DISEASE CONTROL PRIORITIES PROJECT

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Drug Resistance

Disease Control is Threatened by Rise in Resistant Microbes

Controlling the deadliest infectious diseases in the world—diarrheal diseases, respiratory tract infections, sexually transmitted infections, meningitis, pneumonia, and hospital-acquired infections—is more difficult today because of the emergence of antimicrobial drug resistance. Resistance has emerged in malaria, HIV, tuberculosis (TB), and most bacterial infections, which together constitute a significant proportion of the burden of disease in developing countries.

Resistant infections lead to increased illness and longer hospital stays, as well as to prolonged periods during which infectious individuals can spread their disease to others. The problem is particularly severe in developing countries where the burden of infectious diseases is relatively greater, and where access to expensive treatment for resistant infections is limited. Other factors, such as poor hygiene, unreliable water supply, civil conflict, and increased numbers of patients with weak immune systems, facilitate the spread of resistant pathogens.

Risk Factors

Using an antimicrobial drug for any infection, in any dose, and over any period of time forces microbes either to adapt or to die; microbes that adapt carry genes for drug resistance that are then passed on. But when an antimicrobial is used inappropriately—for too short a time, at too low a dose, at inadequate potency—or for the wrong disease, microbes are more likely to develop resistance to that drug. Drug resistance is facilitated by a number of factors, including:

- Excessive use of antibiotics and antimalarials;
- Insufficient control on drug prescribing;
- Inadequate compliance with treatment regimens;
- Prescribing inappropriate doses;
- Lack of infection control; and
- Increasing frequency and speed of travel.

The risk factors for the emergence of resistance *(de novo resistance)* differ from those driving the spread of resistance *(primary resistance)*. *De novo* or acquired resistance refers to the emergence of a resistant strain in a single patient. Primary resistance emerges if the drug-resistant microbe is transmitted to others and the disease becomes drug-resistant. Drug-resistant microbes, like all infectious organisms, can spread through unsafe drinking water, unsanitary conditions, and poor infection control in hospitals.

Many developed countries use antibiotics for veterinary purposes—to accelerate weight gain and to prevent and treat disease in animals. But evidence strongly suggests that the use of antibiotics in farm animals promotes the development of drug-resistant microbes in those animals. Drug resistance in animals may lead to drug resistance in humans, because the drug-resistant bacteria can be transmitted from animals to humans.

Disease Burden

Drug resistance is considered an important contributor to the burden of infectious diseases. Although there are no current estimates of the magnitude of that burden, there are scores of documented examples of the growing problem presented by drug-resistant microbes:

- Surveillance of drug resistance in *pneumococcal* bacteria indicate that the number of strains that are fully susceptible to penicillin, once the most effective antibiotic in most of the world--has declined to 50 percent, and in some countries by 75 percent, as resistant strains have spread.

- *Shigella dysenteriae*, an important cause of infant mortality, has developed resistance to first-, second-, and third-line drugs, which in many places are the last effective oral drugs available, leading to recent high fatality rates from dysentery outbreaks. Alternative drugs are more expensive and are not always available in developing countries.

- The emergence and spread of multidrug-resistant TB (MDRTB) threatens global TB control. Patients infected with MDRTB are difficult to cure, and alternative treatment is toxic and expensive. A patient with MDRTB may remain infectious much longer than a patient with drug-susceptible TB. Among new TB cases, drug resistance to at least one drug is as high as 57 percent in Kazakhstan, with a median of 10 percent globally.

- Strains of *Plasmodium falciparum* malaria resistant to first-line drugs have been documented for half a century in Southeast Asia and South America and more recently in Africa. Current levels of failed treatment are as high as 75 percent in some parts of Africa, and there is evidence that malaria mortality, especially in children under the age of 5, is rising as a consequence of increasing resistance.

Economic Burden

The expanding scope of drug-resistance among major infectious diseases also carries a substantial economic burden in developing countries, although the full amount has not been assessed. In the United States, estimates of the loss of antibiotic effectiveness in outpatient prescriptions because of drug resistance range from US$378 million up to US$18.6 billion. Patients infected with resistant strains are more likely to be sicker, to spend more time in the hospital, and to die of the infection. Another important cost of resistance comes from the need to move to much more expensive second-line or third-line treatments when first-line drugs fail.

Interventions

One way to fight drug resistance to a disease is to decrease the number of people affected by that disease. Reducing disease incidence through better hospital infection control, for instance, diminishes the need for drug treatment and lowers the likelihood that resistant strains will emerge. Some interventions, such as using combinations of drugs, reduce the likelihood that resistance will emerge, while others, such as ensuring that health professionals prescribe the proper drug dose and that patients comply with the treatment regimen, reduce the likelihood that a resistant pathogen will survive and proliferate.

IMPROVE DRUG TREATMENT STRATEGIES

Choosing and using the right drug at the right dose is an important way to combat drug resistance. Combinations of drugs, such as those used to treat malaria or HIV, have been successful because they reduce the likelihood that a resistant strain of the disease-causing organism will arise. Artemisinin was developed as a first-line antimalarial because of widespread resistance to chloroquine. Artemisinin acts against the malaria parasite rapidly, potently, and with few side effects. But artemisinin has recently been shown to promote drug resistance when used alone, prompting the World Health Organization (WHO) to recommend that it be used only in combination with other drugs to prolong its effective therapeutic benefits.

