drug effectiveness if the negative biological externality is dominated by the "business stealing" effect noted earlier. To see when this would *not* occur, consider the extreme case of an identical substitute to the pioneer drug — effectively, biologically and economically

[39]It should be noted that these results generalize to n competing drugs. (Derivations are available from the authors.) Two interesting results emerge: First, optimal patent duration, L_n, increases in n according to $L_n = T - 1/(\theta + (n-1)\phi)$. Again, this is based on the assumption that the firms can coordinate the cost of the negative externality ϕ imposed on their rivals. Second, the condition in (24) is independent of n; that is, competitiion regardless of how intense, can improve upon resistance generated by monopoly as long as (23) is satisfied. The intuition for this result is that as patent life increases in n, the output of each firm in the oligopoly decreases proportionately.

equivalent (i.e., $\phi = \theta$ and $\gamma = 1$); from (23), competition would never be preferred to a single drug. Although competition brings lower prices, the resistance problem is so severe that it would not be efficient to allow its entry. At the other end of the spectrum, when $\gamma = \phi = 0$, it is also intuitive that the benefit of adding a drug—the left-hand side of (23)—is at a maximum. That is, the more differentiated the product and the smaller the cross-externality, the more likely it is that a competing drug will be socially preferred. In that latter case, and more generally when γ and ϕ are sufficiently low, Proposition 6 reveals that accumulated resistance generated under competition compared to monopoly will also be lower. While reduced resistance is neither necessary nor sufficient to guarantee social optimality of competition, Proposition 7 states that it does increase the "likelihood" that competition will be preferred to monopoly.[40] More precisely, the set of drugs—characterized by (γ, ϕ/θ)— that will satisfy (23) for a given K has larger measure under (24) than under the converse of (24).

This idea is illustrated in Figure 4. The "iso-benefit" curves from competition between γ and ϕ/θ, derived from the left-hand side of (23) holding constant other parameters (α, T, θ), are negatively sloped and linear in (γ, ϕ/θ) space (see the proof of Proposition 7). An iso-benefit line in Figure 4 represents the net utility value of adding a second drug, which is given by the left hand-side of (23), and those values are higher for lower curves. On line BC (the only such iso-benefit line shown) the net benefit is exactly equal to K. The 45° line OA is where $\gamma = \phi/\theta$, and so combinations of (γ, ϕ/θ) that fall above OA satisfy (24) and those that fall below satisfy the converse of (24). As shown, all the (γ, ϕ/θ) combinations in the triangle ODB—where (24) is satisfied—is larger than the area of the triangle OCD for which resistance under competition is higher, as stated in Proposition 7. Note the range of economic and biological substitutes that can be accommodated: both γ and ϕ/θ can be high or low, owing to the trade-off between cross-resistance and the business-stealing effect. However, if the second drug is a very strong substitute (as in point B in Figure 4), such that there is little benefit from differentiation, the cross-resistance effect must be sufficiently low for the second drug to be socially beneficial.

3.3 The Scientific Case for Competition

The result in Proposition 6 delivers an important insight: competition can be a mechanism for slowing down resistance. In this section we elaborate on the social benefits of competition, not only economically (in providing variety) and biologically (in reducing resistance), but also scientifically in the search for cures for bacterial diseases.

[40] It is not sufficient: even if (24) is satisfied, (23) may not be because the benefits generated by competition may not cover the research costs. It is also not necessary: if (24) is not satisfied, the lower competitive prices may offset the cost of resistance, thereby making it socially preferred to monopoly.

The direction of the inequality in (24) 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 medical literature suggesting that imperfect 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 (Masterton (2010), Sandiumenge et al (2006)). So even though the total amount of drug consumption may increase with the introduction of more drugs, the evolution of aggregate resistance can be slower if cross-resistance is sufficiently low compared to own-resistance.[41]

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.[42]

For example, in neonatal intensive care units, broad-based antibiotics are usually prescribed for babies as a precaution against infection. 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

[41] Laxminarayan (2001) also reports that scientists have shown for two antibiotics, identical except in mode of operation, the two should be used equally and simultaneously on all patients. But if they differ in price, initial effectiveness or rate at which resistance develops, then the more effective, less costly or slower to resist would be used until the cost per resistance is equilibrated.

[42] 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 plagues health-care facilities in North America and around the world. 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. MRSA causes anywhere from about half to about two-thirds of the health-care related infections in the U.S. Jernigan and Kallen (2010).

18 times more likely with the use of broad-based antibiotics. In a more recent study of broad-spectrum vs. narrow-spectrum antibiotics to treat pneumonia in children,[43] the authors found no statistically discernible differences in the health outcomes. Given that 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, despite the presence of cross-resistance.[44]

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,[45] and is standard treatment for tuberculosis and HIV.

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,[46]more recent attempts at cycling — 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.[47] The collateral sensitivity identified from their study is highlighted by the

[43]The data came from 43 U.S. hospitals over the period 2005 to 2011 [Williams et al (2014)].

[44]The use of narrow-spectrum antibiotics, however, would require better diagnostic technologies so as to identify the precise bacterium that is causing the illness in an individual.

[45]For example, with a combination of clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), rifampin, doxyclycline, or a quinolone. 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.

[46]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 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.

[47]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.

blue cells in Figure 2.

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 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.[48] 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 turn now to an analysis of competition and innovation in antibiotic markets.

4 Incentives to Innovate in Markets for Antibiotics

The previous section focused on optimal policies for ensuring efficient usage of antibiotics. Since resistance is an inevitable outcome of evolution, it cannot be eliminated; however, it can be tricked into slowing down by altering economic incentives through carefully designed policies. Doing so corrects the market failure of socially excessive consumption but it also can affect innovation incentives, potentially adversely.

The relationship between policies for reducing demand and increasing innovation is central to the antibiotic crisis. On the one hand, mitigating resistance through reduced demand extends the effectiveness of drugs in the pipeline and increases the lead time available to develop new antibiotics.[49] It also improves the ecological environment in which new antibiotics operate — with less cross-resistance in the environment, entrants can expect a higher rate of return on their R&D investment. Potentially countering these positive effects is the negative one that some demand-reducing policies may reduce the profitability of the drug during its patent life. In this section we ask: Under what conditions will policies for solving the market failure problem in consumption increase or decrease incentives to innovate?

