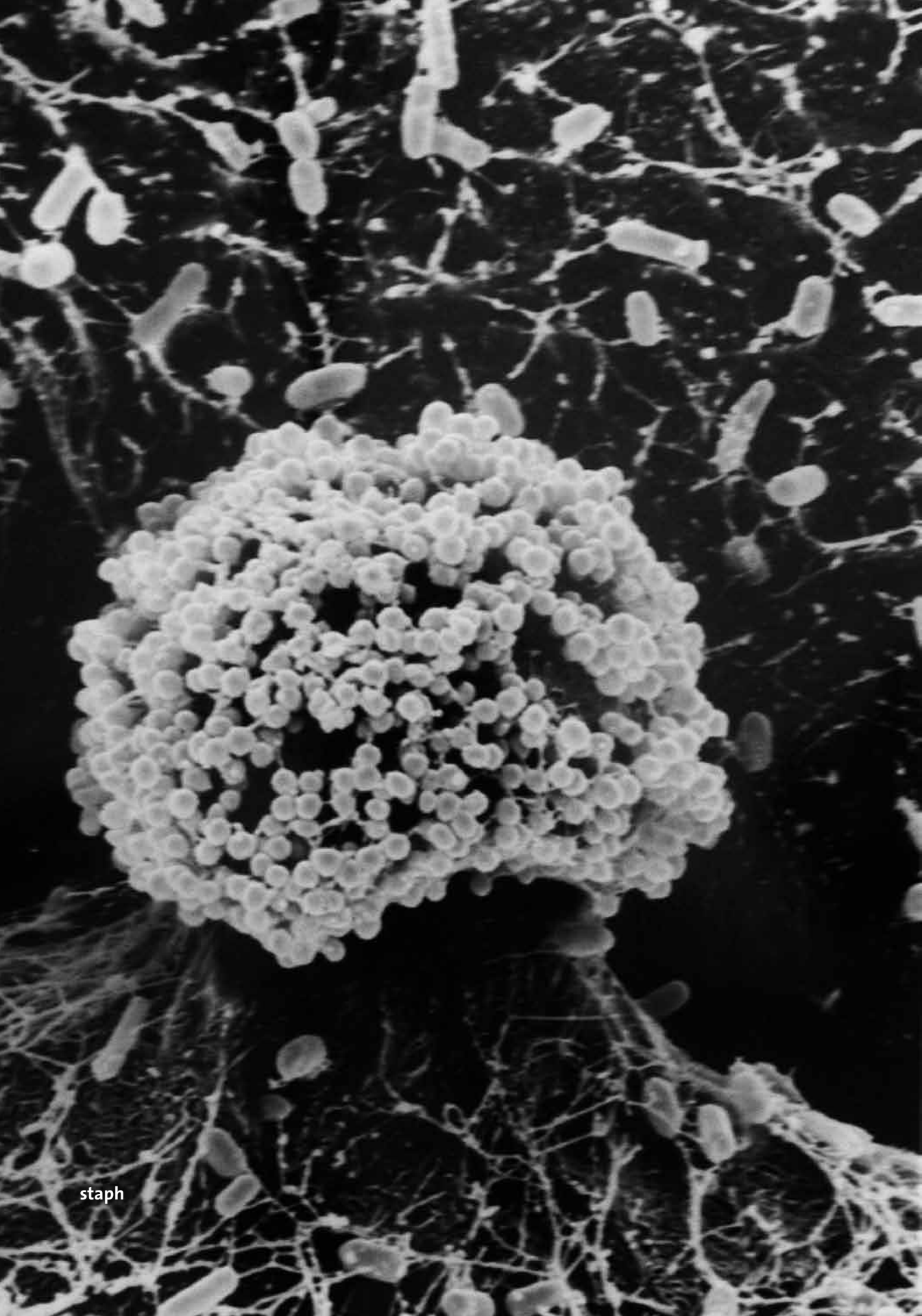
staph

A Matter OF Life AND Death

The Economics of Antibiotic Resistance

BY RAMANAN LAXMINARAYAN

Sixty years after antibiotics were first routinely used to treat infectious diseases, biological resistance to these remarkable defenders against micro-organisms is widespread.

