Bacterial cross-resistance and entry deterrence in a market for antibiotics

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Abstract

Purpose – The goal of the paper is to explore the deterrence strategy of a firm holding a patent on an antibiotic drug when confronting a threat of entry under varying conditions regarding bacterial cross-resistance to prospective competing antibiotic drugs. A second goal is to draw policy implications regarding patent policy as an instrument for combating antibiotic resistance.

Design/methodology/approach – A two-period model is used to study the output decisions of a patent-holding incumbent confronting potential entry in the second period. First-period output decisions influence the effectiveness of the incumbent antibiotic and prospective competitors in the second period. We compare equilibrium output decisions under varying conditions regarding (1) the duration and scope of patent protection and (2) the degree of bacterial cross-resistance to prospective second-period entrants.

Findings – Entry deterrence is more likely (less costly) as prospective entry costs for rivals increase. Whereas entry deterrence against generic competitors requires incumbents to increase output in the first period relative to a setting wherein the threat of entry is absent, a lower output level in the first period is a feature of an optimal entry deterrence strategy when prospective rivals benefit from a low level of bacterial cross-resistance. Stronger patent protection will not necessarily incentivize the patent holder to moderate current use such as to preserve antibiotic drug's future effectiveness.

Originality/value – The model contributes an important theoretical counterpoint to policy proposals advocating for stronger patents in response to the problem of antibiotic resistance. It also enriches the industrial organization literature on product quality differentiation (incumbent choice of first-period output affects the quality differential between antibiotics in the second period).

Keywords Antibiotic resistance, Entry deterrence, Antibiotic drug patents

Paper type Research paper

1. Introduction

Reducing the use of existing antibiotic drugs and promoting the development of novel ones are well-established goals of policy initiatives aimed at combating the threat of bacterial resistance to antibiotics (Center for Disease Control and Prevention, 2019; Wellcome, 2020; Antimicrobial Resistance Collaborators, 2022; Ready, 2023) [1]. Whereas multi-drug resistant bacteria have proliferated, the pace at which new antibiotic drugs have been discovered and commercialized slowed down considerably since the 1980s and 1990s (Thomas & Wessel, 2022). In light of the role played by pharmaceutical firms in promoting the overuse of antibiotics (Morel *et al.*, 2020), it has been proposed that extensions of the breadth and duration of patent rights on future antibiotics could align their holders' incentive to profit from their innovation with society's interest in managing the antibiotic drugs' effectiveness efficiently (Outterson, Samora, & Keller-Cuda, 2007; Kades, 2005; Gonzalez, 2022) [2].

Stronger patents would effectively privatize the commons of antibiotic effectiveness (Hardin, 1968; Tisdell, 1982) and thus undermine the holders' incentive to promote the excess use of antibiotic drugs in anticipation of the patent expiration date [3]. In contrast, when patents are finitely-lived and narrowly defined, sellers of patented antibiotic drugs would promote

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over-use of a drug in order to deter entry by rivals or to extract greater profits from the relevant market before entry by generics and competitors [4]. Can broader and longer-lasting patent rights address the crisis of bacterial resistance to antibiotics? Using a simple two-period entry deterrence game, we evaluate the validity of this claim, and consequently of the policy prescription in favor of stronger patent protection for antibiotics.

The key contribution is that our study of entry deterrence accounts for the documented variation in the degree of bacterial cross-resistance to different antibiotics [5]. Whereas bacterial resistance to a generic antibiotic is essentially the same as resistance to the original patented drug, novel antibiotics may display low levels of bacterial cross-resistance and thus represent different a threat from the viewpoint of the incumbent. Comparing the subgame perfect equilibria of the resulting entry-deterrence games we can study how the degree of bacterial cross-resistance confronting a potential entrant influences the strategic behavior of an incumbent patent-holding firm. We find conditions under which the incumbent firm would optimally deter entry. Further, we find that when deterrence is optimal, the incumbent will promote overuse of its own drug when the potential entrant is a generic or a novel drug for which bacterial cross-resistance is close enough to the incumbent drug's own-resistance. Instead, deterring entrants when bacterial cross-resistance is low requires conserving the effectiveness of the incumbent firm's antibiotic by reducing its use during the first period.

The model contributes an interesting case to the industrial organization literature on entry and vertical differentiation. In our model, the profitability of entry in the antibiotic market depends on both the size of the market and the "quality gap" between the incumbent firm's antibiotic and the entrant's. Accordingly, the relationship between bacterial own-resistance to the incumbent drug and cross-resistance to the entrant influences the incumbent firm's strategy. Deterring entry by a generic antibiotic requires reducing the size of the market by overproducing given the absence of a quality gap. Instead, low bacterial cross-resistance confers a quality advantage to the entrant that would become greater as the incumbent's quality falls due to overuse. Thus, entry deterrence would require the incumbent to keep the quality gap from getting too large by underproducing in the first period.

Although the model is highly stylized, it is worthwhile considering its policy implications. While delaying generic entry by extending the duration of antibiotic patents may be a useful policy, delaying or preempting entry by competing novel antibiotics by broadening the scope of antibiotic patents may be bad policy when bacterial cross-resistance to novel antibiotics is low. Not only such policy could delay or deny access to innovative antibiotics, but also it could eliminate the incumbent firm's strategic interest in conserving the effectiveness of existing antibiotic drugs to deter entrants.

2. Literature review

The model presented in this paper relates to two strands of theoretical literature concerned respectively with: (1) the welfare implications of competition and the characteristics of patent protection in the market for antibiotics; and (2) with entry deterrence under conditions of vertical differentiation.

Following the suggestion that broader and longer-lasting patent protection may solve the problem of too rapid a decline in antibiotic effectiveness, a number of papers explored in theoretical terms the trade-offs involved in strengthening patent rights. Horowitz and Moehring (2004) introduce a formal model illustrating the possible benefits of changes in the duration and breadth of patent protection. While acknowledging that patent policy may be a useful tool for ameliorating the inefficiencies associated with use of an antibiotic in conditions of open access, Horowitz and Moehring also point out that in theoretical terms efficient use of antibiotics could only be attained by conferring infinite patents reserving exclusive right over all antibiotics to a single economic actor. When patents have finite duration, they argue that the patent holder would have an incentive to promote overuse when the expiration of the patent is near. Moreover, when the scope of protection is limited (perhaps to just one class of

antibiotics), conservation efforts by firm A would generate benefits for others and others' production decisions would impose external costs on it.

Laxminarayan (2002) argues that the proposed strengthening of patent protection would substitute a possibly competitive market with a monopolistic market structure. Doing so would exacerbate deadweight losses associated with the presence of market power and reduce access to antibiotic treatment. Thus, the proposed policy would have benefits but also costs, and its overall desirability would come to depend on the resolution of complex tradeoffs between the well-being of present users whose access to antibiotic would be curtailed and that of future users who would benefit from more effective antibiotic treatment. Using a numerical illustration of his model, Laxminarayan suggests that the optimal organization of the market may involve competition among a small number of firms.

A recent paper by Eswaran and Gallini (2021) argues that a permanent monopoly over the antibiotic market would be an inefficient arrangement. Their model distinguishes between a biological and an economic externality associated with the use of either of two antibiotics. Bacterial cross-resistance explains how greater use of one drug will reduce the effectiveness of the other, and vice versa. This is the biological externality. But if the two drugs are also substitutes one for the other, each drug's output at the duopolistic market equilibrium would be smaller than the output of either one in a monopolistic market. As long as the cross-resistance effect is not too strong, Eswaran and Gallini find that antibiotic drug effectiveness could be greater when the market is a duopoly rather than a monopoly.

None of these papers directly addresses the question whether or not an incumbent firm whose drug is protected by a finite-life patent would rationally deter entry by increasing the output of its drug during the life of the patent, the primary question that the model in this paper wishes to explore. Accordingly, the model presented in this paper draws inspiration from and contributes to the streams of economic literature concerned with analyzing entry deterrence strategies broadly, and deterrence strategies related to vertical or quality-based differentiation more narrowly [6].