[48] 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."

[49] Costs of bringing antimicrobials to market is estimated at over $800 million (U.S., 2001), with a lag time of over 10 years from the time it is discovered to when it can be launched in the market [Power (2006)].

4.1 Monopoly vs. Contemporaneous Competition

First, consider the case in which the converse of (23) is true: $\mathbf{V}^d(x_d^*) - \mathbf{V}^m(x_m^*) < K$ in which case a protected monopoly dominates a duopoly in terms of social efficiency. By Proposition 5, a broad patent set at $L = L_m$ 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 (17) 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 two policies in (a) and (b) 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 Mechlouchan (2006), who caution that Piguovian taxes to correct for externalities can dilute R&D incentives and so induce dynamic inefficiency. In conventional innovation markets there is typically a tension between efficient usage of a new product and incentives to innovate [Nordhaus, 1969]. Here, a policy of extending patent life has the attractive feature of improving both usage of the drug, in encouraging the patentee to internalize the market failure, and providing innovation incentives. This observation, recognized by Laxminarayan [2001, 2002] and others, is an important one.

Extending patent life may not always be efficient, however, as we have seen. If $L > L_m$, the pioneer is underproducing 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 actually be shortened. However, doing so can reduce innovation incentives. And so, for sufficiently long patent lives, we get the familiar usage-innovation trade-off: to encourage R&D, patent life is extended but at the cost of dead-weight loss in consumption.

Several legal scholars and policy makers argue against extending patent life in order to encourage further research in antibiotics [Outterson, 2007]. Their recommended position is based on estimates of the inadequacy of sale-based awards for providing the necessary private return on investment to undertake critical antibiotic research with huge social returns. Therefore, they argue that innovation rewards need to be delinked from pharmaceutical sales.[50]

We find their recommendation compelling, based on the economic analysis developed here. But we do see an important role for sales-based rewards in moderating resistance and, as a by-product, providing partial rewards for innovation. To the extent that the latter are not sufficient, subsidies, prizes or patent buy-outs, funded from tax revenues collected under generic production, should be used to make up for the shortfall.[51] The message here is that the patent system should be used strictly

[50] This argument is made in an ongoing study on the antibiotic crisis, with a focus on new business methods for antibiotic research [Outterson (2014), Paper 1 of the Chatham Report].

[51] Of course, awards that are delinked from sales are not without implementation challenges.

for the purpose of ensuring efficient usage of the antibiotic, and leave incentives to innovate to other supplementary instruments that are not dependent on revenues generated by the innovator [Outterson, 2014]. This recommendation to use the patent system to correct the market failure in consumption is in stark contrast to the traditional justification for patents as a mechanism for encouraging innovation. Here, the traditional cost of the patent system in facilitating too little output becomes a virtue by weakening the growth of resistance in antibiotic markets.

Next, consider the case satisfied by (23) in which imperfect competition is socially preferred to monopoly. If the firms are allowed to internalize the cross-resistance externality, then as noted in the previous section, 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 $\phi < \gamma\theta$. The question we ask here is how this efficient usage aligns with the firms' incentives to develop the drugs in the first place.

Intuition suggests that greater competition could stifle incentives to innovate; that is, a protected pioneer suddenly faced with a competing drug would expect to see a reduction in profits. However, if the pioneer can cooperate, either directly or indirectly, with the rival to internalize the cost of cross-resistance, duopoly can yield higher profits than monopoly. The reason for this is two-fold. First, the value of a second drug can exceed research costs if the drugs are sufficiently differentiated economically (small γ) and biologically (small ϕ). Second, since $L_d \geq L_m$, it may be that even if the per period duopoly profit is less than monopoly, profits generated over the patent life under duopoly can be greater.

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 total equilibrium profits in monopoly and duopoly, respectively. If a pioneer with a broad patent of duration L_m has the incentive to perform R&D, then so also will duopolists with patents of duration L_d; that is, if $\Pi_m > K$, it follows that $\Pi_d - \Pi_m > K$, since $\Pi_d = 2\Pi_m$. Then, by continuity of Π_d in both ϕ and γ, the gain in profits from duopoly over monopoly will exceed research costs for sufficiently small ϕ and/or γ.[52]

In fact, it is possible to show that duopoly can actually provide greater incentives than monopoly to undertake R&D. This result is stated in the proposition below.

Proposition 8. If two drugs are economically independent (i.e., $\gamma = 0$), then for sufficiently low own-resistance, θ, duopoly profits can increase in cross-resistance, when evaluated at $\phi = 0$. Therefore, for relatively low values of own- and cross-resistance, allowing more competition can increase the profits of a pioneer relative to

(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.

[52] The monopoly and duopoly profits in terms of exogenous variables are given in (B1) of the Appendix.

what she would earn in the absence of competition.

Proof: In the Appendix.

Because each duopolist's profits equal monopoly profits when $\gamma = \phi = 0$, Proposition 8 implies that duopolists of independent goods will be better off than a monopolist of a single good for small levels of cross-resistance. The reason for this result is the fact that optimal patent life under competition increases with ϕ, as we found earlier. However, countering this positive effect on duopoly profits is the decline in the output in each of the periods due to added resistance. Denoting average per period profits of a firm by π_d, the change in Π_d with respect to ϕ is roughly given by: $2(\pi_d \partial L_d/\partial\phi|_{\phi=0} + L_d \partial\pi_d/\partial\phi|_{\phi=0})$, where the first term is positive and the second is negative. Note that because $L_d = T - 1/(\phi + \theta)$, the positive term in the above derivative will be larger and the negative term smaller when own-resistance θ is small. Of course, were ϕ and γ allowed to be large, each duopolist's profits will be less than the monopoly's due to greater competition.[53]

As the example below shows, this result can hold for nontrivial amounts of cross-resistance as well as for moderate substitutes. 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 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 $\frac{1}{2}\Pi_d = 5\alpha^2/18 > K$ and so $\Pi_d > 2\Pi_m$. Therefore, if it is profitable to perform R&D under monopoly, it will be profitable to develop both drugs under duopoly. Moreover, given the expression (A2) generated in the Appendix for (23) expressed in terms of exogenous parameters, it can also be shown that developing a second drug is socially efficient.