In the United States, for example, resistance to the bacterium methicillin-resistant *Staphylococcus aureus* (MRSA), has reached 60 percent. This means six out of 10 patients with this virulent staph infection can no longer be treated with oxacillin, a relatively low cost drug. But what still amounts to a cost problem in rich countries is becoming a serious threat to public health in the developing world: lower-income countries face a growing toll of death and morbidity from curable infections because the generally available antibiotics no longer work.

Resistance is a natural phenomenon associated with any human effort to control biological organisms – be they weeds, insects, bacteria or viruses. Darwinian selection leads to the survival of the organisms most fit to reproduce in the presence of the control agent. Eventually, resistant organisms dominate and control measures fail.

The relevance of resistance in this context was predicted by Alexander Fleming, a pioneer in the field of antibiotics. In a 1945 interview, he warned that the consequences of "the misuse of penicillin could be the propagation of mutant forms of bacteria that would resist the new miracle drug."

Fortunately, as resistance to older antibiotics has developed, new ones have been discovered. But each succeeding generation has been more expensive to produce than the last. And, ominously, the pace of development is slowing: 14 of the 16 classes of antibiotics in use were introduced before 1970. Accordingly, options for treating patients who do not respond to older, less effective antibiotics are shrinking.

Resistance is hastened by the fact that no individual patient, physician, hospital, insurer or pharmaceutical company has much incentive to care about it. Not surprisingly, then, one survey of physicians showed they were most likely to choose the broadest spectrum agent to treat pneumonia, despite guidelines to the contrary; contributing to resistance rated lowest among seven determinants of their choices. Another found that 87 percent of physicians acknowledged that antimicrobial resistance was a national problem, but only 55 percent believed it was a problem at their own institutions.

Note that the issue of antibiotic overuse is not just a matter of what economists call "externalities" – the failure of physicians to take account of the broader societal cost in prescribing antibiotics to individual patients. The market for antibiotics may fail to produce economically efficient outcomes for other reasons – notably underinvestment in other means of infection control like vaccinations and good hospital management practices.

The potential consequences of unchecked antibiotic resistance, whatever the source, are staggering. While there has been much focus on higher costs associated with longer hospital stays and the use of pricier drugs, the most serious problem is the effect on the rest of the health-care system.

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syphilis

Even before antibiotics were introduced in the 1940s, infectious diseases were in decline in high-income countries, thanks to improvements in sanitation and the introduction of vaccines. Antibiotics do more than treat infections, however; they are uniquely capable of preventing them. Many surgical procedures like transplants and bypass operations depend on effective antibiotics to keep patients free of infection when they are most vulnerable to them. Before the advent of antibiotics, even a simple appendectomy would often end in death because of the high probability of a bloodstream infection.

What could be done to ensure the availability of effective, affordable antibiotics? Two not-mutually-exclusive paths are open: increase incentives for conservation of antibiotic effectiveness, or increase incentives for finding new antibiotics and bringing them to market.

INCENTIVES FOR CONSERVATION

Start with the reality that antibiotics are most often prescribed for bronchitis, sinusitis and acute otitis media (ear infections) – indications for which the value of antibiotics is questionable. Antibiotics are also commonly prescribed for colds and flu, viral infections where they have no value at all. Many physicians view the use of antibiotics as a substitute for time spent with patients to explain why drugs are unnecessary or even counterproductive. Since there is no penalty for writing prescriptions for antibiotics, but no compensation for spending the time to withhold them, prescription rates remain excessive.

One could, of course, deter overuse by charging more to patients. The only published study evaluating the impact of cost sharing on antibiotic use is the RAND Health Insurance Experiment conducted between 1974 and 1982. Consumers in the free care plan, where all medical expenses were covered by insurance, used 85 percent more antibiotics than consumers in plans that required a co-payment.