Pioneering work on entry deterrence such as Spence (1977) and Dixit (1980) highlights the role played by investment in production capacity as the instrument for altering the competitive landscape confronting a potential entrant. Deterrence can also be attained by taking actions that influence future demand such as to make entry unattractive for potential competitors (Schmalensee, 1978; Hoppe & Lee, 2003). Lutz (1997) extends this type of analysis to the case of entry deterrence in a model of vertical product differentiation where firms incur quality-dependent fixed set-up costs in a market where consumers differ in terms of their willingness to pay for quality. Lutz studies the conditions under which entry deterrence through the choice of a limit quality can be rational for an incumbent. Lutz shows further that the limit quality choice necessary to preempt entry can be lower or higher than the quality choice that the incumbent would choose in the absence of a threat of entry depending on whether the quality-dependent costs of the entrant are identical or lower than those of the incumbent. Noh and Moschini (2006) evaluate the incumbent firm's strategy in a similar model of vertical product differentiation where variable production costs are also quality-dependent. They find that while incumbency is the source of a first-mover advantage, the threat of entry will lead the incumbent firm to choose a higher quality than an unconstrained monopolist would choose regardless of whether accommodation or deterrence is the preferred strategy. In contrast, Karaer and Erhun (2015) conclude that incumbent firms may over-invest in quality –relative to an unconstrained monopolist—in order to deter entry but under-invest in quality when accommodation is their preferred strategy.

These models are close in spirit to the work presented in the following sections. A common feature of them is that firms are in control of the quality of the product they bring to the market –typically the result of an investment decision or of an explicit choice by each firm. In this paper instead, a two-period model is presented where the quality of the entrant's drug –and its relation to the quality of the incumbent's—depends partly on the actions taken by an incumbent firm [7]. Because of the phenomenon of cross-resistance, the incumbent firm responds to the threat of entry in the second period by choosing what would be the respective quality of the competing novel antibiotic in case entry were to occur. The choice is made by

deciding the level of first-period output. While producing more in the first-period has the well-known impact on first-period profits, it also impacts negatively the effectiveness of antibiotics available in the market during the second period. The nature of these impacts differs between the incumbent and the entrant firm when differences are present in bacterial own- and cross-resistance.

3. A two-period model of competitive entry and deterrence

We capture the effects of the competitive interactions between an incumbent and an entrant firm on antibiotic resistance in the simplest possible setting of a two-period model. During the first period, an incumbent firm operates as a monopolist. During the second period, entry by a single rival firm becomes possible. A successful entrant in the second period would bring about duopolistic competition between firms producing two possibly differentiated antibiotics. Vertical differentiation results from differences between bacterial own- and cross-resistance affecting the demand for respectively the incumbent and the entrant drug. The degrees of own- and cross-resistance will be treated as exogenous parameters. The antibiotic commercialized by the entrant will be a substitute for the incumbent antibiotic from the viewpoint of its therapeutic indications (that is, the range of bacterial infections for which drugs are effective). Moreover, the new antibiotic's effectiveness at the beginning of its commercialization will be determined by the cross-resistance resulting from the prior use of the incumbent antibiotic.

Before studying the competitive interactions between the incumbent and the potential entrant, we analyze the pricing and output decisions of a two-period monopolist whose antibiotic drug is subject to the onset of bacterial resistance in the second period. Throughout the paper we will assume a conventional specification of linear market demand for all antibiotics, consistent with the Quasilinear Quadratic Utility Model and commonly used in oligopoly models (Choné & Linnemer, 2020). Noting that I will use uppercase letters to indicate first period variables and lowercase letters to indicate second period variables, the first- and second-period demand functions will be derived from the following general utility functions:

$$U^d(X) = \alpha X - \frac{\beta}{2}X^2 + K \tag{1a}$$

$$U^d(x, y, X) = \alpha[x + y] - \frac{\beta}{2}\left[x^2 + y^2\right] - \theta[xX] - \phi[yX] + K \tag{1b}$$

where X and x represent the first and second period output of the incumbent antibiotic manufacturer, and y represents the second-period output of the entrant [8]. The parameters θ and ϕ represent respectively the levels of own- and cross-resistance induced by the incumbent drug's first-period output.

3.1 Two-period monopoly

In this scenario, entry is not possible in the second period –arguably as a result of a long-lived broad patent effectively reserving the market to the incumbent firm. When y is set equal to zero, then the linear demand functions for the incumbent's antibiotic drug are:

$$P = \alpha - \beta X \tag{2a}$$

$$p = (\alpha - \theta X) - \beta x \tag{2b}$$

Assuming a constant marginal cost of production c lower than α, the profits for the incumbent firm can be expressed as:

$$\Pi = \begin{cases} \{(\alpha - \beta X - c)X\} + \{(\alpha - \theta X - \beta x - c)x\} & \text{if } X < \dfrac{\alpha - c}{\theta} \\ \{(\alpha - \beta X - c)X\} & \text{if } X \geq \dfrac{\alpha - c}{\theta} \end{cases} \tag{3}$$

The conditions in (3) implies that second period output (x) and profits will be zero if and only if first period output is such that the loss of effectiveness of the drug is such as to make the primary mark-up in the second period non-positive (that is, $\alpha - \theta X \leq c$). When the condition does not hold, so that the second-period demand condition is consistent with profitability, the optimal second-period output will be set equal to:

$$x^* = \frac{(a - \theta X) - c}{2\beta} \tag{3a}$$

and the second-period profits for the incumbent firm would be:

$$\pi = \frac{1}{\beta}\left(\frac{\alpha - \theta X - c}{2}\right)^2 \tag{3b}$$

Substituting this expression into (3), we can rewrite (3) as:

$$\Pi = \begin{cases} \{(\alpha - \beta X - c)X\} + \dfrac{1}{\beta}\left(\dfrac{\alpha - \theta X - c}{2}\right)^2 & \text{if } X < \dfrac{\alpha - c}{\theta} \\ \{(\alpha - \beta X - c)X\} & \text{if } X \geq \dfrac{\alpha - c}{\theta} \end{cases} \tag{3c}$$

Differentiating (3c) with respect to X, we find that:

$$\frac{\partial \Pi}{\partial X} = \begin{cases} (\alpha - c)\dfrac{2\beta - \theta}{2\beta} - X\dfrac{4\beta^2 - \theta^2}{2\beta} & \text{if } X < \dfrac{\alpha - c}{\theta} \\ \alpha - 2\beta X - c & \text{if } X \geq \dfrac{\alpha - c}{\theta} \end{cases} \tag{4a}$$

Before analyzing the first-order conditions for a maximum, it is useful to note that whereas the second derivative of $\Pi(X)$ is always negative for $X \geq (\alpha - c)/\theta$, the same is not true when $X < (\alpha - c)/\theta$:

$$\frac{\partial^2 \Pi}{\partial X^2} = \begin{cases} -\dfrac{4\beta^2 - \theta^2}{2\beta} = -\dfrac{(2\beta + \theta)(2\beta - \theta)}{2\beta} & \text{if } X < \dfrac{\alpha - c}{\theta} \\ -2\beta < 0 & \text{if } X \geq \dfrac{\alpha - c}{\theta} \end{cases} \tag{4b}$$

The sign of the second derivative when $X < (\alpha - c)/\theta$ depends on the relative magnitude of the two parameters β and θ. Specifically, $\Pi(X)$ is strictly concave over the interval $0 \leq X < (\alpha - c)/\theta$ if and only if $\theta < 2\beta$. Only in this case, the first order condition would identify the profit-maximizing value of X. When $\theta > 2\beta$, the first order condition would identify a local minimum. For $\theta = 2\beta$, $\Pi(X) = \frac{1}{\beta}\left(\frac{\alpha - c}{2}\right)^2$, so it would become independent of X for $X < \frac{\alpha - c}{\theta}$. Given the role played by the two parameters β and θ, the following proposition identifies the profit-maximizing first-period output of the incumbent monopolist as follows:

Proposition 1. When second-period entry is restricted (not possible), an incumbent monopolist would maximize profits by choosing:

$$X^* = x^* = \frac{\alpha - c}{2\beta + \theta} \quad \textit{if and only if } \theta < 2\beta \tag{5}$$

and

$$X^* = \frac{\alpha - c}{2\beta}, x^* = 0 \quad \textit{if and only if } \theta \geq 2\beta \tag{6}$$

The intuition behind this result (proof is in Appendix A) is that when the impact of first period output on the antibiotic drug's second period effectiveness is low, the monopolist finds it worthwhile to give up profits in the first period by producing less than the output that would maximize first-period profits. Vice versa, when antibiotic effectiveness declines very rapidly with first period output, the incumbent firm rationally extracts all the profits during the first-period and reduces output to zero during the second period. We note further that the profit-maximizing first-period output choice of the incumbent firm when antibiotic resistance is absent ($\theta = 0$) is the same as that when antibiotic resistance is very strong ($\theta \geq 2\beta$). For intermediate values of antibiotic resistance ($0 < \theta < 2\beta$), the optimal first-period output choice is instead a decreasing function of θ.