4.2 Competition with a Lag

The previous analysis focused on the incentives of contemporaneous drug producers to develop new drugs and to produce them efficiently. The environment they entered was assumed to be biologically friendly, although over time it became less friendly as the firms produced and generated resistance to their own drug and that of their rival. The reality is that the environment for new antibiotics can be hostile from the start, as a result of drug-resistant pathogens that transfer DNA to bacteria targeted by the new drugs. Therefore, new drugs can lose effectiveness even before they start becoming available for consumption. We examine the latter situation by allowing an entrant, who introduces a competing but differentiated drug into a market occupied

[53] More generally, strong substitutes will be optimal neither socially nor privately, though inequality (24) can be satisfied with a high ϕ/θ and strong substitutes (high γ). This is because the planner prefers greater variety (that is low γ) to less, and an increase in substitutability erodes the firms' profits.

by a pioneer, to enter with a lag.[54]

Lagged entry has two effects on incentives to innovate. First, because such drugs have not yet confronted any resistance from their own production and along this dimension, they will be more effective against the bacteria relative to the pioneer drug.[55] Second, because the pioneer has been producing in the market, the resistance bacteria that emerged in response may also impact negatively on the new drug.

In this analysis, we highlight how the asymmetry between own-resistance (θ) and cross-resistance (ϕ) plays on incentives to innovate with an example with parameters similar to those for contemporaneous entry. Here, drug X has been in production longer than drug Y and therefore is less effective against the resistant bacterium. However, drug Y does not escape resistance upon its arrival if the bacterium's resistance to X "crosses over" to Y. As a result, X will have been inflicted with own-resistance when Y shows up and Y will encounter cross-resistance from X when it makes its entry.

The game proceeds as follows: in period one, a pioneering drug, X, has a monopoly patent; a new antibiotic, Y, enters in period two and the two drugs compete. After the patent on X expires at the end of period 2, it passes into the public domain and is produced by generics,[56]and so Y competes with the perfectly competitive generic version of X in period 3. The game is over after $T = 4$, when both drugs compete as generics. In contrast to the previous example, the biological processes of own- and cross-resistance will affect the two generations of drugs asymmetrically because of the staggered arrival of the drugs to market.

We assume the players entertain Nash conjectures. Because of the overlapping nature of the competition, we solve the subgame perfect equilibrium, working backward as usual, starting from period 3. Since the procedure is routine, we suppress the algebraic details here. Denote by Π^X and Π^Y the maximized aggregate profits of Firms X and Y in the subgame perfect equilibrium. Particular attention will be given to the following parameters: γ (degree of substitutability between the drugs), θ (own-resistance), and ϕ (cross-resistance).

Role of Own-Resistance

The first issue we address is the effect of own-resistance on profitability in the absence of cross-resistance. It is obvious that when $\phi = 0$ and the firms are nearly independent ($\gamma \approx 0$) that an increase in own-resistance, θ, will decrease the profitability of both Firms X and Y. Naturally, a higher θ unambiguously lowers profitability in

[54]The firm may enter with a drug that attacks the same bacterium but does so with a lag because it is strategic to do so, Alternatively, it may enter with a second-generation drugs, intended to attack the evolved bacterium that is resistant to the first-generation drug. The latter group includes those representing a sequence of improvements over previous generations that bacteria have become resistant to. The long chain of improvements in penicillin over decades since the first signs of resistance were detected is an example of this vertical differentiation.

[55]In this sense, it is analytically equivalent to an "improvement" over the pioneer's drug.

[56]The patent length has to be a minimum of two periods here so an entrant can anticipate the impact of own-resistance on its profits.

the second period of patent protection for both firms even though each firm curtails its first-period production in order to temper the effect. When γ is small, the two drugs will have some but very limited strategic interactions in all but period 1 and so higher θ lowers profits for both firms. Nevertheless, the following proposition reveals that θ affects the two firms asymmetrically.

Proposition 9: For a two-period patent, in the absence of cross-resistance ($\phi = 0$) and in the neighborhood of low economic substitutability (low γ):

(a) the profits of the incumbent fall unambiguously in θ; but the profits of the entrant fall by less and could even increase,

(b) the effect on both firms' profits of a marginal increase in own-resistance increases with the degree of economic substitutability of the drugs, and this effect is stronger for the entrant.

Proof in the Appendix.

Part (a) of Proposition 9 notes that when the two drugs are sufficiently substitutable, the entrant can gain from own-resistance. The reason is the asymmetry between X and Y. In particular, when incumbent drug X competes with the new drug Y in period 2, it experiences resistance from its period 1 output and so is a weakened competitor. That is, own-resistance plays to the advantage of drug Y at the expense of drug X, thereby generating higher profits in the duopoly setting in period 2. In period 3, the effect of own-resistance on the period 3 profit of drug Y is ambiguous because both Y and the generic version of X suffer from it. Although the profit from drug X will be unambiguously lower, the profit of drug Y could well increase if its profit advantage vis-a-vis drug X in period 2 more than offsets its potential reduction in period 3.

Part (b) of the Proposition indicates that when the drugs are better substitutes, the incumbent's disadvantage from own-resistance enhances the relative benefit of the entrant. This has interesting implications related to the previous section: greater own-resistance can increase incentives to introduce close substitutes to drugs currently available in the market by raising profitability relative to a situation in which own-resistance is lower. An increase in both θ and γ would render the inequality in (24) more likely to hold, raising the social benefits from competition. This leads to the important conclusion that the private and social incentives for introducing a substitute drug into the market are aligned when own-resistance is significant. Of course, γ cannot be too high: if the new drug is too close to the pioneer's drug, duopoly profits will fall as will the incentive to develop the drug in the first place.[57]

The message here is that profits to an entrant introducing a strong economic substitute to an incumbent's drug can counterintuitively *increase* in its own-resistance. Own-resistance, in eventually reducing a drug's effectiveness, brings about the incumbent's obsolescence and increases the entrant's competitive advantage. This idea is supported by the simulations in Figure 5, which adopt the same parameter values used in the numerical example given above (at the end of Section 4.1) on contempo-

[57] This is evident from the impact of γ on the entrant's profits in (C1) of the Appendix.

raneous entry: $\gamma = 1/2$, $\phi = 1/6$, $T = 4$ and $L_d = 2$; here θ is allowed to vary.[58] Illustrated are the present value profits, Π^X and Π^Y, of Firms X and Y as a function of θ. We see from the Figure that, as θ increases, the present value profit of drug X falls monotonically while that of drug Y rises monotonically; that is, the first effect described above overwhelms the second, and drug Y benefits on balance from higher own-resistance. Furthermore, the simulations support the result stated in part (a) of Proposition 9 by illustrating that even when ϕ is not close to zero and γ is not small the entrant's profits from an increase in θ can actually increase.

