SUSTAINABLE DEVELOPMENT

Antibiotic Resistance: An Emerging Environmental Health Threat

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Introduction

Modern medicine depends on the availability of affordable and effective antibiotics. However, widespread reliance on antibiotics has spurred an alarming rise in resistant strains of bacteria, complicating the treatment of infectious diseases. Many blame the situation on doctors, patients, and livestock farmers who overuse, and sometimes even misuse, antibiotics. These factors have led to increasing antibiotic concentration in the natural environment, which in turn has facilitated the development of resistance both in disease- and in nondisease-causing bacterial organisms.

The growing frequency of resistant microbes in wastewater streams, sewers, soil, and other environmental reservoirs represents a large pool of antibiotic-resistant microbes from which resistance could be transferred into human and animal disease organisms. The challenge for policymakers is to create the right incentives for those who manufacture and use antibiotics to consider the societal costs, as well as the benefits, of using these powerful drugs.

From a human health perspective, increasing bacterial resistance and, consequently, our inability to rely on the availability of an arsenal of effective antibiotics place enormous costs on society in the form of increased hospitalizations, higher mortality rates, and the diversion of resources from other medical needs to the development of new and more powerful antibiotics. Nevertheless, physicians understandably focus on the benefits to the patient, and not the risks to society, when they prescribe an antibiotic. Similarly, livestock producers who use antibiotics in animal feed are motivated by the incentive of increased profits, and drug companies that encourage antibiotic use are motivated largely by objective to profit from the antibiotic before expiration of its patent life.

Such economic incentives drive the evolution of antibiotic resistance. As more antibiotics are used, bacterial resistance increases—a cycle that is exacerbated by the failure of antibiotic users to consider the full costs of their activity. Because resistance results from the selective use of drugs on sensitive strains of bacteria, it is likely to remain a pressing issue as long as we rely on antibiotics.

The magnitude of costs that antibiotic resistance imposes worldwide is not known. In the United States, the most common estimates range from $350 million to $35 billion, depending on how long resistance persists in the bacterial population, and whether or not the cost of deaths is considered. Even such country-specific assessments are incomplete, however, because they fail to take into account the biological dynamics of resistance and infection. Data on antibiotic use and bacterial resistance are very limited, making it difficult for economists to compare costs when trying to evaluate alternatives to antibiotic use.

If antibiotics are to be used judiciously, it may be necessary to create a system that forces users to recognize the economic value of preserving the effectiveness of the drugs. In the language of economists, antibiotic resistance is a negative "externality" associated with antibiotic use, much as pollution is an undesirable externality associated with the generation of power at a thermal power plant. Neither the user of antibiotics nor the operators of power plants have an incentive to take into account the negative impact of their actions on the rest of society. In the case of power plants, government agencies impose emissions restraints in the form of taxes and quotas to force them to take the cost of pollution into account when determining how much power to generate. Similarly, society should devise mechanisms by which the cost of antibiotic resistance is taken into account—or, in economic terms, "internalized"—in decisions regarding the use of the drugs. However, the externalities associated with antibiotic use are not all negative: antibiotics may also cure infections, thereby reducing the likelihood of the infection being transmitted to uninfected individuals. Therefore, the favorable and unfavorable effects must be weighed to determine the optimal use policy.

Antibiotic effectiveness as a natural resource

Antibiotic effectiveness may be thought of as an economic or natural resource that is of value to society because it enables doctors to both prevent and treat infections. Current antibiotic use lowers the stock of antibiotic effectiveness, and the current concern is based on the belief that this resource is being depleted at a rate that is higher than is optimal for society. Economists have experience determining both the optimal management of natural resources such as oil, trees and fisheries, as well as the optimal design of incentives to influence the behavior of individuals and corporate entities. Thinking about antibiotic or pest effectiveness as a social resource could help devise strategies to use antibiotics in a manner that benefits society. Economists could help design incentives to encourage firms to come up with new products that will replace antibiotics and pesticides that are no longer effective, as well as to take resistance into consideration when deciding on strategies to market existing products.

