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The Economics of Antibiotics: An Exploratory Study

*Sara Fisher Ellison and
Judith K. Hellerstein*

ANTIBIOTICS ARE ARGUABLY the most effective class of drugs ever developed. Before the advent of antibiotics, bacterial infections such as tuberculosis and pneumonia were leading killers of adults, and children routinely died of such bacterial infectious diseases as tuberculosis, meningitis, pertussis (whooping cough), scarlet fever, and rheumatic fever. The introduction of penicillin in clinical use in the 1940s marked the beginning of our ability to fight bacterial infections. During the 1950s and 1960s, the development of amoxicillin, erythromycin, tetracycline, cephalosporins, and other broad spectrum antibiotics furthered this process, as has the more recent development of other broad spectrum antibiotics such as fluoroquinolones. Antibiotics, together with advances in vaccines against some bacterial infections, have significantly reduced childhood morbidity and mortality. Indeed, of the above-listed childhood diseases, only meningitis continues to be a real threat to children in the United States.

Antibiotics differ from other prescription drugs in their pharmacological characteristics, of course, as well as in their regulatory treatment and in the way demand for their use arises. All of these factors contribute to explaining today's market structure for antibiotics, one with many unusual characteristics that distinguish it from the market structures for other pharmaceuticals. In particular, as we argue in detail below, incen-

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tives for pharmaceutical companies to innovate and develop new antibiotics are different from incentives to develop drugs that do not treat infectious diseases.

In this chapter, we contribute two main findings that may differ from the conventional wisdom about antibiotics. First, we conduct a detailed analysis of wholesale price growth over the last decade in one large class of antibiotics. As part of this analysis, we consider how wholesale prices have differed across various retail markets to which they are sold in order to get a sense of how the changing market for pharmaceuticals may be affecting prices. We also compare our price indexes to the comparable official government price index for the class of antibiotics that we consider. Our main finding is that prices have been growing very slowly even in nominal terms, much more slowly than official government statistics suggest. This should be good news for consumers of antibiotics.

Second, we consider how innovation of new antibiotics may be affected by the growth of antibiotic-resistant bacteria. We demonstrate that because of drug resistance, innovation of new antibiotics may be less than would be optimal for society in a way that has not previously been demonstrated. So although the fact that prices of existing antibiotics have not been increasing over the last decade is good news for consumers, the growth of drug resistance and its impact on innovation may be bad news.

Institutional Facts about Antibiotics

Antibiotics are different from other prescription drugs along many dimensions, all of which affect the various competitive aspects of this market including pricing and research and development. First, the Food and Drug Administration approval process for antibiotics is different from that for other drugs. Approvals for new and generic antibiotics have always been granted by a different branch of the FDA than have those for other drugs. Because the production process for early antibiotics essentially was as easy as following a recipe, the FDA was not as concerned with quality control for generic antibiotics as it was with other classes of drugs.¹ As a result, approval for generic antibiotics has always been reasonably easy to obtain. This situation, coupled with the fact that some early antibiotics never had patent protection, has resulted in higher market penetration of generic antibiotics relative to other types of

1. See Hellerstein (1995) for more on the FDA approval process for antibiotics.

drugs.² In addition to price competition resulting from generic penetration, there may also be price competition across different types of antibiotics, since many different antibiotics are often indicated for use against the same bacteria. Evidence on this is somewhat weak, however.³ The efficacy and success of antibiotics also set them apart from other drugs. Before the advent of antibiotics, bacterial infections such as tuberculosis, pneumonia, and typhoid fever were leading killers of people worldwide. By the mid-1980s, however, these infections either were cured easily by readily available (and inexpensive) antibiotics or had been virtually eradicated in the developed world. The success of antibiotics was so great that the public largely believed the war against bacterial infections had been won. It is not surprising, then, that public and government attention has focused on more contemporary killers, such as AIDS and cancer. Moreover, with perceived fierce generic price competition and the impressive efficacy of inexpensive and effective antibiotics, it is equally unsurprising that pharmaceutical manufacturers may have found little reason recently to allocate scarce R&D resources to the development of antibiotics.

It is difficult to obtain direct or indirect empirical evidence on how incentives to pharmaceutical companies to invest in R&D in antibiotics have changed. An informal telephone survey of major U.S. and Japanese pharmaceutical companies conducted during a workshop sponsored by the National Institutes of Health found that half of the firms had reduced or completely phased out research on antibiotics.⁴ This is not to say that no research is being done. Some companies have been reported to be beginning new research initiatives to combat the problem of resistant bacteria.⁵ Data from the FDA for the past thirteen years show no discernible trend in approvals of new antibiotics, but the sample sizes are small—the average number of approvals per year is two. Moreover, with the lag in time from the beginning of development of a drug to its eventual FDA approval, it is not clear what time frame to consider when thinking about how innovation has changed.

Pricing Patterns

Long-term price trends are one of the most important features to consider when examining the economics of antibiotics. The last decade

2. Hellerstein (1995).

3. Ellison and others (1997).

4. Tomasz (1994).

5. "Drug Makers Go All out to Squash 'Superbugs' (1996).

has been a particularly interesting one for pharmaceuticals in general and antibiotics in particular. The most important and salient change over this period has probably been the phenomenal restructuring of health care in this country with a marked shift toward managed care.⁶ Whereas in the mid-1980s relatively few patients had outpatient insurance coverage of pharmaceuticals, managed care drug benefits of one type or another have become increasingly prevalent. As pharmaceuticals have been increasingly included in patients' benefit packages, much of the decisionmaking about the type of prescription written and dispensed has shifted from the physician and patient to the managed care company. In addition to managed care growth, there has been some change in this period in state laws requiring pharmacists to dispense lower-priced generic versions of drugs. Finally, there has been growing public awareness of antibiotic resistance over the past two or three years. With these changes in mind, we examine prices across different types of manufacturers and across different markets, or "channels of distribution," to get a better sense of whether these changes may lead to changes in the competitive structure of the antibiotics market.

The retail price of a course of an antibiotic to treat a typical adult bacterial infection ranges from around \$10 for generic amoxicillin, an old off-patent antibiotic, to around \$50 for Zithromax, a new on-patent antibiotic, and around \$80 for Ceclor, the branded version of cefaclor, a drug that only recently went off patent and has a very complicated and expensive manufacturing process. A course of generic cefaclor sells for around \$55. We do not have any information on the extent of markups in antibiotics. Even with information on marginal costs, it is difficult to know whether and how to account for the large fixed costs of R&D when calculating markups. Perhaps the best way, then, to decide whether antibiotics are inexpensive (relative to their value to consumers) is to note the willingness of physicians and patients to use antibiotics inappropriately. For example, one study reports that in a careful analysis of the impacts of health insurance on utilization, approximately 16 percent of antibiotics prescriptions filled were indicated for treating viral infections, where there is no evidence that they are effective.⁷ Moreover, this occurred frequently even in cases when patients had to pay copayments for their prescription drugs, so people are willing to pay for antibiotics that may not help them.