But interpretation of this evidence is problematic. Because cost-sharing requirements are applied to all types of medical services, it is difficult to isolate the impact on antibiotic use from the impact of cost-sharing for complementary services, like physician office visits. Sharing costs did not appear to differentially

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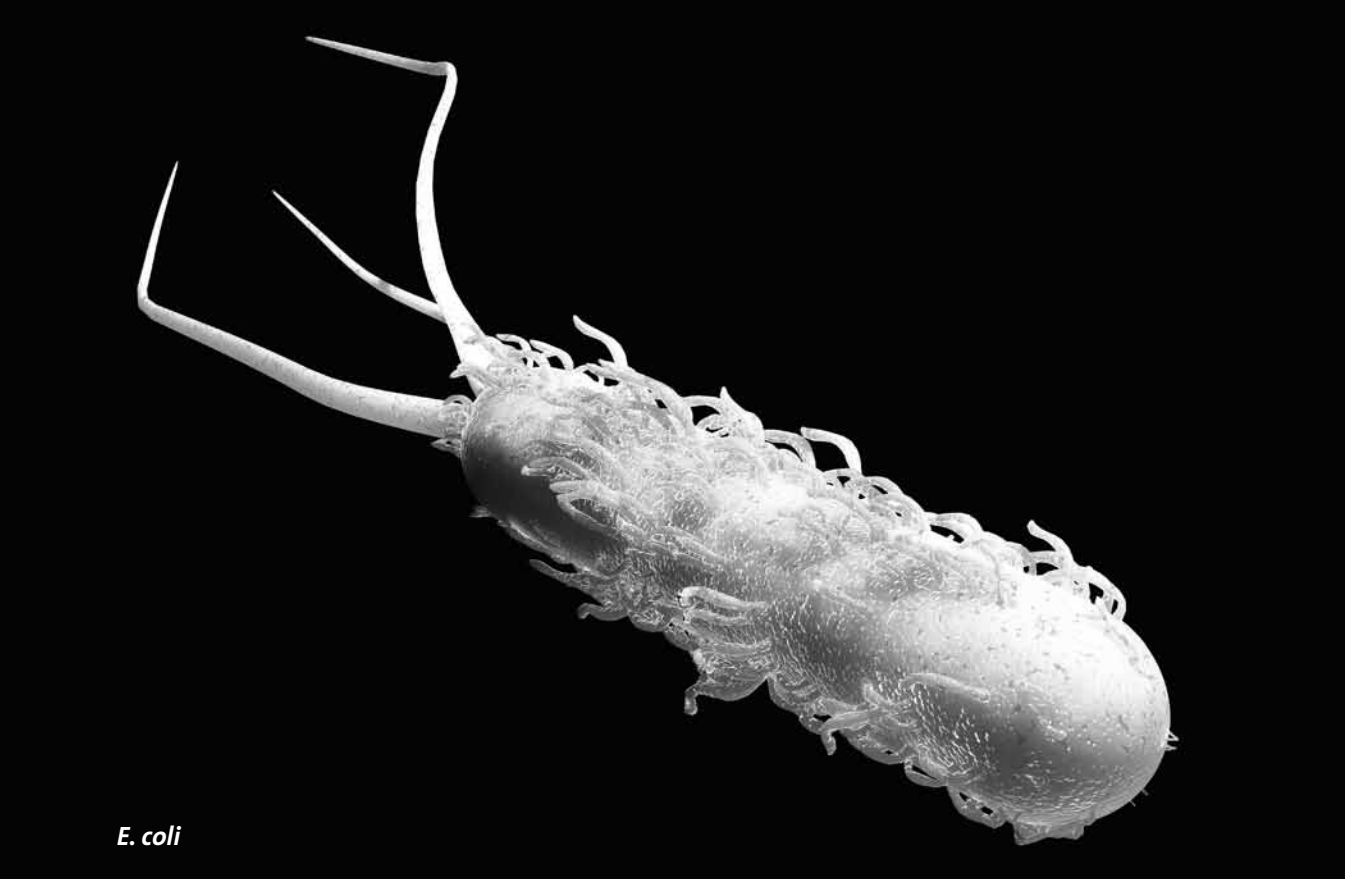

E. coli

reduce antibiotic prescriptions for conditions that were primarily viral, suggesting it reduced both appropriate and inappropriate consumption. In theory, insurers could vary cost-sharing amounts based on patients' diagnoses and the appropriateness of the prescriptions. This would be very difficult to carry out, however.