These effects have important implications for R&D incentives by an entrant. Although usage of the drug will bring about its eventual demise, initially it is in a stronger position vis-a-vis the incumbent, and that advantage increases in θ. Significantly for the discussion here, this bacterial adaptability and resilience can provide an inducement for innovative drugs to enter by weakening the incumbent competition.[59] Of course, the entrant's profits overall are lower when facing an incumbent than when not, but given that competition cannot be avoided, a moderate level of own-resistance may work in its favour. This possibility supports the intuition that resistance may actually stimulate innovation for reasons analogous to those discussed above suggested in the literature (Laxminarayan (2001), Outterson (2010)).[60] To our knowledge, our model presents the first formal demonstration of this possibility.

The dynamic described above fits in well with the evolution of antibiotics for battling the multidrug-resistant bacteria MRSA, referred to in the previous section.[61] Resistance to the penicillin, first observed even before the drug was mass-produced in 1944, became significant in the 1950s. This gave scope for replacement drugs, giving rise to methicillin and flucoxacillin. But in the early 1960s, resistance to methicillin started emerging and this was the beginning of the contemporary scourge, MRSA, a very adaptive pathogen; flucoxacillin was also undermined by this development. This pathogen was held at bay by another antibiotic, gentamicin, but by the 1970s, MRSA had evolved to resist gentamicin.[62] In view of the inevitability of resistance, vancomycin is now reserved for serious and life-threatening illnesses from bacteria

[58] In addition, α is normalized to 1 and patent life is fixed at $L_d = 2$ as θ and ϕ are allowed to increase. Because optimal L_d would, in fact, increase in that case, the profits derived represent a lower bound. Also, note that ϕ is set equal to 1/6, consistent with previous example, although simulations for different values of ϕ (including $\phi = 0$ as in the proposition) give qualitatively similar results.

[59] As Shlaes et al (2004) put it, "Resistance creates markets, use creates resistance." (caption for Figure 2, p. 279).

[60] In particular, Laxminarayan (2001) notes that while bacterial resistance can reduce the effectiveness of a drug, "(o)n the other hand, the resistance makes old drugs obsolete and can therefore encourage investment in new antibiotics."

[61] See the report of the Standing Medical Advisory Committee [SMAC (1998)], Shlaes and Projan (2009), and Outterson (2010).

[62] This led to the development of other antibiotics, many using different mechanisms, for example, glycopeptides, vancomycin, teocoplanin, rifampicin, ciproflaxin, linezolid, with most showing signs, to various degrees, of vulnerability to resistance.

that are resistant to other antibiotics.[63] Thus there has a been a series of antibiotics that appeared on the scene, each offering temporary reprieve against evolving bacteria and carrying within themselves the seeds of their own destruction.

Role of Cross-Resistance

Lastly, what is the role of cross-resistance on the profitability of Firm Y? Cross-resistance is an important phenomenon. In addition to the examples noted earlier, we mention that Lazar et al (2014) have demonstrated recently in a laboratory setting with the E. coli bacterium and 11 different antibiotics that exposure to one drug frequently conferred resistance not only to that drug but also to several others. In the sample of drugs used, 52% showed cross-resistance in at least one direction.[64]

What happens in the more realistic scenario when both own-resistance and cross-resistance are present? Note that cross-resistance has no effect on Firm X, since it is a monopoly in period 1 and in period 2's duopoly Firm Y is yet to produce output that would inflict cross-resistance on X. And so, over its patent life drug Y experiences cross-resistance in both periods; whereas drug X experiences it only after it enters the public domain in our model.[65] In light of this asymmetry, cross-resistance has the opposite effect from own-resistance on the entrants' profits: whereas own-resistance benefits entry, cross-resistance can be a serious deterrent.[66] That is, cross-resistance appears to be the relatively more serious biological culprit in discouraging drug development for replenishing the antibiotics pipeline.

As the above analysis reveals, cross-resistance — resistance generated from production of other drugs — may be the more serious deterrent to innovation than own-resistance. While this is not to say that own-resistance is not problematic in reducing the overall life of the drug, it has the redeeming feature of opening up room in the market for new entrants while making incumbent drugs obsolete. In contrast, cross-resistance unambiguously dilutes incentives to do R&D for new antibiotics in markets that are already being served.

If cross-resistance is relatively more severe than own-resistance, it would seem that eliminating competition between drugs, for example through broad protective patents, would attenuate this problem. In fact, as we found, reducing competition may not be the best way to reduce *overall* resistance (own plus cross-resistance)

[63] In his exhaustive case study of the antibiotic vancomycin, Outterson (2010) found that when the drug metronidazole was rendered ineffective by the resistance *C. difficile*, it paved the way for the oral version of vancomycin.

[64] Similar findings were obtained by Suzuki et al (2014), mentioned earlier.

[65] Presumably, when firm X entered the market, it also experienced cross-resistance from existing drugs. But, to the extent that cross resistance accumulates, Y would inherit that resistance as well. Hence, adding an initial level of cross resistance at the beginning of the game would not have a qualitative effect on the results.