6. "A Shift of Power in Pharmaceuticals" (1994); "The Changing Environment for U.S. Pharmaceuticals" (1993).

7. Newhouse and Insurance Experiment Group (1993).

In order to calculate price indexes, we use two data sets. Our first data set, collected by IMS America, contains wholesale quantities and revenues of all prescription antibiotics sold in the United States from October 1985 to December 1991. These quantities and revenues are those from transactions between manufacturers or distributors and two separate groups of retailers: hospitals and retail pharmacies. The data are at the level of presentation for each pharmaceutical product.⁸ Our second data set, also collected by IMS America, has a similar structure but covers the months September 1990 through August 1996. The other main difference is that after January 1992 the data in this second set are divided into a richer group of retailers, or channels of distribution: federal facilities, clinics, HMOs, nonfederal facilities, chain drugstores, independent drugstores, food stores, and long-term care.⁹ Note that the definition of "hospitals" in the first data set corresponds closely to that of "nonfederal facilities" in the second and that "retail pharmacies" corresponds to the sum of "independent drugstores," "chain drugstores," and "food stores."

We examine in detail price growth in one important subclass of antibiotics, cephalosporins.¹⁰ The first cephalosporin, cephalixin, was introduced by Eli Lilly in 1971 under the brand name Keflex. Other so-called first generation cephalosporins, such as cefadroxil and cephadrine, entered soon thereafter. Now in existence are second and third generation cephalosporins, so classified because of similarities in their molecular structures. Our data sets contain a total of twenty-four chemically distinct cephalosporins.

We focus on cephalosporins for a number of reasons. First, it is a large and important subclass of antibiotics. For example, over the six years ending in August 1996, cephalosporins comprised approximately 40 percent of total revenues of antibiotics in the United States.¹¹ Second, it is a subclass of antibiotics that is active against a wide range of bacteria, indicated for a wide range of infections, used in many different clinical settings, and sold in all different channels of distribution. Given this, we

8. A presentation is a particular choice of packaging and dose-form for a product, for example, 150 mg coated tablets in bottles of 100, or 25 ml of 5 percent aqueous solution in a vial for intravenous injection. A drug will often be sold in many presentations simultaneously.

9. Note that the category for HMOs only includes prescriptions dispensed at HMO-owned hospitals and pharmacies, not prescriptions dispensed elsewhere but paid for by an HMO drug benefit. The HMO channel of distribution, then, reflects only a small portion of the influence that HMOs and other managed care have had on pharmaceutical purchasing.

10. The name is derived from the Greek island of Cephalos, where antibiotic activity was observed in isolates from shellfish.

11. Authors' calculation.

can examine pricing patterns in all channels of distribution from which IMS collects data and be fairly confident that our findings for cephalosporins are not special to a particular clinical or market setting. In addition, cephalosporins are a group of drugs in which innovating manufacturers are quite important, in part because cephalosporins are among the newer antibiotics (relative to, say, penicillins), but have also been subject to generic entry. Finally, cephalosporins is a subclass that has been analyzed in the economics literature previously.¹²

To look at broad pricing patterns, we need to aggregate over the thousands of products for which we have data. We do this by computing monthly price indexes where the index is calculated as the weighted sum of price changes for all presentations sold in a month. In particular, we compute Tornqvist price indexes using as weights the average revenue share of each presentation in the two months for which we calculate the price change.¹³ Tornqvist indexes have the advantage (over, for example, traditional fixed-weight Laspeyres indexes) that the weights are allowed to vary from month to month as different drugs lose or gain relative importance in the market. In addition, new drugs can enter the price index in their second month, which is the first month for which one can compute a price change.

Price indexes usually start at one in the first month of the data, but we are interested not just in price growth over the period of our two data sets but also in differences in the levels of prices across the different channels of distribution. We therefore normalize our price indexes to reflect relative price differences across markets. For example, in the first data set, which begins in October 1985, we start the price index for cephalosporins sold to hospitals at a base price of 1.00, but we normalize the pharmacy price index to start at a base price of 1.26. To compute this figure of 1.26, we calculate a weighted sum of the price ratios of all the presentations sold to both pharmacies and hospitals. The weights are total revenues (in pharmacies and hospitals) of each presentation as a share of the total across all identical presentations. As our results show, normalizing the

12. See, for example, Griliches and Cockburn (1994); Ellison and others (1997).

13. The Tornqvist price index calculated for N products in a month t is

$$I_t = \exp \left(\sum_{n=1}^N s_{nt} \log \left(\frac{P_{nt}}{P_{n,t-1}} \right) \right) I_{t-1},$$

where P_{nt} is the price of the n th product in month t , $s_{nt} = 0.5(s_{nt} + s_{n,t-1})$, Q is quantity, and

$$s_{nt} = \frac{P_{nt} Q_{nt}}{\sum_{n=1}^N P_{nt} Q_{nt}}.$$

indexes in this way is important to understanding the pricing patterns of wholesale cephalosporins.

Figure 4-1 contains the summary findings of our price index calculations. We calculate an overall Tornqvist price index for all cephalosporins and compare our index to the official producer price index for cephalosporins. We find an overall annual average growth rate (AAGR) of prices for cephalosporins over the period January 1988 to August 1996 of 0.76 percent. (We report the index over this period because the Bureau of Labor Statistics [BLS] only started computing a producer price index for cephalosporins in January 1988.) Note also from the figure a pronounced fall of the index over more recent months.

The AAGR of the BLS official producer price index for cephalosporins over this period is markedly different at 4.54 percent.¹⁴ These basic results are consistent with other literature addressing upward biases in the BLS's price index calculations for pharmaceuticals.¹⁵ By virtually any standard, the increase we find in the price of cephalosporins is modest and suggests that there have been significant competitive pressures to keep price increases low over this period.¹⁶

There are three possible reasons why our price index for cephalosporins differs so dramatically from the official BLS price index.¹⁷ First, our index incorporates new products immediately, whereas the BLS only does so every four to seven years.¹⁸ Second, our index allows for changing weights to reflect changing revenue shares of products. Third, our data are a near census of sales made by both manufacturers and distributors, whereas the BLS uses only a sample of products, and that sample is only from production facilities.

A formal examination of the BLS price index for cephalosporins is beyond the scope of this chapter.¹⁹ Although we cannot mimic the BLS's

14. Even the official rate of overall inflation as reflected in the consumer price index over this period was much higher than our figure, with an AAGR of 3.55 percent.