Another limitation in using cost-sharing to reduce antibiotic use is that the common drugs are generally inexpensive: at current co-payment levels, most insured consumers are already paying a large share of the price out of their own pockets. Indeed, for off-patent antibiotics, co-payments typically exceed the wholesale price of the drug. Increased cost-sharing might still induce consumers to switch from newer, more expensive antibiotics to older drugs, but evidence on the potential impact is lacking.

Clinical guidelines frequently recommend that broad-spectrum drugs be held in reserve. This may have a perverse supply-side effect, however, diminishing incentives for R&D for new antibiotics. Ironically, too, it might contribute to the development of antibiotic resistance by loading natural selection pressure on a handful of older drugs.

Antibiotics are also used intensively to treat infections that occur as a consequence of hospitalization. Here, antibiotics serve as substitutes for infection control. And as noted earlier, the costs of antibiotics can be billed to patients, while the costs of infection control cannot. Consequently, antibiotics are a more cost-effective approach to controlling infections from the hospital's perspective than investing in direct control measures like barrier protection (caps, gloves and gowns).

One could imagine two fixes for this glaring market failure: subsidies for hospital infection control or taxes on hospitals tied to the incidence of infections.

The greatest quantities of antibiotics in the United States – 80 percent by weight – are actually used in agriculture, rather than in

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treatment of humans. While an antibiotic purchase for human use requires a prescription, no such requirement limits veterinary or agricultural use. In fact, it is easy to purchase pharmacy-quality antibiotics over the Internet, even for use in home fish tanks. In April, the FDA announced that the agency would no longer permit antibiotic use to promote growth (as opposed to curing or preventing infection) and that purchases would eventually require a prescription. But at least for the moment, the initiative has no teeth; compliance will be largely voluntary.

Yet evidence from the European Union, where antibiotic use for the promotion of animal growth is banned, shows that most animal producers were able to manage well without them. Only farms marred by crowding, inadequate ventilation and poor hygiene apparently need regimes of low-dose antibiotics to compensate. Note the parallels between farms and hospitals: antibiotics constitute a lower-cost substitute for better hygiene or infection control, which would prevent disease in the first place.

Consider one other point here. Although reducing overall antibiotic selection pressure is desirable, the same effect could be accomplished without reducing the total quantity of antibiotics used. (The trade-off between economic costs and epidemiological advantage is described in an article that I wrote with Martin Weitzman.) From society's point of view, it may be optimal to use different antibiotics on patients with identical illnesses with the goal of minimizing the build-up of resistance.

INCENTIVES FOR INNOVATION

Increasing supply is generally more attractive politically than limiting demand, and antibiotics are no exception. Last year, a bipartisan group of congressmen introduced a bill, the Generating Antibiotic Incentives Now (GAIN) Act, that would strengthen patent protection and streamline approval of antibiotics. Meanwhile, an agency within the federal government, the Biomedical Advanced Research and Development Authority (Barda), is tasked with investing in defenses against public health crises ranging from epidemics to bioterrorism. Barda is supporting late-stage trials of a novel broad spectrum antibacterial from Glaxo SmithKline.

It's important to remember, though, that market failure associated with antibiotics on the demand side does not necessarily justify public intervention on the supply side. I see only three valid reasons for intervention.

First, from a public health perspective, narrow-spectrum antibiotics may be worth more to society than broad-spectrum formulations because the latter attack bacteria that protect us from colonization and infection with pathogenic organisms. However, the incentives to create and market antibiotics are quite the reverse: the revenue from antibiotics that can be used for a variety of conditions is likely to be greater.

Second, the market does not give pharmaceutical companies appropriate incentives to ensure that their products are used judiciously. Antibiotics are prescribed for a range of conditions, some life threatening, others self-resolving. And the effort to maximize sales runs counter to the objective of minimizing the evolution of resistant pathogens. If anything, pharmaceutical companies with big portfolios of antibiotics are better off in an environment with more resistance, since this creates more demand for a variety of antimicrobial agents.