Before turning to the analysis of entry decisions, the monopoly outcomes can be characterized further in terms of the prices and profits at the equilibrium levels of output. When (5) holds, the price of the drug will decline from the first to the second period. Substituting from (5) into (2) and (3), it follows that:

$$P^* = \frac{(\alpha + c)\beta + \alpha\theta}{2\beta + \theta}, p^* = \frac{(\alpha + c)\beta + c\theta}{2\beta + \theta} \tag{7}$$

At the optimal output and price plan, the incumbent firm's overall profits would be equal to:

$$\Pi^* = \frac{(\alpha - c)^2}{2\beta + \theta} \tag{8}$$

When (6) holds, the price of the drug in the first period will be (no activity takes place in the second period):

$$P^* = \frac{\alpha + c}{2} \tag{9}$$

and the incumbent firm's profits will be $\Pi^* = \frac{1}{\beta}\left(\frac{\alpha - c}{2}\right)^2$.

In order to simplify the presentation of the main analytical results of the model, we will focus the presentation on the case in which own-resistance is not too large ($\theta \leq \beta$) so that condition (5) holds a fortiori.

3.2 Entry by a generic competitor ($\phi = \theta$)

In this section, we examine how the threat of entry by a generic competitor would affect the behavior of the incumbent firm. In fact, whether or not entry will take place depends on the first-period behavior of the incumbent firm and the research or entry costs that the potential entrant has to incur in order to participate in the second-period market. We model this as a two-period game in which: (1) the incumbent chooses output in the first period; (2) the entrant decides whether or not to enter the market before the second period; (3) if entry occurs, the two

firms compete as a Cournot duopoly in the second period. If entry does not occur, the incumbent firm operates as a monopolist in the second-period market. The analysis will focus on the subgame perfect Nash equilibrium of the two-period game.

We begin by studying the Cournot equilibrium of the second period duopolistic market under the assumption that entry has occurred. The demand for the antibiotic will be:

$$p = (\alpha - \theta X) - \beta(x + y) \tag{10}$$

Assuming that both firms incur identical constant marginal cost of production, the resulting symmetric Cournot Nash equilibrium will be:

$$x^* = y^* = \begin{cases} \dfrac{\alpha - \theta X - c}{3\beta} & \text{if } X < \dfrac{\alpha - c}{\theta} \\ 0 \quad \text{if } X \geq \dfrac{\alpha - c}{\theta} \end{cases} \tag{11}$$

At the equilibrium with positive output, price and second-period profits for each of the two firms will be:

$$p^* = \frac{\alpha - \theta X + 2c}{3} \tag{12}$$

$$\pi_x = \frac{1}{\beta}\left(\frac{\alpha - \theta X - c}{3}\right)^2, \pi_y = \frac{1}{\beta}\left(\frac{\alpha - \theta X - c}{3}\right)^2 - R \tag{13}$$

All second period equilibrium values of the variables depend on the incumbent's choice of first period output. In particular, the profits for the entrant firm suggest that the entry decision will depend on (1) the first period output choice of the incumbent –as that determines the profitability of the duopolistic market; and (2) the entry costs R to be incurred (see Figure 1).

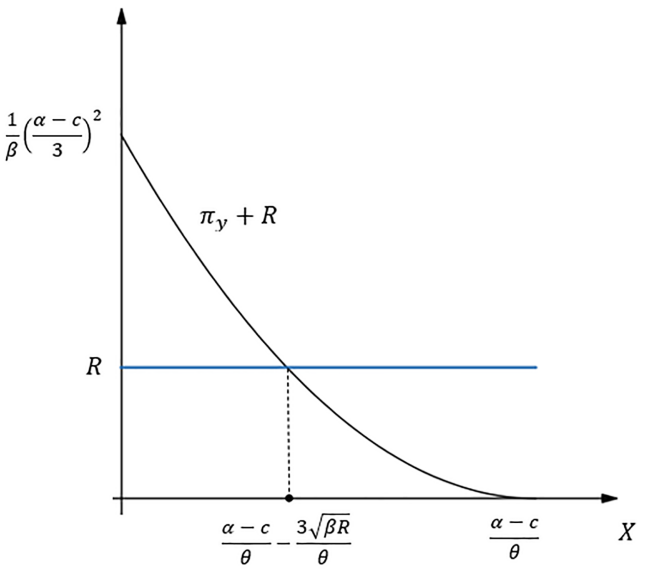

Figure 1. First-period output and entrant's profits (generic rival). **Source(s):** Figure by author

From (13), the entry condition can be characterized as:

$$\pi_y > 0 \Leftrightarrow \frac{1}{\beta}\left(\frac{\alpha-\theta X-c}{3}\right)^2 > R \Leftrightarrow X < \frac{\alpha-c}{\theta} - \frac{3(\beta R)^{\frac{1}{2}}}{\theta} \tag{14}$$

Conditions (14) and (11) partition the set of possible values of X in three subsets consistent with entry accommodation, entry deterrence, and exit of the incumbent from the market, respectively:

$$\mathbb{X}_A = \left\{X \,|\, X < \frac{\alpha-c}{\theta} - \frac{3(\beta R)^{\frac{1}{2}}}{\theta}\right\} \tag{14a}$$

$$\mathbb{X}_D = \left\{X \,|\, \frac{\alpha-c}{\theta} - \frac{3(\beta R)^{\frac{1}{2}}}{\theta} \leq X < \frac{\alpha-c}{\theta}\right\} \tag{14b}$$

$$\mathbb{X}_E = \left\{X \,|\, X \geq \frac{\alpha-c}{\theta}\right\} \tag{14c}$$

The Cournot equilibria of the corresponding second-period subgames can then be characterized as follows:

$$x^* = y^* = \frac{\alpha-\theta X-c}{3\beta} \quad for\, X \in \mathbb{X}_A \tag{15a}$$

$$x^* = \frac{\alpha-\theta X-c}{2\beta}, y^* = 0 \quad for\, X \in \mathbb{X}_D \tag{15b}$$

$$x^* = y^* = 0 \quad for\, X \in \mathbb{X}_E \tag{15c}$$

Outcomes (15a) and (15b) capture the strategic dilemma confronting the incumbent firm in the first period between accommodating entry by a generic rival and preempting it with a larger first-period output [9]. By backward induction, the incumbent firm's overall profits can be expressed as follows:

$$\Pi = \begin{cases} \Pi_A = \{(\alpha-\beta X-c)X\} + \frac{1}{\beta}\left(\frac{\alpha-\theta X-c}{3}\right)^2 & for\, X \in \mathbb{X}_A \\ \Pi_D = \{(\alpha-\beta X-c)X\} + \frac{1}{\beta}\left(\frac{\alpha-\theta X-c}{2}\right)^2 & for\, X \in \mathbb{X}_D \\ \Pi_E = \{(\alpha-\beta X-c)X\} & for\, X \in \mathbb{X}_E \end{cases} \tag{16a,b,c}$$

We note that the optimal level of first period output cannot be a value from the set $\mathbb{X}_E$ [10]. Both Π_A and Π_D are strictly concave functions of first-period output attaining an unconstrained maximum at respectively:

$$\widehat{X}_A = \frac{\alpha-c}{2}\,\frac{9\beta-2\theta}{(3\beta+\theta)(3\beta-\theta)} \tag{17a}$$

$$\widehat{X}_D = \frac{\alpha - c}{2\beta + \theta} \tag{17b}$$

where $\widehat{X}_D < \widehat{X}_A$. It is straightforward to see that Π_A attains its constrained maximum value Π_A^* at the smallest of either $\widehat{X}_A$ or the supremum of $\mathbb{X}_A$, whereas Π_D attains its constrained maximum Π_D^* at the largest of either $\widehat{X}_D$ or the lower bound of $\mathbb{X}_D$. When $R = 0, \Pi_A^* > \Pi_D^*$ so accommodation is the profit maximizing strategy and the incumbent sets the first period output at $\widehat{X}_A$ (see Appendix B). But as R increases, so will Π_D^*. It can be shown (see Appendix C) that there is a threshold level $\overline{R}$ of entry costs (equivalently, a threshold level $\underline{X}_{D,L}$ of the lower bound of $\mathbb{X}_D$) such that:

$$\Pi_D^* \geq \Pi_A^* \Leftrightarrow R \geq \overline{R} \; or \; equivalently \; X \leq \underline{X}_{D,L}$$

so that entry is deterred at the subgame perfect Nash equilibrium of the game (this outcome if described in Figure 2). Further, there is a threshold level $\overline{\overline{R}} > \overline{R}$ such that $\widehat{X}_D \in \mathbb{X}_D$ so that entry is blockaded and the incumbent firm chooses the same output levels for the first- and second-period as an unconstrained monopolist.