[66] There is the logical possibility, of course, that the first mover may strategically choose output so that, through its drug's cross-resistance, it could adversely affect the profitability of potential incumbents. We do not pursue this argument because it seems too far removed from the contemporary antibiotic scene.

generated in an antibiotics market. Competition may be socially desirable, even while contributing to cross-resistance, because competing firms steal business from each other, thereby reducing usage of (and own-resistance to) each drug. That is to say, it is total resistance that ultimately matters to the overall effectiveness and life of a drug, and this will be lower under differentiated competition if the relative degree of cross-resistance (ϕ/θ) is lower than the relative substitutability between drugs (γ). And importantly, competition can facilitate new scientific approaches of mixing, cycling, and combining complementary drugs to mitigate resistance. It is when the drugs are effectively identical substitutes to each other (e.g., generic or "me-too" drugs), that competition loses its redeeming features and resistance is accelerated. Constraints on cross-resistance from new drugs, for example the breadth requirement described in (24), are important to impose not only to reduce the resistance afflicting competing drugs but also to improve the overall environment for future entrants. While containing cross-resistance by admitting only new drugs that satisfy (24) can have a moderating effect, it will offer only a temporary reprieve unless a tax is imposed post-patent on production from generics firms.

Lastly, we note a serious difficulty in controlling cross-resistance that arises from the extensive use of antibiotics on farm animals, especially in developed countries. While some of the antibiotics may be used for legitimate therapeutic ends, much of it is also used for non-therapeutic purposes such as promoting growth in animals meant for human food.[67] Many countries (including those in the European Union) have banned the use of antibiotics for growth promotion of animals when the drugs are also used for therapy for humans, but the practice continues with antibiotics that are not used for humans.[68] To add to the problem, antibiotics are also used extensively in aquaculture, though reliable data on this is not available [World Health Organization (2006)]. The disincentives for pharmaceutical companies to develop new antibiotics are as above: If bacteria resistant to antibiotics used on animals can transfer to bacteria attacked by new drugs for human use, then profits could be undermined from the very start, which would make drugs for chronic diseases and life style drugs relatively more attractive pursuits.

[67] According to a recent FDA report, almost 80% of antibiotics are used to fatten cows, pigs and chickens of which 70% are deemed "medically important" to humans. Mellon et al (2001) estimate that the nontherapeutic use in U.S. agriculture exceeds the therapeutic use by humans by a factor of 8.

[68] Avoparcin is one such antibiotic that is used for growth promotion in the developed world, and resistance has naturally developed to it. The drugs avoparcin and vancomycin share the same chemical structure (both belong to the family of glycopeptides). The evolved resistance to avoparcin, as a result, has also resulted in some resistance to vancomycin [Bates et al (1994), Marshall and Levy (2011), Wegener (2012)]. As we have noted, vancomycin is frequently used as a last-resort antibiotic for some human bacterial illnesses that do not respond to other antibiotics.

5 Discussion and 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 resistance bacteria. 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.

The crisis of antibiotics can be attributed, at least in part, to a classic market failure in which users myopically consume the scarce resource at prices far below the true social cost of consuming antibiotics. This disregard for the externality of consumption on future effectiveness has accelerated the process of natural selection, which ultimately has rendered many antibiotics ineffective. 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.

Building upon a limited but important but literature in economics and a rich array of science and policy studies, we have sought to understand this process with a simple framework. Our approach highlights the interplay between economics and biology, explaining how we got here and identifying how we might reverse the trend.

Our main findings revolve around the role that competition can play in mitigating the market failure and, in doing so, possibly generate greater returns on R&D investment. Competition in the context of antibiotics exposes a fundamental interplay between economics and biology underlying the antibiotic crisis. In particular, market competition interacts with cross-resistance that arises from a competing drug's production, and own-resistance that arises from a drug's own production to affect the rate of decay of the drug. If the effect of cross-resistance between imperfect substitutes is less than the business-stealing effect, accumulated resistance generated by competition can be lower than under a protected monopoly. This implies an inherent non-monotonicity between drug output and biological resistance: an increase in market output does not necessarily imply an increase in bacterial resistance to a drug. And when competition reduces overall resistance, it will also be socially preferred to monopoly in a larger set of market and ecological environments.

Furthermore, we show these benefits of competition may be realized, in some circumstances, without diluting incentives to innovate. R&D incentives can be strengthened further if the entrant faces incumbent drugs that are losing effectiveness due to accumulated bacterial resistance against them. Importantly, an increase in own-resistance, even though it eventually also afflicts the entrant's drug, gives the entrant a competitive advantage against the incumbent. The greater disincentive for antibiotic R&D appears to be cross-resistance. When the targeted bacterium is able to develop resistance to multiple drugs, and that effect is significant, incentives to develop new antibiotics are blunted.

Our results on competition are in stark contrast to the view, advanced in the

literature, that the patent component of any strategy going forward should be broad and long, protected from competition. Doing so—it is argued—would provide greater incentives for the monopolist to internalize the true user cost as well as greater incentives to perform research. In contrast, competition could worsen the resistance problem by lowering prices, increasing market output, and compromising a pioneer's return on its R&D investment. Indeed, it is true that some forms of competition could worsen the crisis, with generic competition being a good example of identical substitutes with high cross resistance. But even then, extending patent life would be efficient only if bacterial resistance is severe during the patent's life. For relatively low resistance, patent extensions could lead to *too little* consumption, driving up the rate of illness and the spread of the disease (not modelled here). In fact empirical evidence for important drugs is consistent with the latter situation in which bacterial resistance is minimal during patent life but grows rapidly during the subsequent generic production. Rather than extending patent life, imposing a Pigouvian tax would be a more efficient policy to quell the post-patent tide of resistance.

We derive a combination of taxes, competition policy and patents that ensure efficient allocation of the drug over time. 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 [Outterson (2007)]. More importantly, by reducing consumption, the accumulation of cross-resistance will be lower, thereby making the environment in which new drugs enter less hostile. That is, the concern that reductions in drug consumption imply lower returns on the R&D investment ignores the fundamental interplay between the economic and biological forces in these markets.

Even aside from these dynamic effects, we show that "demand-side policies" that account for the true user cost of consumption, in some circumstances, can provide indirect but adequate incentives for research. Where the drug sales do not generate a sufficient return on investment, we recommend that they should be supplemented with compensation, which is independent of sales (e.g., prizes, regulatory cost reductions, or patent buyouts). Our analysis, therefore, provides strong support for the emerging view that the award to the antibiotics innovator should be independent of sales.[69] We nevertheless consider patents to be an important policy lever for moderating consumption. In a sense, that role reverses the conventional justification for patents: in antibiotics markets, plagued as they are by a severe market failure, patents are more effective as a mechanism for moderating consumption than at providing research incentives. This is in contrast to the conventional purpose of patents, which is to motivate research at the cost of suboptimal consumption.