15. Baye, Maness, and Wiggins (1990); Berndt, Griliches, and Rossett (1993); and Griliches and Cockburn (1994).

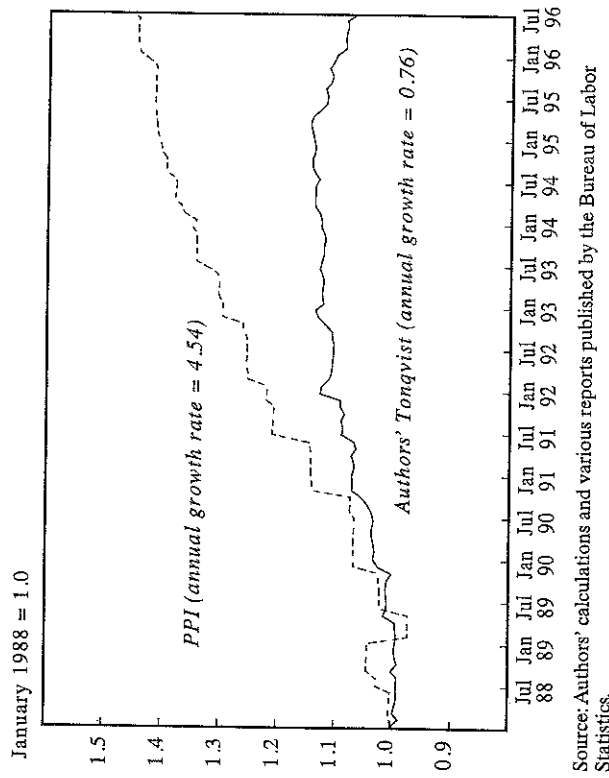
16. We have not completed as comprehensive a study of the prices of other antibiotics, but computation of a general price index for each of penicillin, erythromycin, trimethoprim, and chloramphenicol suggests similarly slow price growth.

17. For a summary of the BLS's procedures in calculating the producer price index, see *BLS Handbook of Methods* (1997).

18. During our sample period, the BLS resampled pharmaceutical products over the course of 1987 and again over 1992. Recently, the BLS adopted a procedure to incorporate generics into the price index when they first enter the market. For a summary of this procedure and information on the timing of the introductions of new goods into the PPI for Prescription Pharmaceuticals, see Kanoza (1996).

19. For an analysis of this kind, see Berndt, Griliches, and Rossett (1993).

Figure 4-1. All Cephalosporins Price Indexes



Source: Authors' calculations and various reports published by the Bureau of Labor Statistics.

Laspeyres index methods exactly, we did attempt to mimic BLS procedures in a variety of ways. First, we calculated a modified Tornqvist index, where we incorporated new products only when the BLS did (rather than instantaneously). For this price index, we calculate an AAGR of 1.45 percent from January 1988 to August 1996. We also calculated a fixed-weight Laspeyres index, but again allowed new products to enter when the BLS did. For this index, we obtain a very similar AAGR over this period of 1.39 percent. These alternative price indexes have AAGRs that are somewhat above the AAGR of our preferred Tornqvist index, but still far below the BLS's AAGR of 4.54 percent.²⁰ Therefore, we suspect that most of the difference between our Tornqvist index and the BLS index is due to sampling issues in the choice of products used to construct the BLS index rather than issues related to the frequency of resampling or the adjustment of weights over time. This is

20. On a related note, this exercise implies that differences in price growth between older and newer cephalosporins over the time period of our sample has not been substantial (at least in revenue-weighted terms). Of course, our index does not tackle the "new goods" problem. This is the difficult problem of adjusting for differences in quality-adjusted relative prices of new drugs versus old drugs; our index only captures revenue weighted price growth of existing drugs. For more on this question, see Griliches and Cockburn (1994).

similar to the conclusion of a related study that attributes approximately half of the difference between their Tornqvist index for prescription pharmaceuticals and the BLS index (from January 1984 to December 1989) to sampling problems in the BLS sample.²¹

Figure 4-2 contains information on price indexes we computed separately for cephalosporins sold to hospitals and pharmacies. We combine both of our data sets and report a price index over the entire period from October 1985 through August 1996.²² The price index for sales to hospitals is normalized to begin at a base price of 1 at the beginning of the period, with the price of sales to pharmacies normalized to a higher level (1.26) to reflect differences in relative prices across the two channels.

The striking feature of figure 4-2 is that the prices of cephalosporins sold to drugstores were higher than those sold to hospitals at the beginning of our data and this gap widened over most of the last decade. In fact, hospital prices have been falling slowly but fairly steadily over the period. This is consistent with increased formulary use in hospitals and the resulting downward pressure on drug prices as hospitals bargain with pharmaceutical companies. At the end of our data pharmacy prices do fall, so it is possible that the trend of widening price differentials across the two channels of distribution is beginning to reverse itself. This is consistent, of course, with recent increased bargaining power by pharmacies. It is also consistent with the increasing pressures of managed care to keep prices of drugs sold in pharmacies low and with public pressure over the last few years to reduce prices. We provide further evidence on this below when we disaggregate the data by finer channels of distribution.

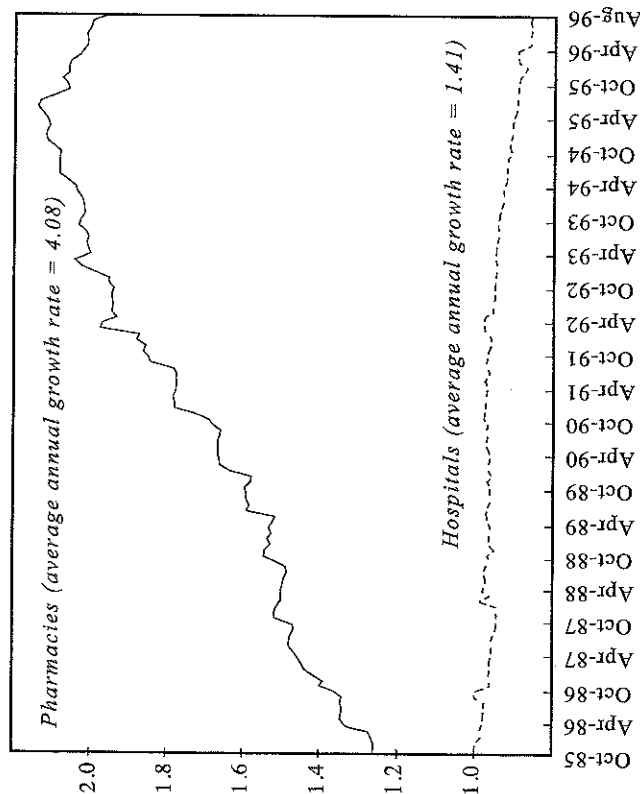
Table 4-1 and figure 4-3 exploit the richer data on channels of distribution that we have in the data since 1992. We compute separate indexes for each of the eight channels. The price of cephalosporins sold to "hospitals" (nonfederal facilities) is normalized to begin at 1 at the beginning of 1992; indexes for sales to other channels are normalized to begin at levels relative to that of hospitals. There is notable variation both in the

21. Berndt, Griliches, and Rosett (1993). We cannot construct a price index for sales made by manufacturers only, which would represent the price index that the BLS sampling methods try to capture. We doubt that the prices of sales by manufacturers have been growing more quickly than sales by distributors, since as we show below, the growth rates of prices of drugs sold to hospitals and chain drugstores are below that of other channels of distribution. We expect that bigger purchasers such as hospitals and chain drugstores are more likely, not less likely, to purchase directly from manufacturers.