The joint role of θ and R in determining the outcome of the entry game can be summarized by noting how for any given level of θ the strategic posture of the incumbent firm varies depending on the entry costs of the prospective generic competitor. These findings are summarized in Table 1, and the following two propositions (proofs in Appendices B and C, respectively).

Proposition 2. When generic entry is possible at zero cost, the incumbent will never find it profitable to preempt entry, but its profit-maximizing strategy will feature a greater first-period output when entry is expected than when monopolistic conditions are expected to prevail through both periods –as they would under a "long-lived" patent that restricts generic entry.

Proposition 3. When generic entry by a competitor is sufficiently costly, a profit-maximizing incumbent will preempt entry by choosing a first-period output level large enough to force the prospective second-period profits of an entrant to zero. Accordingly, the second-period effectiveness of the

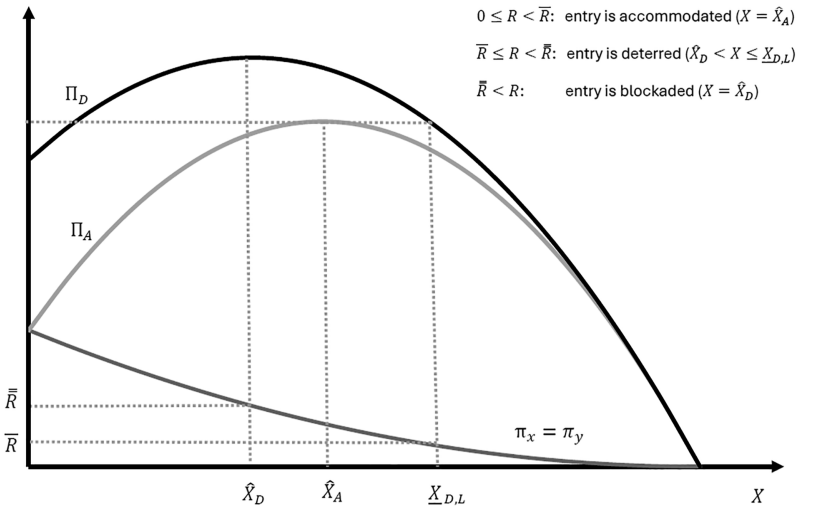

Figure 2. Incumbent's optimal strategy under threat of entry by generic rival. **Source(s):** Figure by author

Table 1. Incumbent's optimal strategy with generic entry

	Entry	Incumbent's profit-maximizing first-period output level	Second-period output at equilibrium
$\theta = 0$	Entry if $R < \frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2$	$x^* = \frac{\alpha-c}{2\beta}$	$x^* + y^* = \frac{2(\alpha-c)}{3\beta}$
	No entry if $R \geq \frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2$		$x^* = \frac{\alpha-c}{2\beta}$
$0 < \theta < 2\beta$	Entry is accommodated if $R < \overline{R}$	$X^* = \frac{\alpha-c}{2}\frac{9\beta-2\theta}{(3\beta+\theta)(3\beta-\theta)}$	$x^* + y^* = (\alpha-c))\frac{3(2\beta-\theta)}{(3\beta+\theta)(3\beta-\theta)}$
	Entry is preempted if $\overline{R} \leq R < \overline{\overline{R}}$	$X^* = \frac{\alpha-c}{\theta} - \frac{3(\beta R)^{\frac{1}{2}}}{\theta}$	$x^* = \frac{3}{2}\left(\frac{R}{\beta}\right)^{\frac{1}{2}}$
	Entry is blockaded if $R \geq \overline{\overline{R}}$	$X^* = \frac{\alpha-c}{2\beta+\theta}$	$x^* = \frac{\alpha-c}{2\beta+\theta}$
$\theta \geq 2\beta$	Entry is blockaded	$X^* = \frac{\alpha-c}{2\beta}$	$x^* = 0$

Source(s): Table by author

incumbent's antibiotic drug will be likely lower than it would be under a two-period monopoly condition. This will not be the case if and only if entry costs are so large for any given value of own resistance that generic entry is blockaded.

4. Entry by a vertically differentiated competitor ($\phi < \theta$)

We now focus on the strategic interaction between the incumbent and an entrant whose antibiotic is subject to weaker bacterial resistance than that affecting the incumbent's drug. The difference between the level of cross- and own-resistance caused by first period output seeds the presence of vertical differentiation in the second-period market: the entrant competes with a higher quality drug than the incumbent. The magnitude of the quality gap depends on the two parameters for own- and cross-resistance as well as the choice of first-period output by the incumbent.

We begin by characterizing the second-period market equilibrium under the assumption that entry has been decided on. The demand for each of the two antibiotics is:

$$p_x = \alpha - \theta X - \beta(x + y) \tag{18a}$$

$$p_y = \alpha - \phi X - \beta(x + y) \tag{18b}$$

The effectiveness gap between the two antibiotic drugs implies that the conditions under which the incumbent will be active in the market are more restrictive than those implied by the requirement that the primary mark-up be positive. Based on the analysis of the best-response function of the incumbent firm, we can establish that when $X < \frac{\alpha-c}{2\theta-\phi}$ both firms will be active in the second-period market. The Nash equilibrium output levels under Cournot competition would be:

$$x^* = \frac{\alpha - c}{3\beta} - \frac{(2\theta - \phi)X}{3\beta} \tag{19a}$$

$$y^* = \frac{\alpha - c}{3\beta} - \frac{(2\phi - \theta)X}{3\beta} \tag{19b}$$

When $X \geq \frac{\alpha - c}{2\theta - \phi}$ instead, then the incumbent would optimally withdraw from the market and the entrant would produce the monopoly output:

$$x^* = 0 \tag{20a}$$

$$y^* = \frac{(\alpha - \phi X - c)}{2\beta} \tag{20b}$$

Notice that $\phi < \theta$ implies that $y^* > x^*$ under either condition. Predictably, the equilibrium prices for the two drugs will also differ under the conditions at (19a) and (19b) ($p_y^* > p_x^*$):

$$P_x^* = \frac{\alpha - (2\theta - \phi)X + 2c}{3}$$

$$P_y^* = \frac{\alpha - (2\phi - \theta)X + 2c}{3}$$

Furthermore, the prospective entrant's second period profits (gross of entry costs) will exceed the incumbent's under the conditions at (19a) and (19b):

$$\pi_x^* = \frac{1}{\beta}\left\{\frac{\alpha - (2\theta - \phi)X - c}{3}\right\}^2 \tag{19c}$$

$$\pi_y^* + R = \frac{1}{\beta}\left\{\frac{\alpha - (2\phi - \theta)X - c}{3}\right\}^2 \tag{19d}$$

as well as under conditions at (20a) and (20b):

$$\pi_x^* = 0 \tag{20c}$$

$$\pi_y^* + R = \frac{1}{\beta}\left\{\frac{\alpha - \phi X - c}{2}\right\}^2 \tag{20d}$$

In light of the role played by the prospective entrant's profits in determining the conditions under which entry can be deterred, it is useful to gather the expressions in (19c), (19d), (20c) and (20d) into the following:

$$\pi_y^* = \begin{cases} \frac{1}{\beta}\left\{\frac{\alpha - (2\phi - \theta)X - c}{3}\right\}^2 - R & for\, X < \frac{\alpha - c}{2\theta - \phi} \\ \frac{1}{\beta}\left\{\frac{\alpha - \phi X - c}{2}\right\}^2 - R & for\, X \geq \frac{\alpha - c}{2\theta - \phi} \end{cases} \tag{21a,b}$$

Whereas the expression in (21b) is a decreasing convex function of X, the effect of the incumbent firm's choice of first-period output on the prospective entrant's gross profits under duopoly conditions (expression at (21a)) may be positive, null or negative depending on the relative magnitude of the own- and cross-resistance parameters θ and ϕ:

$$\frac{\partial \pi_y}{\partial X} \gtreqless 0 \Leftrightarrow \phi \gtreqless \frac{\theta}{2} for\, X < \frac{\alpha - c}{2\theta - \phi} \tag{22}$$

Thus, when the level of cross-resistance is low ($\phi < \theta/2$), π_y^* is a convex increasing function of X over the interval $\left[0, \frac{\alpha - c}{2\theta - \phi}\right)$ so that an increase in first-period output will increase the second-period profits for the entrant firm (see Figure 3). Vice versa, π_y^* will be a convex decreasing functions of X in the same interval when $\phi > \theta/2$ (see Figure 4), and independent of X when $\phi = \theta/2$. This observation has important implications for the analysis of entry deterrence.