A recent economic analysis showed that when resistance arises as a consequence of antibiotic use, it may be shortsighted to use a single antibiotic on all patients just because that antibiotic appears to be the most cost-effective option. Indeed, it may be optimal, from society's point of view, to use different drugs on different, but observationally identical, patients and include among this menu of drugs some that may not be cost-effective from the individual patient's perspective. The design of an optimal antibiotic use policy depends on whether effectiveness is a renewable resource (like trees or fish) or a nonrenewable resource (like oil or mineral deposits). This distinction is facilitated by the biological concept of fitness cost. Fitness cost is the evolutionary disadvantage placed on resistant strains in an environment where antibiotic selection pressure has been removed. If the fitness cost associated with resistance is high, then one can conceive of periodically removing an antibiotic from active use to enable it to recover its effectiveness before bringing it back into active use. Antibiotic effectiveness would then be characterized as a renewable resource, in much the same way as a stock of fish. On the other hand, if fitness cost is insignificant, then antibiotic effectiveness always declines even if antibiotic use is terminated. Effectiveness is therefore treated as a nonrenewable or exhaustible resource, similar to a mineral deposit. While some studies have shown that fitness cost can be quite large, other studies question whether decreasing antibiotic use will result in a decrease in the incidence of drug resistance.

Reducing antibiotic use comes at a cost. If hospitals lower their use of antibiotics, they must be willing to bear the costs of strengthening infection control measures. Infection control measures, such as enforcing frequent hand-washing by nursing staff and physicians, and sequestering nursing staff to a limited number of patients, can be effective in reducing the spread of infections in hospitals. A recent study has shown that these policies also can reduce microbial resistance in hospital settings. Further studies are required to develop the optimal mix of strategies to reduce resistance in an economically efficient manner.

From a patient's perspective, the decision to request an antibiotic is based on two factors: the benefit of quickly recovering from an infection and the cost (minimized by insurance coverage) of taking the medication. But patients may not be aware of studies that have demonstrated conclusively that prior use of antibiotics increases a person's risk of acquiring a resistant infection. Patients who are educated about the risks of antibiotics may be more careful about demanding such medication from the doctor. In addition, policymakers may want to consider such economic instruments as taxes, subsidies, and redesigned prescription drug insurance programs to ensure that incentives faced by both doctors and patients are aligned with the interests of society.

To date, most efforts to control resistance have focused on using physician guidelines for limiting the use of antibiotics. But neither such guidelines nor educational efforts have been successful in curtailing antibiotic use. Short of directly monitoring clinical practice, which would be extremely expensive, public health policymakers can do little to enforce restrictions on antibiotic use; any attempt to admonish doctors for overusing antibiotics is likely to spark strong opposition from the medical community.

Antibiotic Use in Food Animals

Antibiotics are used in the animal industry for improving feed efficiency and rate of weight gain, and for disease prevention and treatment. Almost half the 50 million pounds of U.S.-produced antibiotics is used on farm animals (of which 80% is used to help animals grow faster and the rest is used to treat disease). Although there is uncertainty about the magnitude of the effect that antibiotic use in animals has on promoting resistant organisms that infect humans, there is growing evidence that antibiotic use for growth promotion in animals also contributes to the pool of resistant pathogens that puts humans at risk. Recognizing the impact of antibiotic use in nonhuman, sub-therapeutic use on the overall level of bacterial resistance in the environment, and in response to the public outcry over the use of antibiotics for growth promotion, many countries in Europe have either banned or restricted the use of antibiotics for this purpose. In 1997, the World Health Organization called for a complete termination of the sub-therapeutic use in animals of any antibiotic agent that is either itself used in humans or known to encourage resistance to antibiotics used in humans. Similar bans are under consideration in the United States, but have met with stiff opposition from both the pharmaceutical industry and the food-animal production industry.