22. The new data are linked to the old data at the midpoint of where they overlap, April 1991. We confirmed that during the period in which the old and new data overlap, the pricing patterns are very similar across the two data sets.

Figure 4-2. *Cephalosporins Price Indexes*

Hospitals, October 1985 = 1.0

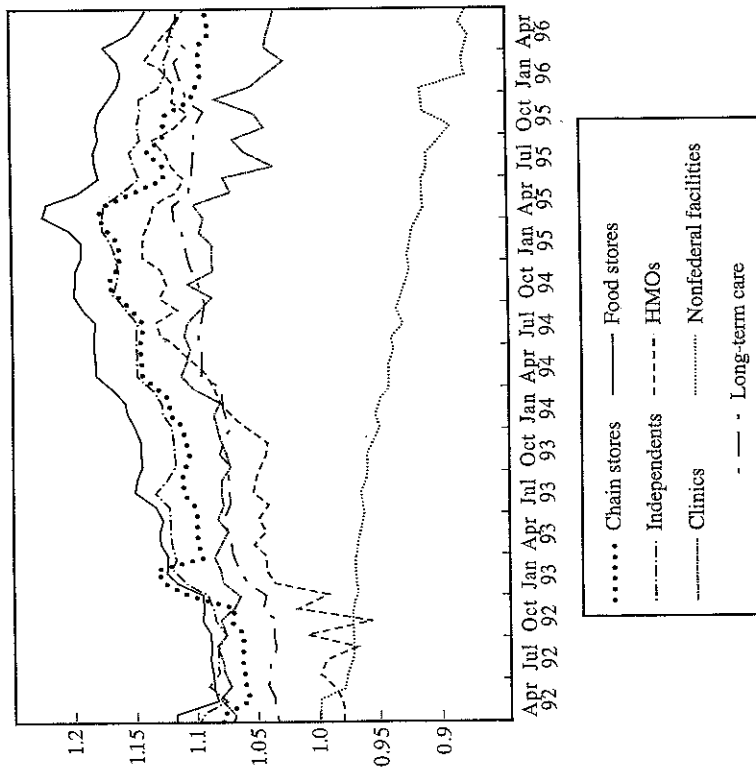


Source: Authors' calculations.

Table 4-1. *Cephalosporins Average Annual Growth Rates, January 1992-August 1996*

| Channel of distribution | Growth rate (percent) | Average monthly revenue (millions of dollars) | Base price |
|-------------------------|-----------------------|---|------------|
| Chain stores | -0.90 | 72.2 | 1.08 |
| Independents | 0.31 | 45.4 | 1.10 |
| Clinics | -0.75 | 3.7 | 1.07 |
| Food stores | 0.40 | 15.2 | 1.12 |
| HMOs | 2.60 | 2.9 | 0.98 |
| Long-term care | 1.52 | 5.2 | 1.03 |
| Nonfederal facilities | -2.68 | 78.9 | 1.00 |
| Federal facilities | -5.41 | 2.7 | 1.01 |

Source: Authors' calculations.

Figure 4-3. *Cephalosporins Price Indexes*

Source: Authors' calculations.

levels of prices and their growth rates across channels.²³ The biggest channels of distribution (in terms of revenue) continue to be nonfederal facilities, and the segment of the pharmacy sector represented by chain drugstores. Of course, the pricing patterns across these two channels of distribution look very similar to those we report in figure 4-2 for the same period.²⁴ Interestingly, the index for cephalosporins sold to independent

23. In figure 4-3, we omit the price index for sales to federal facilities. Prices have been falling dramatically in that small market, and including that price index obscures differences across the other bigger, more interesting channels. Summary statistics on sales to federal facilities do appear in table 4-1.

24. We note that these diverging price indexes are *not* a function of the changing mix of products used in hospitals versus other channels of distribution. When we compute price indexes for only those products sold in hospitals and in each other channel of distribution at the beginning of the period, the price index patterns are very similar.

drugstores closely follows that of chain drugstores, with the exceptions that independent drugstore prices start higher than prices to chains and have fallen recently by less than prices to chain drugstores. The trend in price growth for sales to food stores is similar to that of independent drugstores, but the level of prices is generally slightly higher. Prices to clinics tend also to move with those of independent drugstores but remain at lower levels throughout the period.

Perhaps the most interesting pattern in figure 4-3 is that of HMOs. Prices of cephalosporins sold to HMOs were lower in January 1992 than those sold to any other channel of distribution, but they experienced by far the largest AAGR (2.6 percent), placing HMO prices in the middle of the pack by August 1996.

The patterns reflected in figure 4-3 make it clear that both the level and growth of prices of cephalosporins sold are quite different across finely defined channels of distribution. The fact that prices to chain drugstores have fallen more recently than prices to food stores or independent drugstores is most consistent with increased bargaining power of chain drugstores relative to other types of drugstores. This may, in turn, be partially a function of pressure by managed care companies to reduce prices charged by chain pharmacies with which these companies often contract, pressure that gets transmitted to the wholesale level. The fact that HMO prices start low but experience the steepest AAGR over this period is consistent with the anecdote we hear of large price concessions being given to HMOs a few years ago coupled with a more recent retreat from this practice. The reason for this may be that HMO pharmacies have not become as prevalent as might have been expected a few years ago; today most HMOs have patients fill prescriptions at retail establishments like chainstore pharmacies.

The richness of our data sets allows us to characterize the level and growth of prices of cephalosporins sold to different channels of distribution. These results suggest that the interaction of supply and demand has a measurable effect on relative prices across channels of distribution. The most salient feature of these indexes is the relatively slow growth rate of prices of sales across *all* channels of distribution.

Price changes themselves cannot lead one to draw firm conclusions about the extent to which pharmaceutical manufacturers are making profits on the sale of cephalosporins. This is particularly true in a market like pharmaceuticals, where it is difficult to account for the high research and development costs when analyzing profits. Nonetheless, the fact that prices have been rising only slowly and appear to be rising most slowly in

markets where buyers have bargaining power suggests that, absent dramatic cost decreases of which we are not aware, profit margins for cephalosporins are declining in real terms and may continue to decline as health care markets continue to consolidate. Consumers should perceive this as one positive by-product of market consolidation in health care. Antibiotics, however, may not remain inexpensive and effective forever.

The Public Health and Economic Implications of Antibiotics Use

The very nature of infectious diseases, such as those treated with antibiotics, results in interesting economic and public health characteristics of the use of antibiotics. In particular, there is a positive externality associated with the use of antibiotics. The benefits of an individual's consumption of an antibiotic do not accrue solely to the patient consuming it. One person's consumption of an antibiotic benefits others because it reduces the probability that others will contract the bacterial infection. One result of this positive externality is that one cannot measure the social benefit of antibiotics simply by summing up the benefits that accrue privately to individuals when they consume antibiotics. If an individual's decision to consume an antibiotic is based solely on the private benefits of consuming that antibiotic, the individual will demand too little of that antibiotic relative to what would be optimal for society. Therefore, overall market demand for the antibiotic will be artificially low relative to the social optimum. If demand is too low, prices may be lower than what they would be in the absence of these positive externalities. If prices of antibiotics are too low relative to the social optimum, this could create conditions where the incentives for private pharmaceutical firms to develop new antibiotics will be lower than they would be in the absence of positive externalities.