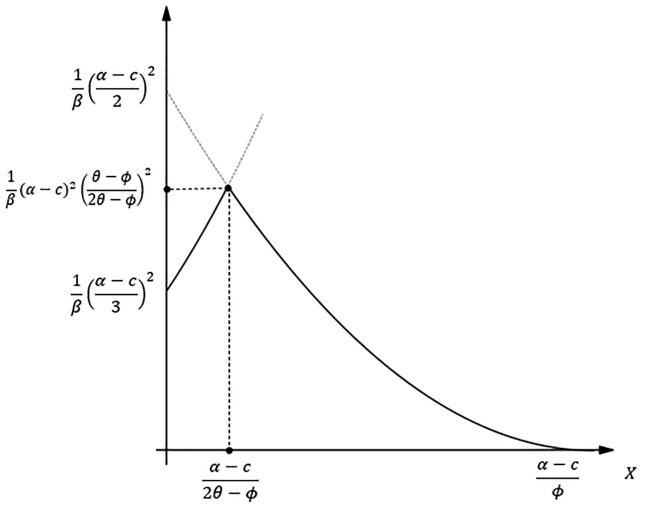

Figure 3. First-period output and entrant's profits (low cross-resistance differentiated rival). **Source(s):** Figure by author

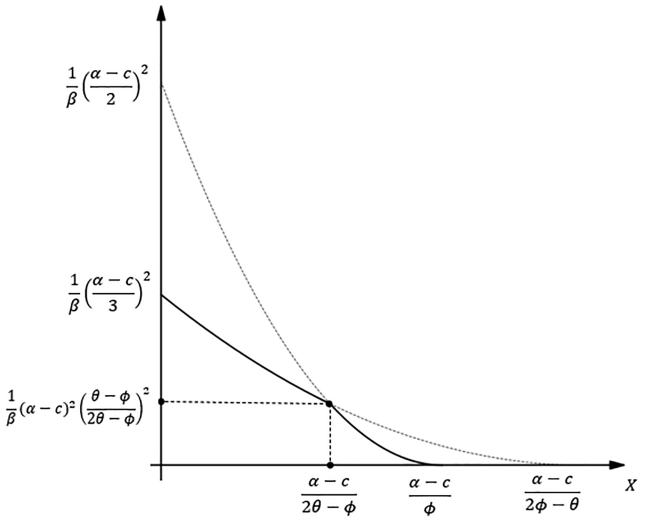

Figure 4. First-period output and entrant's profits (high cross-resistance differentiated rival). **Source(s):** Figure by author

When cross-resistance is lower than own-resistance but not by much ($\theta/2 < \phi < \theta$), the entrant's profits (22) are a decreasing function of X for all values of X. Accordingly, the conditions according to which entry will occur will be qualitatively similar to those at (14):

$$\pi_y > 0 \Leftrightarrow X < \widetilde{X} = \min\left\{\frac{\alpha - c}{2\phi - \theta} - \frac{3(\beta R)^{\frac{1}{2}}}{2\phi - \theta}\,;\ \frac{\alpha - c}{\phi} - \frac{2(\beta R)^{\frac{1}{2}}}{\phi}\right\} \tag{23}$$

where $\widetilde{X}$ is a threshold value dependent on R.

Instead, when cross-resistance is much lower than own-resistance ($\phi < \theta/2$), the entrant's profit are an increasing function of X in the range $X < \frac{\alpha - c}{2\theta - \phi}$, and a decreasing function in the range $X \geq \frac{\alpha - c}{2\theta - \phi}$. The conditions for entry will then be contingent on the magnitude of the entry costs R:

$$\pi_y > 0 \Leftrightarrow X < \frac{\alpha - c}{\phi} - \frac{2(\beta R)^{\frac{1}{2}}}{\phi} \quad for\, 0 \leq R < \frac{1}{\beta}\left\{\frac{\alpha - c}{3}\right\}^2 \tag{24a}$$

$$\pi_y > 0 \Leftrightarrow \frac{\alpha - c}{2\phi - \theta} - \frac{3(\beta R)^{\frac{1}{2}}}{2\phi - \theta} < X < \frac{\alpha - c}{\phi} - \frac{2(\beta R)^{\frac{1}{2}}}{\phi} \quad for\, R \geq \frac{1}{\beta}\left\{\frac{\alpha - c}{3}\right\}^2 \tag{24b}$$

The foregoing analysis will distinguish then between the two cases.

4.1 Entry deterrence when $\phi > \frac{\theta}{2}$

This case is qualitatively similar to the case of generic entry. When deterrence is optimal, it requires a higher level of first-period output than an unconstrained monopolist would choose. How large an increase in first-period output is necessary to achieve deterrence depends on the magnitude of the entry costs facing the potential competitor and the quality gap between the incumbent's and the entrant's antibiotic drugs (the gap between θ and ϕ). The condition at (23) induces a partition of the set of possible values for X analogous to that at (14a-c).

$$\mathbb{X}_A = \left\{X \,|\, X < \widetilde{X} = \min\left\{\frac{\alpha - c}{2\phi - \theta} - \frac{3(\beta R)^{\frac{1}{2}}}{2\phi - \theta}\,;\ \frac{\alpha - c}{\phi} - \frac{2(\beta R)^{\frac{1}{2}}}{\phi}\right\}\right\}$$

$$\mathbb{X}_D = \left\{X \,|\, \widetilde{X} = \min\left\{\frac{\alpha - c}{2\phi - \theta} - \frac{3(\beta R)^{\frac{1}{2}}}{2\phi - \theta}\,;\ \frac{\alpha - c}{\phi} - \frac{2(\beta R)^{\frac{1}{2}}}{\phi}\right\} \leq X\right\}$$

When $X \geq \widetilde{X}$, entry is deterred and the incumbent firm would be the only active firm in the second period market unless X is large enough to induce the incumbent firm to optimally withdraw from the second-period market (that is, unless $X \geq \frac{\alpha - c}{\theta}$). When $X < \widetilde{X}$, entry will be accommodated and the second period market will feature either a duopolistic structure or a monopoly held by the entrant firm in case $X \geq \frac{\alpha - c}{2\theta - \phi}$.

In light of these considerations, the first period output choice of the incumbent will be the solution to the following maximization problem:

$$\max_X \Pi(X) = \begin{cases} \Pi_A(X) & for\, X \in \mathbb{X}_A \\ \Pi_D(X) & for\, X \in \mathbb{X}_D \end{cases} \tag{25}$$

When entry is accommodated, the relevant profit function is:

$$\Pi_A(X) = \begin{cases} (\alpha - \beta X - c)X + \frac{1}{\beta}\left\{\frac{\alpha - (2\theta - \phi)X - c}{3}\right\}^2 & for\, 0 \le X < min\left(\frac{\alpha - c}{2\theta - \phi};\, \widetilde{X}\right) \\ (\alpha - \beta X - c)X & for\, min\left(\frac{\alpha - c}{2\theta - \phi};\, \widetilde{X}\right) \le X < \widetilde{X} \end{cases} \tag{25a,b}$$

It can be shown that the function Π_A attains its maximum over the set $\mathbb{X}_A$ at either an interior optimum or at the extremum of $\mathbb{X}_A$:

$$X_A^* = \min\left(\widetilde{X}, \frac{\alpha - c}{2\beta}\ \frac{9\beta^2 - 2\beta(2\theta - \phi)}{9\beta^2 - (2\theta - \phi)^2}\right) \tag{25c}$$

When entry is deterred, the relevant profit function is instead:

$$\Pi_D(X) = \begin{cases} (\alpha - \beta X - c)X + \frac{1}{\beta}\left\{\frac{\alpha - \theta X - c}{2}\right\}^2 & for\, \widetilde{X} \le X < max\left(\widetilde{X};\ \frac{\alpha - c}{\theta}\right) \\ (\alpha - \beta X - c)X & for\, max\left(\widetilde{X};\ \frac{\alpha - c}{\theta}\right) \le X \end{cases} \tag{26a,b}$$