Third, the more diverse the classes of antibiotics the better, since this reduces the likelihood that resistance will develop to any single class. The history of antimicrobial development, however, shows that it is easier (both in

technological and economic terms) to develop another antibiotic within a given class rather than to develop a novel group.

Other reasons have been put forth to justify government intervention in antibiotic development. The most important one: the pharmaceutical industry has simply not succeeded in producing an adequate supply of new ones in recent years. However, the evidence suggests a secular decline in drug development across all therapeutic areas, which implies there are problems in drug discovery and development that are not unique to antibiotics. Furthermore, it's important to consider the kinds of antibiotics approved, not just the number, in assessing resistance issues.

Of 29 antimicrobials approved by the FDA in the 1980s, 24 were in the beta-lactam class; many of these were oral drugs approved for self-resolving diseases. These drugs did little to address issues related to resistance – except perhaps to promote the development of resistance by inappropriate use as noted above. Meanwhile, 5 of the 12 antibiotics known as quinolones that were developed in the 1990s were withdrawn because of the risks from side effects.

Fortunately, there seems to be a glimmer at the end of this tunnel. Two new antibiotic drug classes have been introduced during the past decade, ending a 40-year drought. Moreover, the pharmaceutical industry seems to be returning to antibiotic development, especially for soft-tissue skin infections caused by the above-mentioned MRSA.

The primary argument for why there has been inadequate investment in antibiotic R&D is that such drugs are not profitable because they are used in treatment for much shorter periods than drugs for chronic diseases. There are two problems here. First, the evidence is weak: antimicrobials are the third most profitable area for drug developers (after central nervous system and cardiovascular drugs), with estimated revenues of $26 billion to $45 billion per year. Second, the issue isn't the relative profitability of R&D in antimicrobials, but whether the absolute expected return is high enough to justify the risk.

The return on capital may, indeed, be greater for chronic disease medications. But that hardly seems relevant to smaller pharmaceutical companies involved only in anti-infective therapies. Consider, too, that the return on capital is determined by many factors, including the number of competitors – and competition is highest in the market for cardiovascular and neuropsychiatric drugs.

In any event, the real problem here (assuming there is a problem) is appropriate reimbursement, since most drugs are paid for by private or public insurance. If antibiotics offer the same advancement to health as other drugs, their makers should be compensated accordingly.

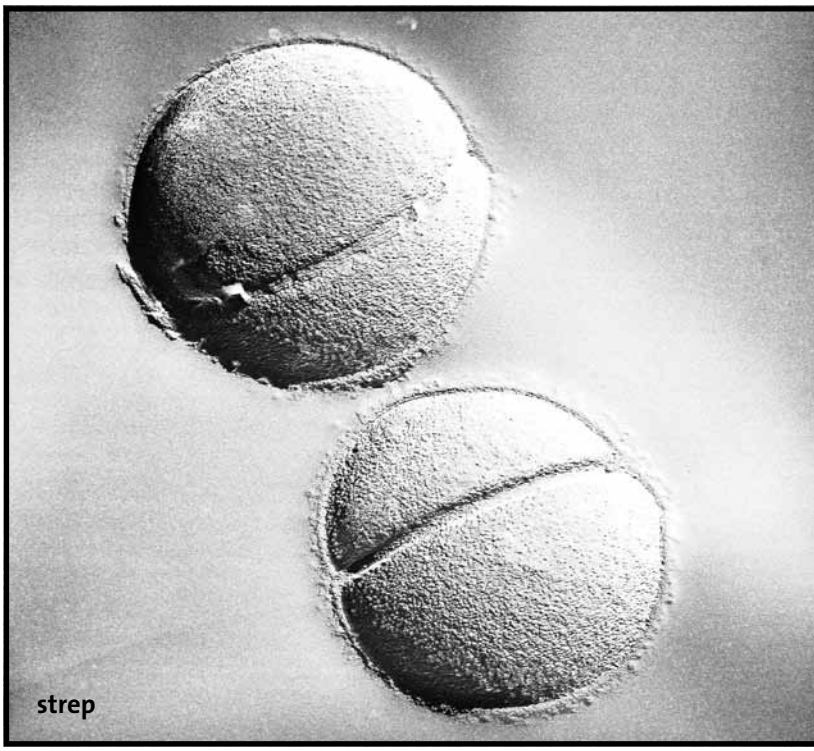
Another argument for adding incentives for antibiotic development is that the market pits best-practice use against private incentives. The hypothesis that clinicians currently keep new broad spectrum antibiotics in reserve, however, is not supported by the survey evidence – they are more likely, not less likely, to use newer ones. Even in situations where overall antibiotic use has decreased, use of newer broad spectrum agents has still increased.