There are a couple of caveats to the magnitude and effects of these positive externalities. First, to the extent that the decisionmaker for the consumption of antibiotics may be the physician rather than the patient, overall market demand will be determined by physicians' preferences. If physicians care about infection transmission, they may incorporate the positive externality of antibiotics use into their decisions, which may mitigate the problem. To our knowledge, there is no evidence on how the existence of externalities actually affects decisions made by physicians. Second, even if demand for antibiotics is too low, prices may not be lower than socially optimal for two reasons. First, if the market is so competitive that no economic profits are being realized on the sale of pharmaceuticals, prices will be equal to marginal costs no matter what demand is. In

this case, however, there is no incentive to innovate and develop new antibiotics since pharmaceutical manufacturers need to be able to set prices above marginal costs in order to recoup the large R&D costs of new drug development. Second and perhaps more important, there are reasons why in the absence of positive externalities prices may be too high relative to the social optimum, so the positive externalities may actually correct this problem. This could occur if, for example, patients' or physicians' private valuation of aspects of antibiotics such as their broad-spectrum capabilities are higher than social valuation. We return to these points below.

Unfortunately, there are also negative externalities associated with the use of antibiotics. Each use of a given antibiotic increases the probability that a particular bacterial strain will become resistant to that antibiotic, and indeed, given that resistance can be spread across genetically different bacteria, each use of a given antibiotic against a particular bacterium increases the probability that other bacterial strains will become resistant to it. Infectious disease specialists and public health officials have sounded warnings about the perils of drug resistance for years, but these warnings have rarely made it into the public consciousness, or the consciousness of health care practitioners, until recently.²⁵ Pharmaceutical manufacturers have traditionally responded to drug resistance by altering existing antibiotics subtly in ways that thwart resistance temporarily and that may not have been costly to develop. Over time, however, even these new generations of drugs have become ineffectual against certain resistant bacterial strains. As a result of this negative externality, the private demand for antibiotics exceeds what would be socially optimal if individuals properly internalized the social cost of antibiotics use. This is the main social cost associated with "overprescription of antibiotics," where antibiotics are prescribed inappropriately (for example, for viral infections).

Recently, the press has reported on three cases, in Japan, Michigan, and New Jersey, of a strain of staphylococcus aureus that showed an intermediate level of resistance to vancomycin.²⁶ Such reports are of particular concern because vancomycin is considered the "last resort" antibiotic for staph infections, for use when a bacterium has proved resistant to all other antibiotics. No strain of staph had before developed resistance to vancomycin in a clinical setting. Since vancomycin is so powerful and its

25. See "Disease 'Crisis' Predicted" (1996); "Bacteria Repel Antibiotics in N.Y. Hospital Patients" (1996); "Incidence of Drug-Resistant Bacteria Soars since '94" (1997); and Gold and Moellering (1996).

26. "Drug-Resistant Germ Shows up in U.S." (1997); "Drug-Resistant Germ Found" (1997).

role as the last resort antibiotic is so important, attempts are being made to severely restrict its use to avoid bacteria developing resistance to it.²⁷ Such use restrictions may have significant effects on firms' incentives to develop new last resort antibiotics.²⁸

In theory, the existence of these negative externalities might increase incentives for pharmaceutical manufacturers to innovate and develop new antibiotics. First, the existence of overprescription may allow manufacturers to keep prices higher than they would otherwise be, increasing profit margins for antibiotics. Second, the growing frequency of drug resistance should induce manufacturers to develop new antibiotics that are not susceptible to resistance. In practice, however, these incentives may not be high enough to induce firms to invest in large, sunk research and development costs.

It might appear, then, that the positive and negative externalities from the use of antibiotics counteract each other, making it difficult to draw conclusions about what the impact of these externalities is on innovation in antibiotics and whether innovation is too high or too low relative to what it should be. Indeed, the question of how externalities are affecting innovation has been the subject of many recent discussions.²⁹ What has been missed in all of these discussions, however, is one feature of resistance transmission that may actually serve to make the negative externality reinforce the impact of the positive externality, and that therefore may be important for thinking about incentives to innovate and develop new antibiotics.

One way to minimize the negative externality of resistance transmission is to rotate the use of different antibiotics in a particular clinical setting, such as a hospital, so that the bacteria cannot "learn" how to become resistant to any particular drug. If decisionmakers do not properly take into account resistance transmission, they will essentially undervalue the use of variety in the choice of antibiotics in treating bacterial infections. What does this imply about incentives to innovate and develop new antibiotics? More variety is brought about by more innovation, so if society undervalues variety, society will undervalue new antibiotics, meaning that the demand for new drugs will be lower than it

27. A recent report, however, states that CDC guidelines for vancomycin use are being violated routinely ("Wide Overuse of Antibiotic Cited in Study" [1997]).

28. At least two new antibiotics that show action against vancomycin-resistant strains are in the pipeline, however: Synercid by Rhone-Poulenc Rorer, which is currently under review for FDA approval; and Daptomycin by Eli Lilly and Company and Cubist Pharmaceuticals.

29. See U.S. Congress (1995) and the references therein.

should be. This is particularly true if newly developed antibiotics are more expensive than existing drugs and if people would prefer, all else equal, to pay less for drugs.³⁰ The negative externality of undervaluation of variety means that there is less incentive to innovate than there would be in the absence of externalities. So in this case, the negative externality of drug resistance, as captured by undervaluation of variety, actually reinforces the reduced incentives to innovate that are created by the positive externalities of antibiotics use.

To help clarify this idea, we develop in the appendix a simple mathematical model of antibiotics use in society where we incorporate the positive externalities of reduced disease transmission and the negative externalities of the undervaluation of variety in antibiotics use and examine the implications of these externalities on private market demand relative to the social optimum.

Ultimately, whether incentives to innovate are too low or too high relative to the social optimum will depend on a host of factors related to the positive and negative externalities. The magnitudes of these different factors are unknown and should be a key feature of future research. We note that an additional and no less important factor determining incentives to innovate is the magnitude of price competition in antibiotics. As we discuss above, our price indexes do not tell us anything directly about price competition in antibiotics, except to suggest that as consolidation in the delivery of health care continues and decisions about pharmaceutical prescriptions are made by agents with more and more bargaining power (such as hospitals and HMOs), there is likely to be less room for large markups in pharmaceuticals.