Both expressions in (26a, b) are strictly concave decreasing functions of X as long as $\widetilde{X} > \frac{\alpha - c}{2\beta + \theta}$ so that Π_D would attain its maximum value over $\mathbb{X}_D$ at $X = \widetilde{X}$. When $\widetilde{X} \le \frac{\alpha - c}{2\beta + \theta}$ instead, then Π_D is maximized at $= \frac{\alpha - c}{2\beta + \theta}$. Accordingly, we can write that:

$$X_D^*(R) = \max\left(\widetilde{X}(R), \frac{\alpha - c}{2\beta + \theta}\right) \tag{26c}$$

Since $\Pi_D^*(R) = \Pi_D(X_D^*(R))$ is an increasing function of R, there is a threshold level $\overline{R}$ of entry costs (equivalently, a threshold level $\underline{X}_{D,L}$ of the lower bound of $\mathbb{X}_D$) such that:

$$\Pi_D^*(R) > \Pi_A^*(R) \Leftrightarrow R \ge \overline{R}\ or\ equivalently\ \widetilde{X} \le \underline{X}_{D,L} \tag{27}$$

so that entry is deterred at the subgame perfect Nash equilibrium of the game. Further, there is a threshold level $\overline{\overline{R}} > \overline{R}$ such that $\widehat{X}_D = \frac{\alpha - c}{2\beta + \theta} \in \mathbb{X}_D$, so that entry is blockaded and the incumbent firm chooses the same output levels for the first- and second-period as an unconstrained monopolist.

Specifically, the incumbent would choose to preempt or blockade entry when:

$$\widetilde{X}(R) \le \underline{X}_{D,L} = \frac{\alpha - c}{2\beta + \theta}\left\{1 + \left[\frac{12\beta + 4\theta}{2\beta - \theta} - \frac{2\beta + \theta}{2\beta - \theta}\frac{[9\beta - 2(2\theta - \phi)]^2}{9\beta^2 - (2\theta - \phi)^2}\right]^{\frac{1}{2}}\right\} \tag{28a}$$

or equivalently when

$$R \ge \overline{R} = \frac{1}{\beta}\left(\frac{\alpha - c}{3}\right)^2\left\{1 - \frac{2\phi - \theta}{2\beta + \theta}\left[1 + \left\{\frac{12\beta + 4\theta}{2\beta - \theta} - \frac{2\beta + \theta}{2\beta - \theta}\frac{[9\beta - 2(2\theta - \phi)]^2}{9\beta^2 - (2\theta - \phi)^2}\right\}^{\frac{1}{2}}\right]\right\}^2 \tag{28b}$$

Table 2 summarizes the strategic behavior of the incumbent by reference to the relevant parameters of the model.

4.2 Entry deterrence when $\phi < \frac{\theta}{2}$

When bacterial cross-resistance to the potential entrant's drug is much lower than the own-resistance, the Nash Equilibrium profits of the entrant firm in the duopolistic market are an increasing function of X so that the incumbent could deter entry by choosing a low level of first-period output. Because of the disparity in the impact that first-period use of the antibiotic drug has on its own effectiveness and that of the potentially rival antibiotic, increasing first-period output actually increases the profitability of the second-period market for the rival firm [11]. The entry conditions at (24a) and (24b) induce different partitions of the set of possible values for X contingent on the level of entry costs.

When $R < \frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2$, the relevant partition is:

$$\mathbb{X}_A = \left\{ X \,|\, X < \widetilde{X}(R) = \frac{\alpha - c}{\phi} - \frac{2(\beta R)^{\frac{1}{2}}}{\phi} \right\} \tag{29a}$$

$$\mathbb{X}_D = \left\{ X \,|\, \widetilde{X}(R) = \frac{\alpha - c}{\phi} - \frac{2(\beta R)^{\frac{1}{2}}}{\phi} \leq X \right\} \tag{29b}$$

When $R \geq \frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2$, the relevant partition is instead:

$$\mathbb{X}_A = \left\{ X \,|\, \widetilde{X}_L(R) = \frac{3(\beta R)^{\frac{1}{2}}}{\theta - 2\phi} - \frac{\alpha - c}{\theta - 2\phi} < X < \frac{\alpha - c}{\phi} - \frac{2(\beta R)^{\frac{1}{2}}}{\phi} = \widetilde{X}_H(R) \right\} \tag{30a}$$

$$\mathbb{X}_D = \mathbb{X}_{D,L} \cup \mathbb{X}_{D,H} = \tag{30b}$$

$$= \left\{ X \,\middle|\, 0 \leq X \leq \widetilde{X}_L(R) = \frac{3(\beta R)^{\frac{1}{2}}}{\theta - 2\phi} - \frac{\alpha - c}{\theta - 2\phi} \right\} \cup \left\{ X \,\middle|\, \widetilde{X}_H(R) = \frac{\alpha - c}{\phi} - \frac{2(\beta R)^{\frac{1}{2}}}{\phi} \leq X \right\}$$

We characterize the solution to the maximization problem (25) by investigating first the values of X that maximize $\Pi_D(X)$ in the domain $\mathbb{X}_D$.

When entry costs are low – so that $\mathbb{X}_D$ is defined by (29b) – $\Pi_D(X)$ is a decreasing function of X in the domain $\mathbb{X}_D$. Therefore, $\Pi_D(X)$ attains its maximum value at the lower bound of $\mathbb{X}_D$ and $\Pi_D^*(R)$ will be an increasing function of R. When entry costs are high and $\mathbb{X}_D$ is defined by (30b), Π_D is a decreasing function of X in the domain $\mathbb{X}_{D,H}$, attaining its (local) maximum level at the domain's lower bound value $\widetilde{X}_H$. Letting $\Pi_{D,H}^*(R)$ indicates the value of the function Π_D

Table 2. Incumbent's optimal strategy with high cross-resistance (ϕ>θ/2)

Entry	Incumbent's profit-maximizing first-period output level	Second-period output at equilibrium
Entry is accommodated if $R < \overline{R}$	$X^* = \frac{\alpha-c}{2\beta}\frac{9\beta^2 - 2\beta(2\theta-\phi)}{9\beta^2 - (2\theta-\phi)^2}$	$x^* = \frac{\alpha-c}{3\beta} - \frac{(2\theta-\phi)X}{3\beta}$, $y^* = \frac{\alpha-c}{3\beta} - \frac{(2\phi-\theta)X}{3\beta}$
Entry is pre-empted if $\overline{R} \leq R < \overline{\overline{R}}$	$X^* = \frac{\alpha-c}{2\phi-\theta} - \frac{3(\beta R)^{\frac{1}{2}}}{2\phi-\theta}$	$x^* = \frac{2\theta(\beta R)^{\frac{1}{2}} - (\theta-\phi)(\alpha-c)}{2\beta\phi}$
Entry is blockaded if $R \geq \overline{\overline{R}}$	$X^* = \frac{\alpha-c}{2\beta+\theta}$	$x^* = \frac{\alpha-c}{2\beta+\theta}$, $y^* = 0$

Source(s): Table by author

at its local optimum over domain $\mathbb{X}_{D,H}$, it can be seen that $\Pi^*_{D,H}(R)$ will also be an increasing function of R.

Note further that $\Pi_D(X)$ is an increasing function of X in the domain $\mathbb{X}_{D,L}$ as long as $\widetilde{X}_L(R) < \frac{\alpha-c}{2\beta+\theta}$. When R is large enough, $\widetilde{X}_L(R) \geq \frac{\alpha-c}{2\beta+\theta}$ so we can conclude that $\Pi_D(X)$ attains its maximum value over domain $\mathbb{X}_{D,L}$ when $X = min\left(\widetilde{X}_L;\ \frac{\alpha-c}{2\beta+\theta}\right)$. Thus, $\Pi^*_{D,L}(R)$ is an increasing function of R for $\frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2 \leq R < \widehat{R}$ and independent of R when $R \geq \widehat{R}$, where $\widehat{R} = \frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2\left\{2\frac{\beta+\theta-\phi}{2\beta+\theta}\right\}^2$ is defined as the value of entry costs such that $\widetilde{X}_L(R) = \frac{\alpha-c}{2\beta+\theta}$. Note that entry is blockaded when $R \geq \widehat{R}$.