The use of antibiotics as growth promoters in cattle and poultry feed has two effects. First, it may increase the level of bacterial resistance to antibiotics used in humans. For instance, there has been a sharp increase in the prevalence of fluoroquinolone resistant *Campylobacter jejuni* in both poultry meat and infected humans since flouroquinolones were approved for use in poultry. Therefore, antibiotic use in animals can have a direct negative impact on human health. Second, the depletion of antibiotic effectiveness due to use in animals may encourage greater antibiotic use in humans, and such use diminishes the antibiotic's future effectiveness and, therefore, its value. The threat of depleted effectiveness caused by antibiotic use in animals reduces incentives for pharmaceutical firms to conserve use of their product; with a looming patent expiration, it makes more sense to exploit the initial value of the antibiotic. Both of these effects have a negative impact on social welfare, especially if the impact of sub-therapeutic use of antibiotics in farm animal feed on resistance in humans is significant, and the demand for growth promoters is more elastic than the demand for antibiotics used to treat diseases in humans.

A contentious debate surrounds the question of the risk that antibiotic use in growth promotion poses for human health. In searching for pathways between environmental reservoirs of resistance and human health, one consideration that has been missing is the potential of antibiotics to become environmental pollutants that create new pools of resistance that, given the new evidence of genetic transfers across species, could accelerate the development of resistance in many disease organisms. If new forms of resistance start to come not only from human treatments and hospital settings, but also from interspecies transfers from the environment, the growing ineffectiveness of present forms of treatment and a revival of major epidemics is a distinct possibility. Therefore, policymakers need to balance the risks to society posed by using antibiotics in animal feed against the benefits (namely more efficient livestock operations) in order to arrive at a rational policy regarding such use of antibiotics.

Antibiotics: A global public good

With global travel and widespread commerce, resistance that develops in one country can spread easily to another. Therefore, nations have an incentive to cooperate to ensure that antibiotics are used responsibly throughout the world. The consequences of resistance are particularly severe for developing countries because of the cost of new antibiotics that are necessitated by growing resistance to older drugs. Unlike in developed countries, where more people can afford more effective and expensive alternatives such as Vancomycin or Synercid, drug resistance in developing countries could suffer significantly greater mortality from common infectious diseases. A comparable situation has already developed with respect to malarial resistance, where most strains of the malarial parasite in India and Southeast Asia are highly resistant to most affordable and commonly available antimalarials. Exacerbating factors such as poor hygiene, lack of reliable water supply, and an increase in the number of immuno-compromised patients attributable to the ongoing HIV epidemic are likely to further increase the cost of antibiotic resistance.

Antibiotic resistance is a global phenomenon with far-reaching implications for development indicators such as infant mortality and life expectancy. Further, health is known to be strongly correlated with economic well-being. Although the level of resistance is dependent, in large part, on local antibiotic use policies, there are global externalities associated with the development of resistant strains in any country and those strains may spread to other countries. While global surveillance is a key component in any strategy to deal with global resistance, international agreements on ways to reduce antibiotic misuse worldwide are also necessary.

The link between antibiotic effectiveness and sustainable development is becoming increasingly evident to policymakers, as is the need for collective action. At its meeting in Helsinki in December 1999, the European Council invited the European Commission to propose a broad strategy for ensuring that environmental and social concerns are fully integrated into economic development, and agreed to act in four areas of environmental concern, one of which was antibiotic resistance (the other three were climate change, sustainable transport and natural resources). The Council recognized the risks posed by antibiotic-resistant strains of some diseases and the potential longer-term effects of the many hazardous chemicals currently in everyday use, and called upon the European Commission to develop a plan of action to address this important environmental health problem.

Encouraging the development of new antibiotics

In spite of our best efforts to manage resistance, antibiotics and pesticides that are currently in use will inevitably be less effective in the future. Economic theory can be used to help in designing incentives to encourage research and development of new products. Policymaking efforts to design such incentives should be guided by two criteria. First, policies to encourage development must be consistent with other policies that influence how firms choose to price and sell their products. While we would want firms to come up with new products, we also want to increase (or not decrease, at any rate) their incentives to care about product effectiveness. Second, the fundamental policy objective is not just to increase incentives for firms to introduce any new antibiotics, but to specifically develop new products that are significantly different from existing ones in their mechanisms of action. This minimizes the common property problem that arises when different firms make products with linked modes of action and, consequently, no single firm has sufficient incentive to care about declining product effectiveness.