Conclusion

The price growth of antibiotics has been very modest over the last decade. Given the institutional history of antibiotics, this may not be surprising, although it is contrary to what government statistics suggest. It is worth noting that the evidence of modest price growth that we find comes solely from computations of traditional price indexes. Since consumers do not care about the intrinsic cost of a given health care treatment but about the cost of treating and curing diseases and maintaining

30. Alternatively, if the new drugs have other positive features that the private market does value, then private demand for new antibiotics will incorporate these positive features but will not fully incorporate the benefits of variety, so demand for the new antibiotic will be lower than it should be.

health, traditional antibiotics price indexes capture only part of the picture. If antibiotics are now being used as substitutes for costlier treatments, such as hospitalization, our traditional price indexes will underestimate the cost savings from using antibiotics to treat bacterial infections.³¹

Normally, low price growth is good news for consumers. There is, however, the potential for very bad news about antibiotics in the not-too-distant future. The growth of drug resistance is generally perceived as a problem for society, but the impact of the negative externality of drug resistance on society has not been fully understood. We present a simple model that illustrates how, contrary to intuition, the positive and negative externalities of antibiotics use may actually reinforce one another and reduce incentives to innovate and develop new drugs that may combat drug resistance. This feature of antibiotics use has been ignored in previous discussions about antibiotics and innovation.

We cannot argue that these factors establish that incentives to innovate in antibiotics are socially suboptimal. Rather, we argue that antibiotics deserve special treatment in discussions of the economics of pharmaceuticals, particularly incentives to innovate, because of their unique economic characteristics. These factors deserve more research and should be kept in mind during policy discussions of potential government involvement in the market for antibiotics, particularly with respect to discussions about public funding of R&D for new antibiotics.

The impact of recent increases in managed care on the structure of the antibiotics market is still unclear. It is likely that price competition will intensify as large managed care companies insist that pharmaceutical companies bid against one another for their business. The effect of the changes in health care on externalities in this market are more ambiguous. Cost containment may induce physicians to disregard externalities to the extent that physicians have to focus more on the private outcomes of patients in their practice. On the other hand, as health systems become more integrated, cost containment may lead to more emphasis on externalities, since effectively they will be internalized by the system. On the private side, cost-sensitive physicians may prescribe antibiotics less often when these prescriptions affect their bottom line, but to the extent that

31. For example, until recently, all very young children with high fevers were routinely hospitalized while awaiting test results to rule out potentially fatal bacterial infections. Only a very small percentage of those hospitalized children actually had a serious bacterial infection. Now, there is an antibiotic (ceftriaxone) that can be given in an outpatient setting to these children while awaiting the test results. The cost savings from eliminating these "rule-out" hospitalizations may be very important in reducing the costs of treating fever in children, but these cost savings are not captured in traditional price indexes, which would solely measure the price growth of ceftriaxone over time.

prescriptions may be a substitute for costlier treatment, such as an office consultation, antibiotics prescriptions could increase.

Appendix: A Model of the Externalities of Antibiotics Use

In the following case of one antibiotic, we examine the countervailing forces of the positive and negative externalities in the simplest setting imaginable. We learn from this case just what ordinary intuition tells us: positive and negative externalities have opposite and offsetting effects on demand, and parameters of the model—how easily resistance is spread, discount factors, and so on—will determine which effect prevails. We offer this case to establish notation and modeling strategy, to make the trade-offs of use of the antibiotic explicit, and to serve as a counterpoint to our results from the case of two antibiotics, by far the more interesting case. In the case of two antibiotics we show the vital importance of introducing variety into the model and find the counterintuitive result that the positive and negative externalities of antibiotics use may actually reinforce rather than cancel out one another.

We have obviously simplified the setting for antibiotics use for modeling purposes, leaving out many important features. We abstract away from a number of the issues critical to the question of innovation in antibiotics, including broad versus narrow spectrum antibiotics, the development of vaccines for use in prevention of bacterial infections, and use of practices that either encourage or inhibit resistance for a given level of antibiotics use.³² As mentioned elsewhere in this chapter, we have chosen to do this because although the interaction between the externalities that our model illustrates has not been previously developed, the other issues related to externalities have been explored.³³ Finally, we have simplified the model itself in many ways in order to ensure tractability and ease of explication, but none of these simplifications (including the two-period, nonoverlapping nature of the model and the functional form assumptions) affects the important intuition.

The Case of One Antibiotic

Consider a two-period world with a population of N individuals who live in period $t = 1$ (and die at the end of the period) and an equally sized population of N individuals who live in period $t = 2$. People are either

32. We do return to a brief discussion of these other issues later.

33. For a comprehensive review, see U.S. Congress (1995).

sick or healthy, and this is known before the consumption decision. All people are endowed with income Y .³⁴ There is a consumption good C with price equal to 1, and one antibiotic with price p . There is no discount rate between the two periods.

When a person alive in period 1 is sick, his utility is defined as

$$(4-1) \quad U(C_1, a_1) = a_1 \left(\alpha + \frac{1}{2} \beta C_1 \right),$$

where a_1 is the level of antibiotic used by the individual and C_1 is his consumption. Note that if the individual uses no antibiotic, utility is 0. The individual alive in period 1 has a budget constraint of

$$(4-2) \quad Y = C_1 + p a_1.$$

For simplicity, assume that in period $t = 1$, all people are sick. The level of antibiotic use, a_1^* , that maximizes utility for each of these N people subject to their budget constraint is:

$$(4-3) \quad a_1^* = \frac{\frac{1}{2} \beta Y}{\beta p}.$$

The addition of the subscript p in equation (4-3) denotes that this is the private (not social) optimal level of antibiotics consumption for period 1 individuals.

In period $t = 2$, however, the probability that an individual is sick is $e^{-rN a_1}$, a decreasing function of the amount of antibiotic used by each individual in the first period.³⁵ This term reflects the positive externality of antibiotic use—when an individual used the antibiotic in period 1, the probability that a person in period 2 will be sick goes down.

Conditional on a person's being sick in period 2, his or her utility function is slightly different than for a period 1 individual:

$$(4-4) \quad U(C_2, a_2 | S_2) = \frac{a_2}{e^{rN a_1}} \left(\alpha + \frac{1}{2} \beta C_2 \right).$$

34. Incomes could differ between the two periods without affecting the results.

35. Since all individuals in period 1 are sick and otherwise identical, they will all choose to consume the same amount of antibiotic.

The extra term in the utility function of sick people in period 2, $e^{-rN a_1}$, is the "resistance effect." This term can be thought of as reflecting the diminished effectiveness of period 2 antibiotic use that comes with drug resistance. Here, r is a constant representing the degree to which extra antibiotic use creates resistance. As the amount of period 1 use of the antibiotic increases, the effectiveness of period 2 antibiotic use, a_2 , goes down and utility decreases as a result. This is the negative externality associated with use of the antibiotic.³⁶

The probability that a period 2 person will be healthy is $(1 - e^{-rN a_1})$, and conditional on being healthy, a person's utility function is

$$(4-5) \quad U(C_2, a_2 | H_2) = \alpha + \frac{1}{2} \beta C_2.$$

So a healthy person in period 2 will not consume any antibiotic.

To summarize, higher period 1 antibiotic use causes lower incidence of illness in period 2, but those illnesses are more serious, require more treatment, and lower utility of those who are sick.

The world ends after period 2. Period 2 individuals, therefore, create no externalities.