It can be shown that $\Pi^*_{D,L}(R) \geq \Pi^*_{D,H}(R)$ when $R \geq \overline{R}_L = \frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2$ where $\overline{R}_L$ is a threshold value dependent on the model parameters (see Appendix C). Accordingly, we can define the function $\Pi^*_D(R)$ as follows:

$$\Pi^*_D(R) = \begin{cases} \Pi^*_{D,H}(R) & for\, R < \overline{R}_L \\ \Pi^*_{D,L}(R) & for\, R \geq \overline{R}_L \end{cases} \tag{31}$$

Having characterized the two functions $\Pi^*_{D,H}(R)$ and $\Pi^*_{D,L}(R)$ as increasing functions of R, we can therefore conclude that $\Pi^*_D(R)$ will also be an increasing function of R. Moreover, we know that the optimal level of first period output choice for an incumbent who wished to deter entry will switch from $\widetilde{X}_H(R)$ to $\widetilde{X}_L(R)$ as R rises above the threshold value at (31). For high entry costs, deterrence will be pursued by restricting first period output below the level that would be chosen by an unthreatened monopolist, rather than by expanding it. Will the incumbent wish to deter entry?

As noted in previous cases, the answer is yes under certain conditions. Note that when $R = 0$ the highest level of profits consistent with accommodating the rival's entry will occur at an interior optimum over $\mathbb{X}_A$, namely at $X = \frac{\alpha-c}{2\beta}\frac{9\beta^2-2\beta(2\theta-\phi)}{9\beta^2-(2\theta-\phi)^2}$. As R increases, the domain $\mathbb{X}_A$ will shrink so that the maximum level of profits attainable while allowing the rival's entry will decrease once the interior optimum will be outside of $\mathbb{X}_A$. Even in this case then, the function $\Pi^*_A(R)$ is a (weakly) decreasing function of R. Accordingly, there is a threshold level of $\overline{R} \geq \overline{R}_L$ of entry costs such that $\Pi^*_D(R) \geq \Pi^*_A(R) \Leftrightarrow R \geq \overline{R}$. Deterrence will occur by underproducing output or entry will be blockaded when $R \geq \widehat{R}$ (see Figure 5).

We summarize these results in the following proposition.

Proposition 4. When bacterial cross-resistance to the potential entrant's drug is substantially lower than own-resistance to the incumbent firm's drug, the incumbent firm will either accommodate entry or deter it. There is a threshold level of entry costs $\overline{R}$ such that entry is accommodated whenever $R < \overline{R}$, and deterred when $R \geq \overline{R}$. When entry is deterred, the incumbent will choose first-period output below the optimal two-period monopolist level. More precisely:

(1) if $R \geq \widehat{R} = \frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2\left\{2\frac{\beta+\theta-\phi}{2\beta+\theta}\right\}^2 > \overline{R}$, *entry will be blockaded and first-period output will be set at* $X = \frac{\alpha-c}{2\beta+\theta}$.

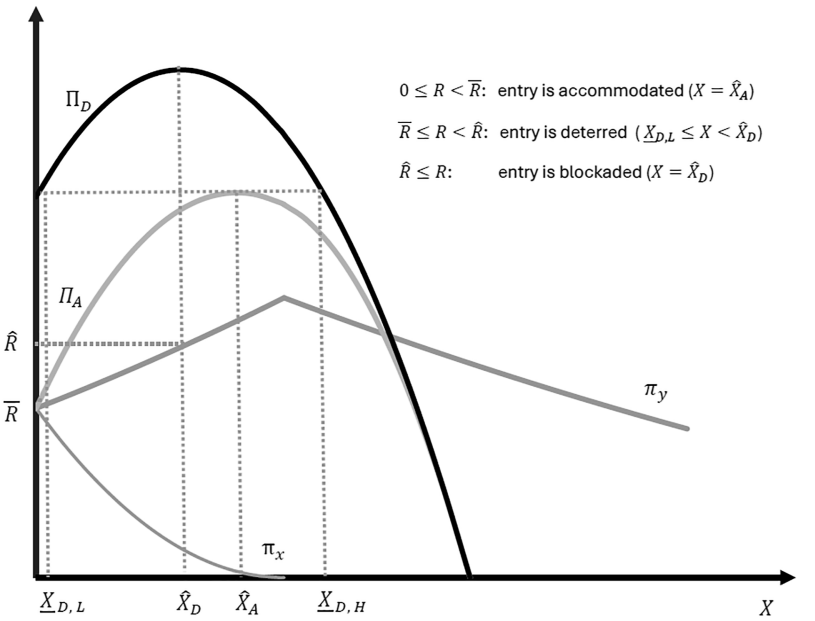

Figure 5. Incumbent's optimal strategy under threat of entry by low cross-resistance differentiated rival.
Source(s): Figure by author

(2) If $max\left\{\overline{R}_L, \frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2\right\} \le R < \frac{1}{\beta}\left(\frac{\alpha-c}{3}\right)^2\left\{2\frac{\beta+\theta-\phi}{2\beta+\theta}\right\}^2$*, entry will be deterred by setting first period output at* $X = \widetilde{X}_L(R) = \frac{3(\beta R)^{\frac{1}{2}}}{\theta-2\phi} - \frac{\alpha-c}{\theta-2\phi} < \frac{\alpha-c}{2\beta+\theta}$

The basic results of this section of the paper are presented in Table 3 below.

We conclude this section by summarizing the main results and relating them to the proposed social benefits of a policy of extended patent protection for antibiotic drugs.

As is well known in the industrial organization literature, incumbents can deter entry by reducing the size of the prospective market for entrant firms. In the market for antibiotics, this would require reducing the effectiveness of the potential entrant's antibiotic drugs and hence the demand for such drugs. Our model shows that this can only happen when the entrant's antibiotics are either (1) generic versions of the incumbent firm's drugs or (2) novel antibiotics

Table 3. Incumbent's optimal strategy with low cross-resistance (ϕ<θ/2)

Entry	Incumbent's profit maximizing first-period output level	Second-period output at equilibrium
Entry is accommodated if $R < \overline{R}$	$X^* = \frac{\alpha-c}{2\beta}\frac{9\beta^2-2\beta(2\theta-\phi)}{9\beta^2-(2\theta-\phi)^2}$	$x^* = \frac{\alpha-c}{3\beta} - \frac{(2\theta-\phi)X}{3\beta}$, $y^* = \frac{\alpha-c}{3\beta} - \frac{(2\phi-\theta)X}{3\beta}$
Entry is pre-empted if $\overline{R} \le R < \widehat{R}$	$X^* = \frac{3(\beta R)^{\frac{1}{2}}}{\theta-2\phi} - \frac{\alpha-c}{\theta-2\phi}$	$x^* = \frac{2(\theta-\phi)(\alpha-c)-3\theta(\beta R)^{\frac{1}{2}}}{2\beta(\theta-2\phi)}$
Entry is blockaded if $R \ge \widehat{R}$	$X^* = \frac{\alpha-c}{2\beta+\theta}$	$x^* = \frac{\alpha-c}{2\beta+\theta}$

Source(s): Table by author

whose quality differentiation from the incumbent is modest ($\phi > \theta/2$). Overproduction is not an effective means of deterring entry by rival firms whose novel drugs are subject to low levels of bacterial cross-resistance ($\phi < \theta/2$). Under these conditions, overproduction widens the prospective quality gap and increases the entrant's prospective profits from entry. Instead, when entry costs are large enough, the incumbent can deter entry by moderating the prospective quality gap, i.e. by underproducing during the life of the patent.

Based on these insights, it is important to note the limitations of policy proposals recommending stronger patent protection of antibiotic drugs as a means to reducing their current use and conserving their effectiveness for future use. To the extent that stronger patent protection would blockade rivals' entry by legal means, the desired reduction of current use would only occur under conditions wherein entry would otherwise be accommodated or deterred by promoting overuse (as shown in Figure 6). When entry would be deterred by restricting current use, stronger patent protection would lead to greater current use. Moreover, a legal blockade would deny the benefits of the development of novel antibiotics by rival firms. Such benefits would obviously be greatest for drugs subject to lower bacterial cross-resistance. The balance of these effects cannot be determined a priori and evaluating them falls outside the scope of the current paper.

Among the limitations of the model, we highlight three. First, the model has characterized the behavior of an incumbent confronting a single entrant under the assumption that the level of bacterial cross-resistance to the rival antibiotic is known or predicted accurately. In future work, we plan to extend the model to analyze the strategic behavior of an incumbent facing multiple entry threats. It is noteworthy that output decisions protecting the incumbent from entry by one type of rival will not deter entry by different types of rivals. Depending on the distribution of entry threats confronting it, the incumbent may face a trade-off between deterring the entry of generic (or minimally differentiated) rivals and deterring that of more effective ones.