One solution is to grant broader patent protection for new antibiotics. Under this proposed policy, the scope of antibiotics patents could cover an entire class of compounds and pre-empt me-too antibiotics that increase competition for the same mechanism of action. This may be a good idea for three reasons. First, this would give drug firms an incentive to care about the evolution of resistance, since the firm owning the patent would have nearly complete control over the effectiveness of the antibiotic. The common property problem arises with antibiotics because different firms sell similar antibiotics with similar modes of action, and no firm bears the full resistance cost of its production decisions. Second, increasing breadth would dramatically increase the returns from investing in new compounds rather than just tinkering with existing compounds, since the innovator will have broad rights over the newly innovated class of antibiotics. The third reason for increasing patent breadth is that it promotes new drug research on increasing the variety of modes of action of antibiotics. Variety has social value that is not fully compensated for in the current market for antibiotics, and increasing patent breadths would encourage variety. The drawback, of course, is that broader patents may give firms too much monopoly power over vital drugs and would therefore hurt societal welfare. These costs will need to be weighed against the resistance related benefits of broad patents in order to arrive at an optimal solution. Treatment homogeneity—in which a single antibiotic or few antibiotics (or pesticides) are widely used, while newer products are kept on the sidelines for use only for resistance infections—should be discouraged.

There is often great emphasis placed on the most cost-effective antibiotic or pesticides, and new products are often kept on the sidelines as backups if the currently use product fails. Such policies could significantly lower incentives for firms to come up with new products given that the possibility that their product would be used widely is remote. Policies that encourage product homogeneity should be sensitive to this effect on producer incentives. The expectation of new antibiotics to arrive on the market cannot be a reason for not using existing drugs judiciously. One needs to consider the relative importance of innovation when compared to measures to manage resistance to existing antibiotics. Clearly, measures need to be taken on both fronts, but we need to have some assessment of the relative importance of these two avenues to addressing the resistance problem. Recent evidence suggests that new antibiotics may have much shorter lifespans than drugs that were introduced a few decades ago.

Research priorities

Research is urgently needed into the environmental impacts of the widespread use of antibiotics on the development of reservoirs of resistant bacteria in nature. The importance of this scientific understanding to providing a reliable foundation for sound economic policy cannot be overstated. As we learn more about the relationship between antibiotic use and resistance, we can better quantify the social costs of overusing the drugs. Similarly, quantifying the relationship between antibiotic use in animal feed and resistance in humans will help us assess the economic tradeoffs involved in using the agents in livestock operations.

Further economic and scientific research could provide guidance for a number of policy issues. First, the problem of optimal use of antibiotics in a community setting remains to be addressed. Ideally, this analysis would take into consideration both patient and physician behavior in an outpatient setting to determine optimal antibiotic therapy. From the practitioner's perspective, it may be useful to determine separate cost-effective empiric antibiotic treatment strategies by geographic region using local surveillance data for résistance. Second, there may be a role for insurance companies to discourage resistance by modifying their reimbursement programs for antibiotics. Under many current programs, patients pay no deductible for prescription drugs and therefore face a zero marginal cost of antibiotics. Research into mechanism design that promotes socially optimal behavior when taking into account both the costs and benefits associated with antibiotic use may be useful. Third, the resistance problem is exacerbated by the failure of patients to complete their prescribed dose of antibiotics. While efforts at educating patients may be useful, the feasibility of innovative incentive programs that ensure that a full course of antibiotics is completed needs to be studied. Finally, economic incentives for investment in the development of new and affordable antibiotics need to be designed. These efforts can help policymakers ensure that antibiotics remain a valuable resource for society.

Further Readings

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