Assume now that there is a social planner whose objective function maximizes the sum of individuals' utilities across both periods. The social planner cannot reallocate income across individuals but can determine optimal consumption and antibiotic use for each individual. So the social planner's objective function is

$$(4-6) \quad \begin{aligned} & \max_{a_1, a_2} N a_1 \left(\alpha + \frac{1}{2} \beta (Y - p a_1) \right) \\ & + N e^{-rN a_1} \frac{a_2}{e^{rN a_1}} \left[\alpha + \frac{1}{2} \beta (Y - p a_2) \right] \\ & + N (1 - e^{-rN a_1}) \left(\alpha + \frac{1}{2} \beta Y \right). \end{aligned}$$

Since period 2 individuals create no externalities, the private optimum that period 2 individuals will choose is equivalent to the social planner's

36. One could augment the model to allow for the possibility of death prior to consumption, where the probability of death would increase with drug resistance. This is done in Garber (1982), where antibiotics are assumed to be costless. Here, adding in death as an outcome does not change the signs of the results of the model, but the fact that there is a cost to antibiotic use in this model makes it difficult to incorporate death and still obtain closed form solutions.

optimum. Period 2 decisions about consumption and antibiotic use can then be left aside, and the decision variable of interest becomes antibiotic use in period 1. Since individuals are identical, the social planner can solve the problem by choosing the optimal antibiotic use for any one individual. The first order condition for the socially optimal level of antibiotic use for each person in period 1 is the a_{1s}^* that solves

$$(4-7) \quad \alpha + \frac{1}{2}\beta Y - \beta p a_{1s}^* - N(1+r)e^{-N(1+r)a_{1s}^*} \\ \left[a_2 \left(\alpha + \frac{1}{2}\beta(Y - p a_2) \right) + N e^{-N a_{1s}^*} \left(\alpha + \frac{1}{2}\beta Y \right) \right] = 0.$$

Rearranging the first order condition in equation (4-7) yields:

$$(4-8) \quad \frac{\alpha + \frac{1}{2}\beta Y}{\beta p} = a_{1s}^* + \left(\frac{1}{\beta p} \right) N e^{-N a_{1s}^*} \\ \left[(1+r)e^{-r N a_{1s}^*} \left(a_2 \left(\alpha + \frac{1}{2}\beta(Y - p a_2) \right) \right) - \left(\alpha + \frac{1}{2}\beta Y \right) \right].$$

Note that the term on the left side of equation (4-8) is the private optimum, a_{1p}^* . Whether the social optimum, a_{1s}^* , will be smaller or larger than the private optimum depends on the relative magnitudes of the two terms inside square brackets. Both terms are positive, and the second, $(\alpha + \frac{1}{2}\beta Y)$, is subtracted from the first, $(1+r)e^{-r N a_{1s}^*} (a_2(\alpha + \frac{1}{2}\beta(Y - p a_2)))$. Note that the second term is the utility of a healthy person in period 2, and the first term is $(1+r)$ times the utility of a sick person in period 2.

If the first term is bigger than the second term, $a_{1s}^* < a_{1p}^*$, this may be interpreted as saying that the relative importance to society of reducing resistance in the second period is greater than that of reducing illness, so the social optimum is below the private optimum. More people will be sick under the social optimum than under the private optimum in this case, but their utility gain from reduced resistance will more than make up for the extra sickness. Conversely, if the second term in the equation is bigger than the first term, then $a_{1s}^* > a_{1p}^*$. In this case, it is relatively

more important to keep people healthy than to keep sick people from suffering a utility loss from drug resistance.

This very simple case is valuable to establish the trade-off between the positive externality (reduced transmission of illness) and the negative externality (increased drug resistance) of antibiotic use. Whether actual antibiotic use in this model is higher or lower than the social optimum is determined by the constant, r , representing the degree to which extra antibiotic use creates resistance. It is clear that for some values of r , those for which resistance is less easily created, demand for the antibiotic will be lower than is socially optimal. Although we do not explicitly model firms' decisions in this context, it is clear that lower than optimal demand would mean lower incentives for firms to incur the costs necessary to bring other antibiotics to market relative to their incentives in the absence of externalities.

In the context of this very simple case, higher values of r would imply the opposite result: demand higher than optimal, leading to higher incentives for firms to innovate. This model, however, abstracts away from a very important feature of the market for antibiotics—variety. Recall that variety and the ability to rotate antibiotics can be effective in decreasing resistance for a given level of antibiotics use. We will see that when we enrich the model to include variety, our result can imply that the negative externality of resistance transmission can actually reinforce the positive externality in lowering incentives to innovate.

The Case of Two Antibiotics

Assume now that there are two antibiotics in the world as otherwise described above, one selling at price p_e and one at price p_n where $p_e > p_n$. One can think of the expensive antibiotic as a new antibiotic that has just appeared on the market. Both antibiotics are equally effective at reducing illness and increasing utility. The only difference between the two antibiotics from an individual's point of view is the price difference between them. Moreover, the rate of sickness transmission between periods 1 and 2 is a function of the total use of antibiotics by period 1 individuals. There is a difference, however, in how resistance is transmitted between the two periods: now, the "resistance effect," r , in the utility function of a sick person in period 2 is not a constant but rather a function of the ratios in which the two drugs are used by society. This means that there is an optimal mix of the two drugs to be used in the first period.

Sick individuals only use one type of antibiotic. Let A_{1r} be the total amount of the inexpensive antibiotic used in the first period, and let A_{1e} be the total amount of the expensive antibiotic used in the first period. Then define A_1 , overall antibiotics use in the first period, to be $A_1 = A_{1r} + A_{1e}$.

Let the resistance effect r be

$$(4-9) \quad r = \frac{\left(A_{1r} - \frac{1}{2} A_1 \right) \left(\frac{1}{2} A_1 - A_{1e} \right)}{A_1 A_1},$$

or

$$(4-10) \quad r = \frac{\left(A_{1r} - \frac{1}{2} A_1 \right)^2}{A_1^2}.$$

Then conditional on being sick, an individual in period 2 has utility function

$$(4-11) \quad U(C_2, a_2 | S_2) = e^{-\frac{(A_{1r} - \frac{1}{2} A_1)^2}{A_1}} a_2 \left(\alpha + \frac{1}{2} \beta (Y - P_n a_2) \right).$$

Note that since sick people in period 2 create no externalities, they will use the inexpensive antibiotic under both the private and the social optimum. The utility functions of all other individuals are the same as in the previous section, and total income and the price of consumption are unchanged.

Obviously, in the case of the private optimum, period 1 individuals will all choose the inexpensive antibiotic, since the only difference to them between the two antibiotics is the price. It is easy to see that having only one type of antibiotic used in period 1 will maximize the level of r in period 2 (conditional on the total amount of antibiotics used.)

To examine the case of the optimal mix of drugs under the social planner's problem, assume that the level of total antibiotics consumed in period 1, A_1 , is fixed. This allows us to focus solely on the optimal mix of the two existing antibiotics.