A more direct approach to encouraging new drugs would be to focus on "supply-

[69] See Outterson (2014) for an excellent review of delinkage models, in which the reward for antibiotics research does not depend on sales.

side" policies, in contrast to the indirect approach explored here of fixing the market failure problem. For example, in an attempt to accelerate the development of drugs, the U.S. and the U.K. have offered prizes, reduced regulatory constraints, and participated in public-private partnerships for cost-sharing [Laxminaryan (2014), Hollis and Maybarduk (2015), Davies (2013)].[70] While both approaches are ultimately needed given the severity of the crisis, we argue that focusing on the supply of drugs without correcting the overconsumption problem will simply accelerate the very costly game of leap-frog as scientists struggle to stay one step ahead of the increasingly resistant bacteria.

The impending crisis of antibiotic resistance is very broad and deep in several dimensions of complexity that are not incorporated in our analysis. Here, we focus on the intertemporal market failure in antibiotics. We do not explicitly model situations in which the drug is misused, for example, because consumers do not take the full course of the antibiotics, physicians diagnose the illness incorrectly, or the drug is used for non-therapeutic purposes. In such extensions of the model, allowing "conservation" policies for addressing those concerns — 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.[71] Furthermore, the role of vaccines for prevening illnesses versus antibiotics that treat already prevalent infections remains for future research.[72]

Most importantly, 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

[70] Recently, 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 (Spellberg, 2007). GAIN (Generating Antibiotics Incentives Now) is another program, not without controversy, signed into law in 2012 that extends the exclusivity period for 5 years and, importantly, fast-tracks FDA approval. While six new drugs have been approved by the FDA, they were modificatons of well-known classes of drugs and it appears that the expedited FDA approval provided at the beginning of the drug's life was the motivation rather than the 5 years tacked on at the end. Moreover, industry, governments and academia are sharing costs of research and development toward discovering new medicines. Demand-side policies to correct overuse have been adopted in Denmark and other European countries that have banned non-therapeutic use of antibiotics in farm animals. Finally, developed countries, including the U.S., the E.U., Canada, Japan and Australia, are engaged in rigorous surveillance programs to monitor the use of antibiotics and impact on resistances (WHO, 2014).

[71] 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.*

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

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 [World Health Organization (2004)], is significantly higher in developing and emerging economies, as are the costs of antibacterial resistance.[73] [74]Better access to antibiotics will constrain the spread of infectious diseases, as well as reduce incentives to misuse the drug.[75] 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?[76] This question remains as a vital piece of the puzzle — complementary to the analysis developed here — that is urgently needed in order to avert the impending global health crisis.

[73]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.

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

[75]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.

[76]Universal insurance for antibiotic coverage could be implemented to address the adverse distributional consequences of higher prices. While the challenges of insurance markets are well-known, this policy could be a fruitful avenue to investigate in future research, especially if conservation policies noted above (for lowering demand from misuse and therefore antibiotic prices) were put in place.

6 APPENDIX

Proof of Proposition 7:

Substitution of the optimal output levels into utilities in (2) and (7) yield social surplus for the monopoly and duopoly cases:

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

where $\mu = \phi/\theta$ and $\nu = \gamma$. Then, using the expressions in (A1), (23) can be written in terms of exogenous variables as:

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

It is easy to see that the iso-benefit curves are negatively sloped; in particular the slope of the iso-benefit curves are:

$$\frac{d\nu}{d\mu} = -\theta(T-1), \tag{A3}$$

holding constant θ and T, and that lower iso-benefit curves yield larger values of Z. To complete the proof, we need to show that when (24) in the text is satisfied, then (A2) will be as well for a larger measure of (μ, ν) combinations. Recall that by Proposition 4 L_m is defined by $\theta(T - L_m) = 1$. But since that holds by definition of x_m^* in (A1), then $\theta(T-1)$ 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, ν) 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.

Proof of Proposition 8:

Monopoly and duopoly profits in terms of exogenous variables are given by:

The profit functions for monopoly and duopoly are easily derived to be:

$$\begin{aligned} \Pi_m &= \frac{\alpha^2 L_m[2+(L_m-1)\theta]}{2[2+(L_m-1)\theta]^2} \\ \Pi_d &= \frac{\alpha^2 L_d[2+(L_d-1)(\theta+\phi)]}{[2+\gamma+(L_d-1)(\theta+\phi)]^2} \end{aligned} \tag{B1}$$

To prove the result in the proposition, set $\gamma = 0$ in Π_d of (B1). Then $\partial\Pi_d/\partial\phi$ is given by:

$$\partial\Pi_d/\partial\phi = \alpha^2 \frac{1+2(T-1))(\theta+\phi) - T(T-1)(\theta+\phi)^2}{(\theta+\phi)^2(1+(T-1)(\theta+\phi))^2}$$

which, when evaluated at $\phi = 0$ gives the result in the proposition for small θ. Then, since $\Pi_d = 2\Pi_m$ for $\phi = \gamma = 0$, and Π_m does not change with ϕ, it follows that for ϕ sufficiently small, $\Pi_d > 2\Pi_m$.□

Proof of Proposition 9:

When $\gamma = 0$, the two drugs are independent and their (identical) profits are readily computed to be $\Pi^X = \Pi^Y = \alpha^2/(2+\theta)$, which is declining in θ. For arbitrary γ the expressions for the present value profits for two drugs can be computed in closed form but are extremely unwieldy. Nevertheless, they are continuous in γ around $\gamma = 0$, and the profits of the two firms to first order in γ are, respectively,

$$\begin{aligned} \Pi^X &= \frac{\alpha^2}{(2+\theta)^2}[2+\theta-\gamma] + O(\gamma^2), \qquad \text{(C1)} \\ \Pi^Y &= \frac{\alpha^2}{(2+\theta)^2}[(2+\theta)-(3-\theta)\gamma] + O(\gamma^2). \end{aligned}$$

Taking the derivatives of these expressions with respect to θ, simplifying, and retaining only terms linear in γ we obtain

$$\begin{aligned} \frac{\partial \Pi^X}{\partial \theta} &= -\frac{\alpha^2}{(2+\theta)^3}[2+\theta-2\gamma], \qquad \text{(C2)} \\ \frac{\partial \Pi^Y}{\partial \theta} &= -\frac{\alpha^2}{(2+\theta)^3}[2+\gamma\theta+(\theta-8\gamma)]. \end{aligned}$$

(a) First note that since $1 \geq \gamma$, $\frac{\partial \Pi^X}{\partial \theta} < 0$. Furthermore, since $\theta < 1$ comparison of the two derivatives above readily shows that $\frac{\partial \Pi^X}{\partial \theta} < \frac{\partial \Pi^Y}{\partial \theta}$. In fact, $\frac{\partial \Pi^Y}{\partial \theta}$ can be positive if the term in brackets on the right hand side of its expression is negative, which occurs when $\gamma > (2+\theta)/(8-\theta)$.

