If bacteria are becoming increasingly resistant to current antibiotics, why is the FDA discouraging the development of new antibiotics?

The FDA's Antibiotic Resistance

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Antibiotic resistance occurs when bacteria evolve under selection pressure from antibiotic use and become resistant to the medication. Because a generation for a bacterium is extremely short (no more than one day, and often less than an hour), such evolution can occur very quickly. The result is that existing antibiotics lose their effectiveness over time.

Both the Food and Drug Administration and the Centers for Disease Control are very concerned about this issue. Both agencies advocate reducing the use of antibiotics in order to slow down or prevent this selection pressure for resistant bacteria. That is, the agencies advocate reduction in demand in order to slow the resistance process.

On the face of it, a demand-side policy is not the obvious solution. There are at least two reasons why such an approach seems problematic. First, we are fighting to the enemy's strength: We are trying to slow down a rapid evolutionary process, but evolution is bacteria's strength. Second, we are smarter than the bugs. And we are now getting even smarter; using gene sequencing and other tools of modern biology, we should be in a position to develop new and more powerful antibiotics. Those factors suggest that we should be concentrating more on the supply side of the issue — trying to invent and market new antibiotics instead of simply trying to slow down the use of those already available.

The current demand-side policy has the unfortunate side effect of reducing the value to a pharmaceutical company of investing in the creation of new antibiotics. As usage is reduced to eliminate resistance, sales are also reduced, and antibiotics become relatively less profitable. Moreover, the market for antibiotics is a fragile one. Unlike medicines for chronic conditions such as high cholesterol or high blood pressure that are taken daily for long periods of time, antibiotics are only taken for a short time and only when a patient suffers particular diseases. Thus, the profitability of this class of medications is limited — and it has become even more limited because of policies of reduced usage advocated by the FDA and CDC. The most profitable current antibiotic, Pfizer's Zithromax, has sales of about $2 billion per year, much less than drugs taken for chronic conditions, such as Lipitor with revenues of about $9 billion per year. As Joseph DiMasi, Henry Grabowski, and John Vernon show in their 2004 *Tufts Center for the Study of Drug Development Impact Report,* the present value of life-cycle sales for anti-infectives is below the average for all drug classes.

EXTERNALITIES IN ANTIBIOTIC USAGE

An "externality" is said to exist when one person's behavior has effects — positive or negative — on another person and those effects are not priced in a market. Externalities lead to non-optimal behavior. When an activity has a positive externality, private agents will not do enough of the activity because an agent does not obtain all the benefits of the action. The converse is true for a negative externality.

Antibiotic usage is associated with three separate externalities, two positive and one negative:

PUBLIC HEALTH EXTERNALITY The most obvious problem is the classic public health externality: If I take an antibiotic and it cures me of an infectious and contagious disease, then I do not spread that disease to others. As a result, others benefit

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from my usage. This is the ultimate theoretical reason for public health interventions and for the existence of the CDC.

ANTIBIOTIC RESISTANCE EXTERNALITY The second externality is negative. If I take an antibiotic, then the bacteria in my system that are not killed might become resistant to the medicine. This is a private (not external) cost; it will now be more difficult for me to overcome future infections. But there is also an externality: I can transmit the resistant bacteria to others, and they will be unable to benefit from the use of the particular antibiotic to which the bacteria have become resistant.

Some of the messages from the CDC and FDA to consumers regarding antibiotic resistance confuse (perhaps intentionally) internal and external effects. It is sometimes harmful to an individual to take antibiotics because he or she will then have resistant bacteria. But it may sometimes be beneficial for the individual to take antibiotics in a situation where harmful externalities will nonetheless be created. That might occur, for example, if the origin of a syndrome (bacterial or viral) is uncertain. Under that scenario, usage of an antibiotic might be beneficial to an individual because of the chance of a more rapid recovery or an avoided repeat trip to the doctor, even adjusting for the internal antibiotic resistance that the medicine might generate. But that course of treatment will also cause an external harm from the antibiotic resistance externality.

Those points are related to the issue of who values antibiotics sufficiently enough to use them. The medical answer might not be the same as the economically efficient answer. Because it costs real resources to go to the doctor and to experiment with various treatment regimens, appropriate economic utilization is almost certainly greater than appropriate medical utilization. If a patient can reduce the need for a second visit when the diagnosis is uncertain, then there is a benefit that the strict medical evaluation might ignore. The resources saved are real, whether paid by the patient himself or by an insurance company, and should be considered in the cost-benefit calculation.

The question is whether the cost of the antibiotic resistance externality generated by the right level of economic utilization is greater than the benefit of reducing the need for further medical treatment. That depends on several factors, including the probability that an antibiotic treatment is useful in a given situation, the question of how fast resistance will arise under different levels of use, and how quickly we can devise alternative treatments. At least some of those issues are important to the patient himself. Some patients might be willing to pay more for antibiotic treatment to avoid a future visit; others may have lower values of time and so be willing to accept a greater chance of a future visit to economize on the cost of medicine.