The social planner has to choose both the overall level of each type of antibiotic to be consumed (which amounts to choosing A_{1r} , since A_1 is fixed) and the number of sick individuals $N_n \leq N$ in period 1 over which to divide A_1 .³⁷

The social planner's problem can therefore be written as

$$(4-12) \quad \begin{aligned} & \max_{N_n, A_{1r}} A_{1r} \left[\alpha + \frac{1}{2} \beta \left(Y - p_n \frac{A_{1r}}{N_n} \right) \right] \\ & + A_{1e} \left[\alpha + \frac{1}{2} \beta \left(Y - p_e \frac{A_{1e}}{N - N_n} \right) \right] \\ & + N e^{-A_1} e^{-\frac{(A_{1r} - \frac{1}{2} A_1)^2}{A_1}} a_2 \left[\alpha + \frac{1}{2} \beta (Y - p_n a_2) \right] \\ & + N (1 - e^{-A_1}) \left[\alpha + \frac{1}{2} \beta Y \right]. \end{aligned}$$

There are two first order conditions, one for A_{1r} , and one for N_n . The equations are complicated, but after manipulating them and substituting the first order condition for N_n into the first order condition for A_{1r} , one can obtain the following equation:

$$(4-13) \quad \begin{aligned} & \beta \sqrt{p_n} \sqrt{p_n} \left(\frac{A_1 - A_{1r}}{N - N_n} \right) + \beta p_e \left(\frac{A_{1r} - A_1}{N - N_n} \right) \\ & + 2N \left(\frac{A_{1r} - \frac{1}{2} A_1}{A_1} \right) e^{-A_1} e^{-\frac{(A_{1r} - \frac{1}{2} A_1)^2}{A_1}} a_2 \left[\alpha + \frac{1}{2} \beta (Y - p_n a_2) \right] = 0. \end{aligned}$$

The first term in equation (4-13) is nonnegative (as long as both antibiotics are consumed in period 1), while the second term is nonpositive. Notice, however, that as long as $A_{1r} < A_1$, the second term is larger than the first in absolute value since $p_e > p_n$. Moreover, it has to be the case that $A_{1r} < A_1$ in order for the equality in equation (4-13) to hold. Therefore, the sum of the first two terms is negative, which means that the third term must be positive. Therefore, the optimal level of A_{1r} is greater than $\frac{1}{2} A_1$, but less than A_1 .

37. Note that this is equivalent to choosing N_n and the level of inexpensive antibiotics consumed by each of these individuals, a_n .

Note that if $p_n = p_e$ so that the drugs are equally priced, then the optimal mix of antibiotics between the expensive and inexpensive drugs splits A_1 equally between them. This makes sense, since if the drugs are equally priced, individuals in period 1 will be indifferent between the two drugs, so conditional on the overall level of antibiotics consumed in the first period, the social planner will want to minimize resistance. This occurs when $A_{1r} = A_{1e} = \frac{1}{2}A_1$. If, however, one drug is less expensive, the social planner will choose to allocate more than half of period 1 consumption to that drug, but it will still be optimal to have some consumption of the more expensive drug in the first period to help lower resistance.

What does this all imply about innovation of new antibiotics? The intuition is straightforward. New innovation brings variety, which, as we noted above, has been found to help combat resistance. But if newly developed drugs are more expensive than existing drugs, the private market will not demand them, so the private market again provides less incentive to innovate than it would in the absence of externalities.³⁸

References

- "Bacteria Repel Antibiotics in N.Y. Hospital Patients." 1996. *USA Today* (November 22).
- Baye, Michael, Robert Maness, and Steven Wiggins. 1992. "Demand Systems and the 'True' Subindex of the Cost-of-Living for Pharmaceuticals." Department of Economics, Texas A&M University.
- Berndt, Ernst R., Zvi Griliches, and Joshua G. Roseett. 1993. "Auditing the Producer Price Index: Micro Evidence from Prescription Pharmaceutical Products." *Journal of Business and Economic Statistics* 11(3): 251-64.
- BLS *Handbook of Methods*. 1997. U.S. Department of Labor, Bureau of Labor Statistics.
- Boston Consulting Group. 1993. "The Changing Environment for U.S. Pharmaceuticals." Mimeo. Boston.
- "Disease 'Crisis' Predicted." 1996. *Boston Globe* (May 20).
- Drug Facts and Comparisons*. 1991. St. Louis: Lippincott.
- "Drug Makers Go All out to Squash 'Superbugs.'" 1996. *Wall Street Journal* (June 25).
- "Drug-Resistant Germ Found." 1997. *New York Times* (September 5).
- "Drug-Resistant Germ Shows up in U.S." 1997. *New York Times* (August 22).
- Ellison, Sara Fisher, and others. 1997. "Characteristics of Demand for Pharmaceutical Products: An Examination of Four Cephalosporins." *RAND Journal of Economics* 28 (3):426-46.
38. Or, if new drugs have other positive features that are valued by the private market, then private demand will be too low.

- Frank, R., and E. Berndt. 1997. "Prices for Treatment of Depression." National Bureau of Economic Research.
- Garber, Alan. 1982. "Cost and Control of Antibiotic Resistance." Ph.D. dissertation, Harvard University.
- Gold, Howard S., and Robert C. Moellering Jr. 1996. "Drug Therapy: Antimicrobial Drug Resistance." *New England Journal of Medicine* 355:1445-52.
- Griliches, Zvi, and Iain Cockburn. 1994. "Generics and New Goods in Pharmaceutical Price Indexes." *American Economic Review* 4(5): 1213-32.
- Hellerstein, Judith K. 1995. "Economic Impediments to the Development of New Antibiotic Drugs." Office of Technology Assessment, U.S. Congress.
- . 1998. "The Importance of the Physician in the Generic versus Trade-Name Prescription Decision." *RAND Journal of Economics* 29(10): 108-36.
- "Incidence of Drug-Resistant Bacteria Soars since '94." 1997. *USA Today* (April 19).
- Kanoza, Douglas. 1996. "Supplemental Sampling in the PPI Pharmaceuticals Index." Bureau of Labor Statistics. *PPI Detailed Report*, 8-10.
- Newhouse, Joseph P., and the Insurance Experiment Group. 1993. *Free for All? Lessons from the Rand Health Insurance Experiment*. Harvard University Press.
- Physicians Desk Reference*. 1993. New York: Medical Economics Data.
- "A Shift of Power in Pharmaceuticals." 1994. *New York Times* (May 9).
- Tomasz, Alexander. 1994. "Multiple-Antibiotic-Resistant Pathogenic Bacteria." *New England Journal of Medicine* 330: 1247-51.
- U.S. Congress, Office of Technology Assessment. 1995. "Impacts of Antibiotic-Resistant Bacteria." OTA-H-629. Washington, D.C.
- "Wide Overuse of Antibiotic Cited in Study." 1997. *Wall Street Journal* (September 4).
- Wiggins, Steven, and Robert Maness. 1995. "Price Competition in Pharmaceuticals: The Case of Antifungals." Department of Economics, Texas A&M University.

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