Nor, for that matter, does it make epidemiological sense to keep new antibiotics with novel mechanisms of action on the sidelines. They add to the diversity of antibiotics, which reduces the likelihood of building resistance to existing antibiotics. This diversity is not socially valued, and therefore there is less development of drugs with fresh mechanisms of action than is socially optimal.

If we were to take the diversity value into

account, we should use more expensive antibiotics alongside the cheapest ones. But, by the same token, we should also compensate manufacturers differently for bringing novel treatments to market, since they allow us to reduce selection pressure on existing antibiotics.

A third concern is that reimbursement for antibiotics does not reflect the true value of these drugs in improving health. There is some truth to this argument. Most antibiotics are out of patent and are made by generics manufacturers. The price paid for these drugs reflects the manufacturing cost, but not the opportunity cost of diminishing effectiveness as micro-organisms build resistance with ongoing use. So the price of older antibiotics is too low. Or, to put it another way, lower-cost generic antibiotics are used where it would make sense from society's perspective to use higher-priced antibiotics still under patent.


strep

Once again, though, it is important to keep in mind that the goal here is to sustain diversity in antibiotic use in order to maintain an effective arsenal against very dangerous pathogens. It is unclear what public health benefit a new drug for sinusitis or bronchitis – self-resolving diseases – would add to this end.

There is a related issue of reimbursement for care provided to patients whose infections were acquired in hospitals and could have been prevented. The Pennsylvania Health Care Cost Containment Council estimated that at least $20 billion was billed nationally to Medicare for hospital-acquired infections in 2004. The average charge for Pennsylvania Medicare patients with such infections was about $160,000 – five times the $32,000 average for Medicare hospital patients who did not contract infections. The difference is even greater with Medicaid. Here, the average charge was approximately $391,000 for patients who contracted infections while hospitalized, compared with $29,700 when infections did not occur.

Note again the market failure: since infection-control costs are not reimbursable but antibiotics are, hospitals and other care facilities tend to spend too little on infection control and use excessive quantities of antibiotics. Recent initiatives by the government's Center for Medicare and Medicaid Services to stop reimbursement for health-care-associated infections have been limited. If this initiative were expanded, though, it would bring hospitals' costs closer to society's costs and give

J.L. CARSON/CMSP

hospitals the right incentives to prevent infections rather than to treat them after the fact.

Finally, there is concern that new antibiotics run the risk of losing effectiveness, reducing their profitable life span – and thus the incentive to produce them. The likelihood of resistance to an antibiotic is partly a consequence of how the drug is used and partly a result of how related antibiotics are used. The first factor is within the control of the manufacturer, which gives it a stake in making sure that its drug is used appropriately and not overprescribed. The second factor is a true failure of the market, and thus may justify government intervention.

The goal of equating private costs to social costs in order to optimize antibiotic innovation seems to be a relatively straightforward process. In practice, though, the process can be very complicated. For example, resistance of *Staphylococcus aureus* to penicillin developed within a decade of the widespread use of the breakthrough drug. However, resistance to penicillin in *Streptococcus pyogenes*, the cause of strep throat and many cases of necrotizing fasciitis (the "flesh eating" disease), is still low 70 years after its first use. In many cases, then, the development of widespread resistance may occur long after patent expiration, so it has little influence on the drug developer's ability to recoup costs.