Good public policy would require truthful discussion of this situation. I am not sure that is what we get from members of the public health community, because they might ignore some of the private benefits from utilization in uncertain situations in order to reduce the antibiotic resistance externality.

SUPPLY-SIDE EXTERNALITY The third externality is mostly neglected. This is the externality from increased investment in new antibiotics that will become more profitable if antibiotics are used more frequently. I call this the "supply side externality." Programs and policies that reduce usage in response to the antibiotic resistance externality also reduce the profitability of new antibiotics and thus decrease the incentives for pharma-

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ceutical firms to invest in this class of medicines. In the long run, more medicines are an effective way to combat the antibiotic resistance externality, and so reducing investment will be counterproductive. This does not argue for deceiving patients into taking unneeded medication, but it might be a partial offset to the antibiotic resistance externality.

COST-BENEFIT ANALYSIS

The FDA does understand supply-side effects. In the Recommendations issued by the FDA Task Force on Antimicrobial Resistance, supply-side effects are considered in Point 3, which urges the FDA to "continue to work within the agency and collaborate with outside experts in order to improve and facilitate innovative product development." Linda Bren, in a 2002 *FDA Consumer Magazine* article, indicates that there are programs to stimulate drug development by increased exclusivity rights, use of an accelerated approval process, and a reduction in the size of the clinical trial process for antibiotics.

But while the FDA has said that it is aware of the problem, its actions have not reflected that awareness. In 1999, the FDA and manufacturers withdrew one antibiotic, Raxar, from the market and greatly curtailed the use of another, Trovan, because of harmful side effects. As a result, the FDA increased scrutiny for antibiotics and began to require increased testing. That may be why DiMasi, Grabowski, and Vernon show that Phase III costs for anti-infectives (which include antibiotics) are 59 percent above the average for all drug classes.

There are sufficient data to undertake a partial cost-benefit analysis of the FDA's policies. In a June 1999 public health advisory regarding Trovan, the FDA indicated that it was aware of 14 cases of acute liver failure, four liver transplants (one leading to death), and five additional deaths associated with the drug. For the recalled antibiotic Raxar, the best information that I can find indicates that it was associated with 13 deaths from heart arrhythmia. Note that in both cases, the drug was approved and sold, and post-approval surveillance found the fatalities that led to the recall. Thus, the average number of deaths for recalled antibiotics undergoing a normal drug approval process seems to be about 10.

I do not have sufficient data to analyze the decision to withdraw Raxar and Trovan, and so I will not address that issue. However, the number of deaths associated with those drugs was less than the average for all new drugs; Mary K. Olson, in a 2002 *Journal of Law and Economics* article, indicates that the average number of deaths per new drug approved in the 1990–1995 period reported to the FDA in the Spontaneous Reporting System of Adverse Drug Reactions was 32. Thus, in terms of deaths, those drugs seem less harmful than average. However, they also led to hospitalizations, and the manufacturers might have feared lawsuits. Moreover, it was argued that there were safe and effective alternatives, though it is not clear how the issue of antibiotic resistance was factored into the decisions to recall or reduce the use of the drugs.

If we increase scrutiny and require more testing of new antibiotics, then fewer deaths may result. Thus, the potential benefit of increased Phase III testing is the cost of the deaths that might occur without the additional tests. There is some debate about the proper monetary value to put on a lost statistical life (see "What is a Life Worth?" p. 60), but current Office of Management and Budget estimates are between $1 and $10 million. Taking $5 million as a reasonable value, it appears that the cost of approving an antibiotic that is later withdrawn is about $50 million. A group of researchers led by Michael Friedman wrote in a 1999 *Journal of the American Medical Association* article that the rate of withdrawal of approved drugs from the market has never been higher than 3.4 percent, and in the early 1990s was 1.2 percent — though it apparently increased later in the decade. If we take 3 percent as an upper bound of the number of approved antibiotics that will turn out to be harmful and so be withdrawn after a normal approval process, then the expected cost of approving and then recalling an antibiotic is about 0.03 x $50 million, or about $1.5 million. If we use the $10 million value of a statistical life figure, the cost is no more than $3 million. Even if we assume that only 50 percent of deaths are reported, the expected cost of deaths associated with an approved antibiotic is no more than $6 million. Moreover, it is by no means certain that increased testing would eliminate all recalls, so this is an upper bound of the benefit of increased delays in approval.

> In the long run, more medicines are an effective way to combat the antibiotic resistance externality, and so reducing investment is counterproductive.