REDUCE SELECTION PRESSURE

Educate Health Workers to Curb Inappropriate Prescribing. Altering prescriber behavior is important to control drug resistance, but the widespread availability of drugs without a prescription can undermine control efforts. Studies in developing countries have shown that as many as one-third of drug prescriptions, accounting for 20 percent to 50 percent of drug costs, are not appropriate, and that antimicrobials are among the most frequently prescribed drugs. Physicians, pharmacists, and patients have few incentives to consider the effects of their prescriptions

or drug use on overall levels of resistance and the burden imposed on the rest of society. Physicians may derive income from selling drugs, which could offer an incentive for them to prescribe antibiotics more frequently than necessary.

Continuing education for health workers has proved to be an effective intervention for controlling drug-resistance by improving certain health outcomes by 5 percent to 20 percent among both private and public providers. Some successful education programs have enhanced the ability to diagnose health conditions, reduced unjustified prescriptions of antimicrobials, and deflected patient pressure to prescribe inappropriate drugs as well as patient use of multiple medications.

Train Drug Dispensers to Require Prescriptions and Make Referrals. Drug distributors—pharmacists, pharmacy attendants, patent medicine stall keepers, and itinerant drug sellers—are an important source of primary care for people in many developing countries, and they often sell drugs without prescription. Many of these dispensers have not been formally trained in diagnosis and prescription and perform those tasks with varying degrees of competence. Educational interventions with drug dispensers have been successful in encouraging them to require prescriptions for drug purchases and asking them to refer customers for additional medical advice when appropriate.

The quality of widely available drugs is important because patients who use suboptimal doses may promote drug resistance. Although only a handful of studies have been done on drug quality, the studies to date show that one-half of the antimicrobials marketed in developing countries do not match their labels—either the dose or the ingredients are wrong. Substandard drugs—those that have degraded as a result of expiration or improper storage, or are counterfeit—also contribute to drug resistance.

Improve Patient Treatment Compliance. Improving communication between patients and providers could improve adherence to prescribed drug regimens and reduce self-medication. In the case of some diseases, such as malaria, compliance can also be positively affected by packaging. Blister packages, with individual doses, are an inexpensive option for administering drugs in durable, transparent, and tamper-proof packaging. When combined with proper instruction about drug use, blister packages have been shown to produce modest increases in antimalarial compliance, especially for long-term regimens. Blister packages are also time savers for health care workers, allowing them more time for advising patients on drug use.

Experience in the treatment of TB provides an illustrative success story. One of the most cost-effective of all public health strategies is DOTS. The DOTS approach can improve patient compliance, cure a majority of new cases, and prevent both the transmission of TB and the emergence of MDRTB. Research has demonstrated that both institutional and community-based DOTS programs are effective, permitting cost-effective implementation even in remote areas. DOTS needs good laboratory support for case identification and is highly labor-intensive because it requires staff to supervise drug ingestion by patients. However, the staff do not need to be highly trained health workers. Studies have shown that DOTS can be effective when drug administration is supervised by appropriately trained volunteers, including storekeepers and former TB patients. DOTS has also been shown to cure 50 percent of MDRTB patients.

DECREASE ANTIBIOTIC USE IN ANIMALS

Antibiotics use in animals can hasten the emergence of resistant pathogens in humans. The WHO has recommended that antimicrobials normally prescribed for humans should no longer be used to promote growth in animals. Some European countries, including Denmark and Sweden, have already phased out use of antibiotics in animals.

CONTAIN THE SPREAD OF RESISTANT MICROORGANISMS

Institute Simple Disease Control Practices. Other simple interventions can contain the spread of disease and of resistant microbes. Hand washing, a simple, cost-effective intervention, has been shown to reduce diarrhea by as much as 47 percent, to interrupt the transmission of hospital pathogens, and to reduce respiratory infection-related mortality and morbidity. Insecticide-treated bednets are important in containing the spread of malaria. Improved infection control practices in hospitals can contain hospital-acquired infections, which rank among the most important direct and indirect cause of death worldwide, but optimal infection-control approaches have yet to be identified.

Coordinate Globally. Drug resistance is spread rapidly through international travel and trade, and may threaten many health gains made in the last half-century. Global coordination is needed to monitor and contain antimicrobial resistance. Private and public investment in the research and development of drugs, vaccines, and other infectious disease-control products is weak, currently amounting to less than 2 percent of total health research expenditures throughout the world. Pharmaceutical companies need incentives to invest in new classes of drugs that are less likely to cause resistance and are more appropriate for low-resource settings.

For More Information

Ramanan Laxminarayan et al. 2006. "Drug Resistance." *In Disease Control Priorities in Developing Countries*, 2nd ed., ed. D.T. Jamison, J.G. Breman, A.R. Measham, G. Alleyne, M. Claeson, D.B. Evans, P. Jha, A. Mills, and P. Musgrove, 1031-51. New York: Oxford University Press.