Consider yet another wrinkle: the notion that resistance limits a sponsor's return on investment is at odds with the idea that we need to develop drugs today in order to address resistance in the future. If a drug is approved now, then resistance may develop to that drug or drug class. So when it is needed down the road, its effectiveness will be compromised.

THE CASE FOR BIG BROTHER

There is certainly a case to be made for intervention in the research and development of new antibiotics – but not always for the reasons asserted. New antibiotics may not be coming to market at an appropriate pace for three reasons.

We should work to conserve the effectiveness of current and future antibiotics, rather than simply priming the pump to generate new therapeutic compounds.

First, antibiotic innovation constitutes a daunting scientific challenge. For years before the discovery of sulfa and penicillin drugs, investigators believed it was beyond their capacity to discover small molecules that would inhibit bacterial growth, yet not be prohibitively toxic in man. The biology of gram-negative organisms, with their surrounding cell wall through which a drug must first penetrate to reach the actual bacterium, only added to the difficulty.

Second, there are not always enough cases of diseases caused by resistant organisms – diseases serious enough to justify huge outlays for treatment – to make drug development worthwhile for the manufacturer. Yet the market has responded adequately in providing new drugs for soft-tissue MRSA infections, and it is possible that the market will also respond to a growing burden of multidrug-resistant gram-negative infections.

Third, the cost of discovering new antibiotics is too high because the lowest-hanging fruit has already been picked, and the growing

prospect of cross-resistance with existing antibiotics reduces their potential for sales. Evidence for this, though, is anecdotal and comes from scientists working within the industry.

To address the challenge of resistance, we should work to conserve the effectiveness of current and future antibiotics, rather than simply priming the pump to generate new therapeutic compounds. There are good reasons to intervene on the supply side to correct market failures that lead to excessively rapid development of resistance. It's important, though, that development incentives be focused where they would have the most impact for public health – that is, on serious and life-threatening diseases, rather than on self-resolving ones.

THE TRAGEDY OF THE COMMONS

The logic of regulating antibiotics differently from other drugs arises from the fact that one person's use contributes to lower effectiveness for everyone else. The spread of resistance by overuse of antibiotics is like other shared-resource problems, such as global warming or overfishing – a phenomenon dubbed "the tragedy of the commons." Approaching antibiotic resistance as a resource problem is not just a convenient metaphor; it can help shape strategies to use antibiotics in ways that provide the greatest benefit to society, both today and in the future. Such incentives would encourage pharmaceutical companies to develop new antibiotics, and patients and health care providers to use existing antibiotics sustainably.

The missing link in this discussion is the one between conservation incentives and R&D incentives.

As we know from the context of oil (another natural resource), incentives for new drilling are likely to reduce incentives for conservation. Similarly, greater incentives for antibiotic conservation are likely to slow the rate of development. Comprehensive regulation should recognize these linkages and attempt to solve the broader market failure.

There is currently little or no regulation of antibiotic effectiveness. However, there is an interesting precedent.

Bacillus thuringiensis (Bt), a bacterium found in soil, produces a chemical that is toxic to many agricultural pests, but is apparently harmless to humans. The Bt toxin is currently synthesized as an insecticide. More important, a variety of commercial crops have been genetically modified to produce their own Bt. The use of Bt raises the same issue of resistance as antibiotic use. And this potential for pest resistance has been the focus of the EPA's regulation of Bt products.

However, no such regulations have been forthcoming in the case of antibiotics for at least two reasons. First, medical practitioners resist any form of regulation that would limit their discretion to prescribe antibiotics. Second, no single federal agency has the authority to intervene. Thus, while the FDA, the Centers for Disease Control and the National Institutes of Health (and perhaps others) have some role to play in ensuring the maintenance of a portfolio of effective antibiotics, the task has largely been ignored.

* * *

The challenges to effective antibiotic regulation are thus technological, economic, political and even moral – a mix that explains why regulators have been reluctant to weigh in. But benign neglect is not a solution. Nor, unfortunately, are initiatives designed to please everyone by concentrating on increasing incentives to antibiotic R&D. One way or another, we need to develop a mix of conservation and innovation incentives that keep antibiotic resistance at bay. The alternatives are unthinkable.