(b) This result is easily seen by taken the derivative of the partials in (C2) with respect to γ:

$$\frac{\partial^2 \Pi^Y}{\partial \gamma \partial \theta} > \frac{\partial^2 \Pi^X}{\partial \gamma \partial \theta} > 0.$$

□

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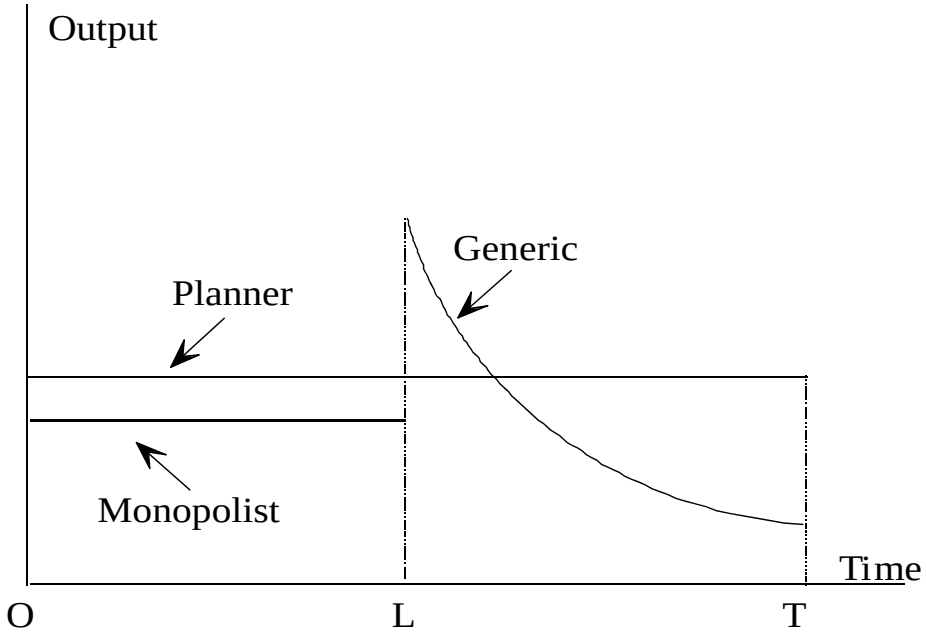

Figure 1: Output profile of industry over time

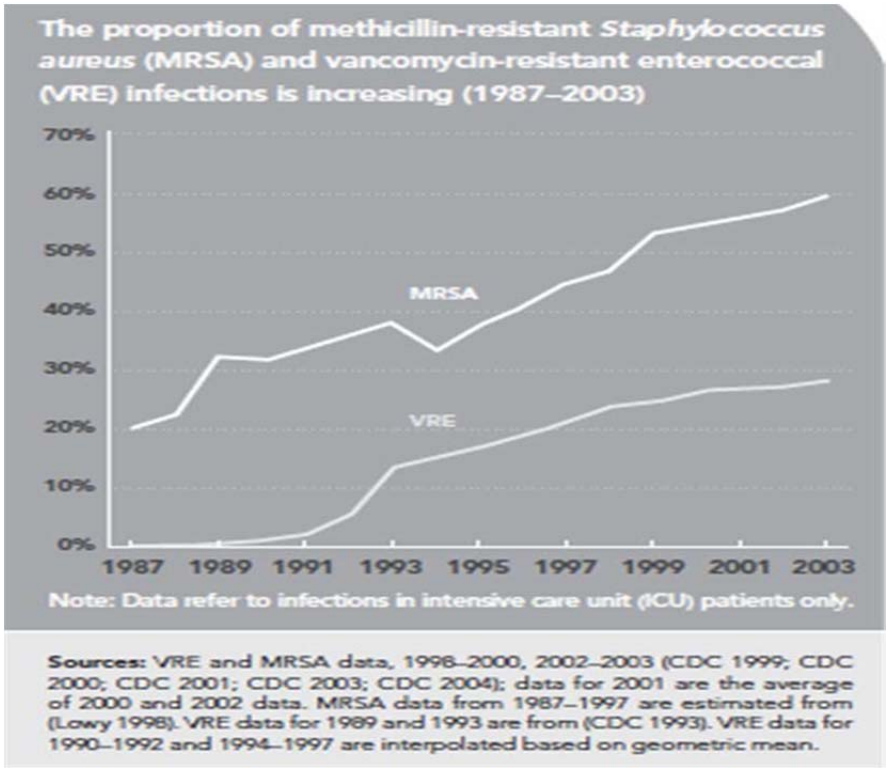

Figure 2: Rates of Resistance for Methicillin and Vancomycin (reprinted from Laxminarayan and Malani, 2007)