What are the costs of delay? Last April, the FDA approved Ketek, a new antibiotic made by Aventis. That approval was first sought in 2000. The drug was approved in Europe in 2001, and later in Japan. The three-year delay in U.S. approval was because of the increased testing mandated by the FDA as a result of the adverse effects associated with Trovan and Raxar. During the delay, Aventis undertook additional Phase III studies of the drug.

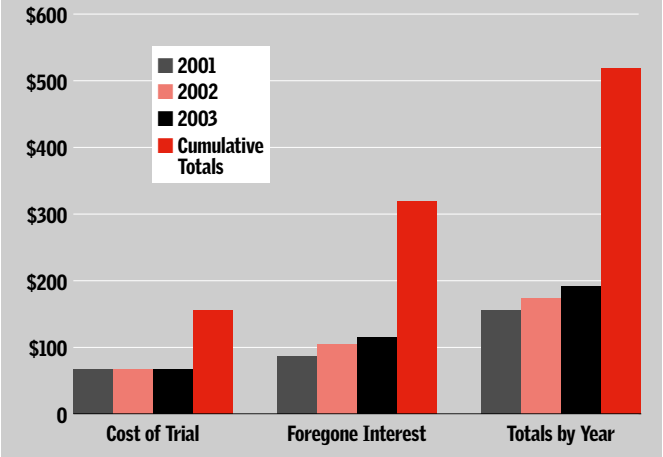
We can calculate some of the costs of that delay. DiMasi, Grabowski, and Ronald Hansen, in a 2003 *Journal of Health Economics* article, provide useful estimates of the cost of drug approval. Their overall estimate is that the average cost of approving a drug is $802 million, while the cost of capital for the pharmaceutical industry is 11 percent. They also estimate

that the median cost of a Phase III trial is $62 million.

The second study undertaken by Aventis enrolled 24,000 patients; the initial study involved 7,000 patients. If the first study was a normal Phase III study, then its expected cost might have been about $60 million, based on the data from DiMasi, Hansen, and Grabowski. The second study was 3.4 times as large, so a reasonable estimate of its cost would be $200 million. I assume that Aventis had spent the average of $802 million on Ketek as of 2000 when it first applied for FDA approval; it then undertook an additional, larger Phase III study over a three-year period, at a cost of $67 million ($200 million ÷ 3) per year; and it suffered a loss in returns at the cost of capital for the industry. The additional cost of the three-year delay is shown in Table 1:

TABLE 1

Cost of Three-Year Delay in Approving Ketek (in Millions of Dollars)



Thus, the cost of delays in approval of Ketek, $518 million, is about 100 times higher than the $6 million upper-bound estimate of the expected benefit from any increase in expected safety because of the longer, more careful approval process.

This is a conservative estimate of the cost. DiMasi, Grabowski, and Vernon estimate that development costs of anti-infectives is higher than the average for all drugs, but I use the average. I have also used the median cost of a Phase III trial, $62 million. The mean cost is $86 million; use of this figure would increase estimated costs by about $100 million. Additionally, this estimate does not include either the lost profits for Aventis or the lost consumer surplus from the delay in approval.

This indicates that the FDA's requiring additional testing for antibiotics is a fairly bizarre policy and makes no sense with respect to any measure of patient welfare. A much more cost-effective alternative would be to approve the drug in the normal manner (or even provide an accelerated approval) and spend additional resources on Phase IV analysis.

EFFECTS ON ANTIBIOTIC RESISTANCE

Moreover, this calculation has not considered the topic of this article — the effect on antibiotic resistance. There are two harmful effects on antibiotic resistance of the FDA policy of increased scrutiny of antibiotics. First, the market was denied the use of an additional antibiotic for a three-year period. Ketek is expected to be particularly useful against resistant strains of bacteria, and because it acts only in the respiratory tract, it will be less likely to lead to increased resistance. More generally, use of additional antibiotics is a promising strategy when resistance is an issue. As a result of the increased cost associated with more stringent FDA policies, drugmakers Eli Lilly and Roche have abandoned research on new antibiotics and Wyeth has slowed down its program. The Web site of the pharmaceutical trade association PhRMA lists all new medicines in development, and it shows only one medicine, tigecycline by Wyeth, as being currently developed for antibiotic-resistant infections.

The CDC is the primary agency with the responsibility for remedying antibiotic resistance. It has chosen to enlist the FDA in its campaign to reduce antibiotic usage. To achieve that goal, it is necessary to convince 290 million Americans and 600,000 physicians to reduce their usage of antibiotics.

It might be easier and more effective for the CDC to convince its sister agency to increase the ease of approval of new antibiotics. Moreover, the FDA might be more effective in its efforts to convince consumers and physicians not to use excessive amounts of antibiotics if its own policies were consistent with its recommendations. R

READINGS

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