A second related limitation concerns the strategic behavior of potential entrants. The model presumed that a set level of bacterial cross-resistance was an exogenous feature of the potential entrant's R&D program. An important extension of the model would be to consider how

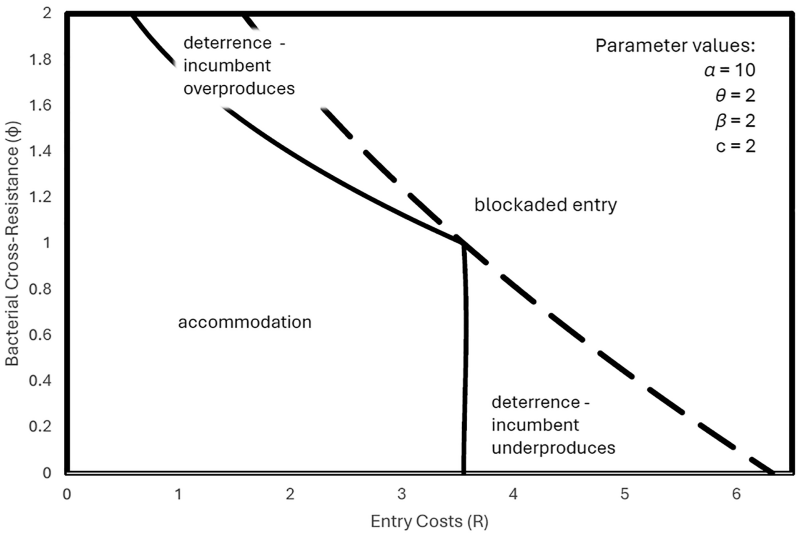

Figure 6. Effects of bacterial cross-resistance and entry costs on incumbent's optimal strategy. **Source(s):** Figure by author

entrants would choose among R&D programs varying both in costs and in terms of the prospective level of bacterial cross-resistance that the resulting drugs will be subject to. These choices are influenced by many factors, possibly including the strategic behavior of incumbent sellers of antibiotics.

The third limitation concerns the assumption of Cournot competition in the market for antibiotic drugs. It is evident that post-entry profitability depends on the pattern of competition between incumbent and entrant firms. In a repeated entry game, deterrence could be achieved by credible threats of aggressive pricing. Some of the empirical evidence on the availability of off-patent antibiotics suggests that indeed profit margins in these markets may be too thin to attract entrants or even to ensure an adequate supply to the market (World Health Organization, 2019). A richer characterization of the strategic options of incumbent firms will be sought in future research.

5. Conclusions: the policy case for stronger patents on antibiotics reconsidered

Renewed interest for the use of stronger patents as a policy to both promote the development innovative antibiotics and slow down the onset of bacterial resistance to them demands a reconsideration of the policy's analytical foundations. While there seems to be no doubt that longer lasting and broader patent protection (or, alternatively, a period of market exclusivity) would increase the incentive to innovate, the effect of such policies on the output decisions of the patent holder are not so clear-cut when their relation to the threat of entry by other antibiotics is accounted for.

In an admittedly simplified two-period model, we show that the strategic actions that an incumbent would undertake to deter entry by rival drugs do depend on the relationship between bacterial resistance to the incumbent's and the entrant's drugs. We show that under conditions wherein an incumbent would deter entry by a more effective rival drug (that is, one subject to low bacterial cross-resistance), the effect of preempting entry by legal means would be to induce the incumbent to promote greater use of its own antibiotic drug. Thus, stronger patents on antibiotic drug innovations could end up both preempting further development of novel and more effective antibiotics and promoting greater use of the *first generation* of novel antibiotics whose development such patent policy could promote.

The theoretical model suggests the following policy implications. Extending the duration of protection for narrowly defined patents on novel antibiotics such as to delay or preempt by legal means the entry of generic versions of innovative antibiotics may indeed increase the prospective profits for innovators and induce them to deplete their antibiotic drugs' effectiveness more slowly. Broadening the scope of protection for such long lasting patents would have negative consequences on future incentives for developing more effective antibiotics and possibly promote faster depletion of those already developed.

In light of the oft-remarked weakness of the incentives for the development of novel antibiotics, the long-term impact of a policy increasing the duration of patent protection for antibiotic drugs is uncertain. Further, holding out the promise of broader patent protection (or equivalently of market exclusivity grants) as an incentive for innovation would run counter to the public interest in promoting the creation and management of a pool of first-, second-, and third-line antibiotics for treating bacterial infections. Other mechanisms for offering a financial reward to companies bringing new antibiotics to market would likely be more effective interventions considering the dual policy goals of promoting innovation and conservation. Examples include subscription models (Barlow, Morton, Megiddo, & Colson, 2022) and antibiotic susceptibility bonuses (Morel *et al.*, 2020).

A virtue of these approaches is that they bundle the rewards for innovators to a more direct public control over the use of the novel antibiotics. This control holds the promise of correcting the overuse and misuse of antibiotics that results from relying on the market as a means for allocating antibiotics. Policy interventions that merely strengthen the patent rights of

innovators are unlikely to address the fundamental misalignment between the social value of antibiotic use and the users' willingness and ability to pay.

Notes

1. Policies of this kind include stewardship programs incentivizing hospitals and prescribing physicians to moderate the use of antibiotics and bans on the use of antibiotics as a growth stimulant in farm animals (Patel, Wellington, Shah, & Ferreira, 2020). While the use of antibiotics in animal production has been often identified as a major driver of the antibiotic crisis, Adda (2020) finds the influence of human use of antibiotics to be a more significant contributor.
2. Outterson (2005) lays out the case against the use of stronger patent rights in response to the crisis of antibiotic resistance. Schulman (2009) argues that extensions of the patent term would be ineffective because pharmaceutical firms' concerns with short-term financial health promote overuse of existing antibiotics regardless of the duration of patents.
3. Hollis and Maybarduk (2015) present an overview of policy responses to the antibiotic resistance crisis from the analytical perspective of the "tragedy of the commons".
4. Should entry be profitable, it can be expected to accelerate the decline of an antibiotic drug's effectiveness as prices decline and usage increases (Horowitz & Moehring, 2004). However, the evidence regarding the effects of generic entry on the overall use of individual types of antibiotic drugs is not strongly supportive (Kållberg *et al.*, 2021).
5. Bacterial cross-resistance to various antibiotics within a class is known to vary so a novel drug reaching the market at the end of an incumbent's patent life may still benefit from a quality advantage over the incumbent if bacterial cross-resistance to it is not as strong as resistance to the incumbent drug (own-resistance). Indeed, a growing body of evidence suggests that bacteria that develop resistance to a class of drugs may become more susceptible to the antibiotic effect of other drugs. Biology and public health specialists have noted the possible benefits of identifying *collateral sensitivity* networks of drugs for designing effective cycling protocols (Imamovic & Sommer, 2013; Aulin, Liakopoulos, van der Graaf, Rozen, & van Hasselt, 2021).
6. We are ignoring the very real possibility of differentiation between branded and generic drugs in order to focus exclusively on the implications of antibiotic resistance. There is otherwise a robust empirical literature substantiating the claim that branded and generic versions of antibiotics (as well as other drugs) are not perceived as perfect substitutes in the marketplace. Excellent examples of this line of work are Ellison, Cockburn, Griliches, and Hausman (1997) and Kaier (2013).
7. The model presented below will treat the degree of cross-resistance or collateral sensitivity of the potential entrant drug as an exogenous parameter. In future research the value of this parameter will be treated as an endogenous variable chosen by the prospective entrant under plausible conditions regarding the relation between research costs and degree of effectiveness of the new antibiotic.
8. Throughout the paper we assume that consumers ignore the effects of first-period consumption of an antibiotic on its second-period effectiveness.
9. We can note that if entry were costless, then preemption would not be viable (the set $\mathbb{X}_D$ would be empty, and entry would be accommodated).
10. The maximum value of the function Π_E occurs at the lower bound of $\mathbb{X}_E$, $X = (\alpha - c)/\theta$. Even then, since $\theta \leq \beta$, it would be possible to increase profits by restricting output to the level $X = (\alpha - c)/2\beta$, regardless of whether or not entry would follow.
11. This is the case at least until first period output is so large as to make the incumbent firm's drug insufficiently effective during the second period for the incumbent to be active in the market (that is, $X \geq \frac{\alpha - c}{2\theta - \phi}$).

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Supplementary material

The supplementary material for this article can be found online.

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