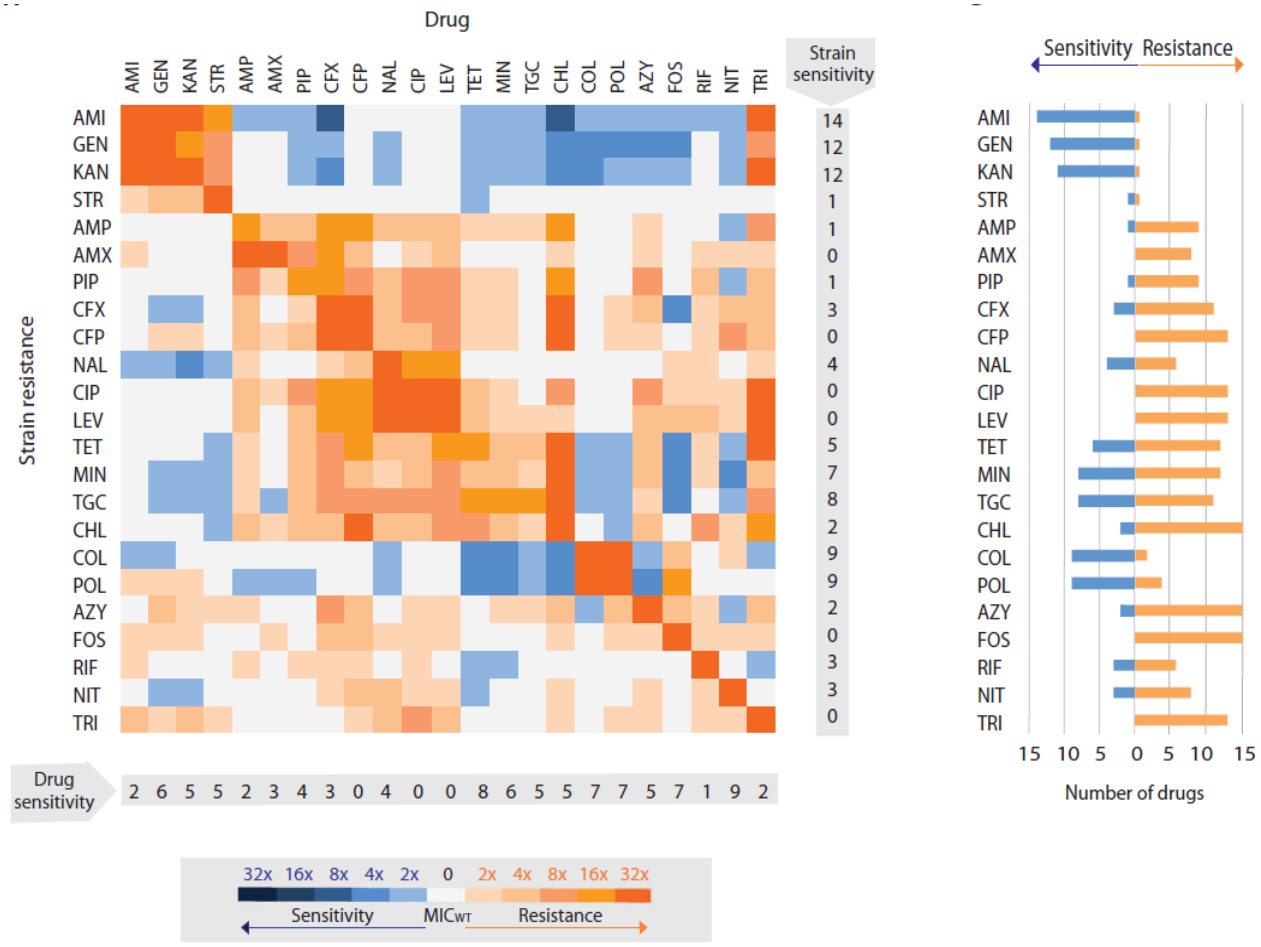

Figure 3: Cross-Resistance and Collateral Sensitivity between Drugs
Source: Imamovic and Sommer (2013)

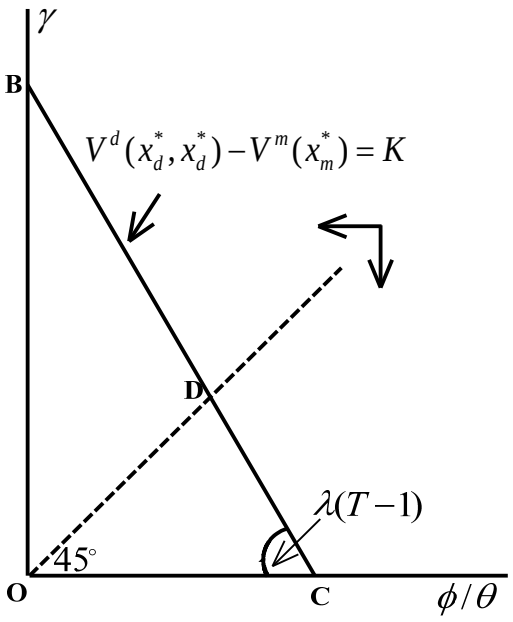

Figure 4: Displays how low cross-resistance is conducive to a socially preferred duopoly.

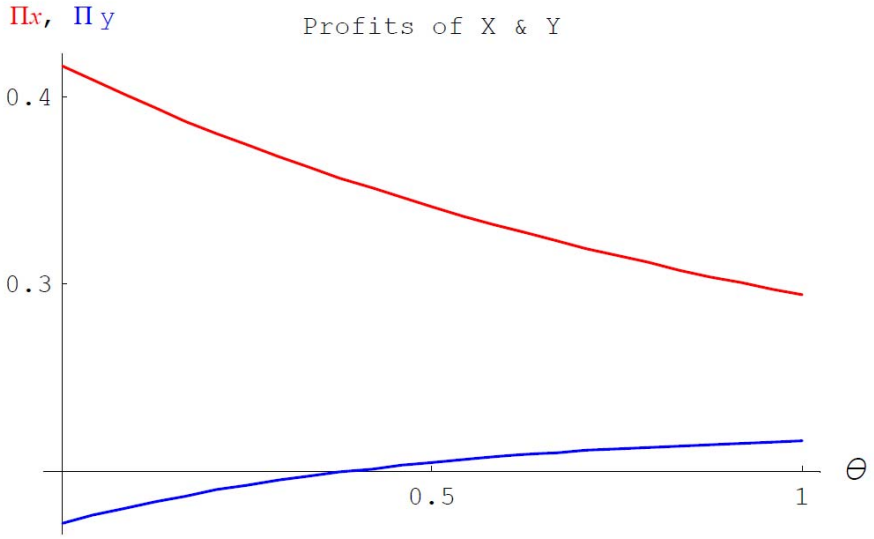

Figure 5: Profits of the two firms as a function of own resistance.