POLICY: BIOMEDICINE

Containment of Antibiotic Resistance

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There is growing concern that the control of infectious diseases is threatened by the upward trend in the numbers of bacteria that are resistant to multiple antibiotics in the medical armamentarium. Resistance costs money and human lives. Resistant infections are associated with increased morbidity, prolonged hospital stays, greater direct and indirect costs, prolonged periods during which individuals are infectious, and greater opportunities for the spread of infection to other individuals (*1*). In many developing countries, the availability and use of antibiotics are poorly controlled, which results in a high rate of resistance, particularly to the older antibiotics (*2*). The high cost of the few remaining second-line antibiotics makes them an unrealistic choice where they are most needed.

As there is no systematic global, and in most cases national, surveillance of antibiotic resistance, insufficient data are available to quantify the problem. However, the trend of increasing prevalence of resistant isolates and increasing requirements for second- or third-line drugs is evident (*3*). Alternatives to antibiotics for patient management must be developed (*4*).

The need to contain resistance

Although there has been a reawakening of interest in the anti-infective therapeutic area among research-based pharmaceutical companies, the development of a new drug is a long and costly process. Furthermore, resistance will inevitably emerge to these new therapeutic agents as well.

To restrain the evolution of resistance, we need to reduce selective pressure from the presence of antibiotics. However, there is a dearth of scientific and medical evidence about how this can be accomplished. Many different aspects of drug use could be addressed, and at present it is not clear which of them is the most important. The impact on human infections of the use of antibiotics in animals and on crops remains unquantified but is cause for concern (*5*). We propose a broad strategy: improve the rational use of antibiotics in human medicine, reduce the global selective pressure of antibiotics by reducing or eliminating uses other than in human medicine, and reduce the spread of resistant organisms by improving hospital hygiene and public health infrastructure. These principles apply to both developed and developing countries, although in practice the balance between activities needs to be tailored to the national situation and to hospital and community settings.

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Improve rational use

The decision about whether to prescribe an antibacterial drug, and which one to prescribe, depends on knowledge of the likely cause of the patient's infection, the correct and appropriate drug to use (which includes considerations of efficacy, safety, and cost), and the drug's availability to the patient. Because incorrect use of antibiotics can augment the development of resistance, sufficient information should be provided so that patients understand how to take the drug, and mechanisms ensuring patient adherence to the full treatment should be explored.

Antibiotic prescribing is usually empiric, without laboratory confirmation of infection. In a study on the management of tonsillitis in 17 European countries, between 68 and 100% of patients were prescribed antibiotics; in over 40% of the cases prescription was empiric (*6*). In Canada, as many as half of the 26 million antibiotic prescriptions dispensed annually have been estimated to be unnecessary (*7*). Twelve million antibiotic prescriptions to adults in the United States in 1992 were for upper respiratory tract infections and bronchitis, on which these drugs have little or no effect (*8*). Such overprescription for upper respiratory infections and bronchitis results from patients' expectations and physicians' habits.

In the absence of laboratory confirmation that an infection would be responsive to antibiotics, prescriptions should be based on treatment guidelines that are updated regularly on the basis of local and national resistance surveillance (*9*). A systematic audit of public and private adherence to these guidelines should be in place (*10*). Treatment guidelines should be linked to a local or national formulary ensuring that essential antibiotic agents are available. In addition, the use of antibiotics for prophylaxis should be restricted to proven indications and be closely monitored.

Self-prescribing, erratic antibiotic supply, and counterfeit or low-quality antibiotics contribute to antibiotic resistance, especially in developing countries (*11*). Antibiotics should be available only when prescribed by a trained and registered health care professional (*12*). There must be a distinction between prescribers and providers so that the prescribers (or their institutions) make no financial gain from the prescription. The provider must be able to ensure the quality of the drugs supplied, and efforts must be sustained to eliminate counterfeit drugs (*12*).

Laboratory workers must be capable of isolating infectious agents or performing appropriate tests to diagnose infections. Antibiotic susceptibility tests should be performed with results made available quickly so that the prescriber can interpret and act on them. The quality of laboratory results should be monitored internally and through an external quality assurance scheme as part of a laboratory accreditation system.

Reduce the spread of resistance

All the principles that apply to the control of the spread of infection apply equally, if not more so, to the control of the spread of resistant pathogens, regardless of whether spread takes place in a hospital ward, between individuals in a community, from contaminated water supplies, or between animals and humans through the food chain. The dramatic increase in international travel has increased the opportunities for same-day global dissemination of resistant organisms.

Infection control practices should be reinforced where they exist and introduced where they are lacking. In the United States, where nosocomial infections affect over two million patients per year and were estimated to cost U.S. $4.5 billion in 1992, an infection control program that prevents at least 6% of the hospital infections would be cost-effective (*13*). An estimated nosocomial infection rate of 5% in South African hospitals represents an estimated annual cost of U.S. $82 million per year. This could increase to U.S. $250 million if the nosocomial infection rate approaches the rates in some developing countries (15%) (*14*). The costs associated with infection control need to be properly identified and offset by direct and indirect cost savings from reductions in morbidity and mortality from infection (*13*).

Implementing a containment strategy

The strategic elements outlined above are not new, and policies incorporating some of them are in place in countries around the

A related commentary on antibiotic use in agriculture appeared in last week's issue.

world. What is lacking is comprehensive implementation of a strategy addressing all of the issues and a means of evaluating success. In the meantime, antibiotic consumption continues to rise and resistance rises along with it. Implementation can be improved by four main approaches: education and training, technical developments, surveillance, and statutory regulation. The development of appropriate public health infrastructures is important to achieve containment in both hospital and community settings.

Education. There is a widespread view that antibiotics are magic bullets that are never harmful and may be beneficial. Modifying this view is essential to improving rational use.

Prescribers need to remain up to date on diagnosis and treatment of infections and not succumb to patient pressure or fear of litigation. The education process must start in the training institutions but continue throughout professional life. It must be unbiased; at present, prescribers receive much of their continuing education from the pharmaceutical industry and this must be balanced by education from other sources. Education must extend to all those who prescribe, be they physicians, pharmacists, or other health care workers. WHO's Model List of Essential Drugs (*15*) and disease-specific treatment guidelines are useful sources of information and models for drafting national guidelines.

Users also need to be educated about the risks and benefits of antibiotics. Consumer organizations and the media can play a valuable role if they are provided with the correct messages. Good hygiene and prevention of infection should be an essential part of every school curriculum.

Laboratory workers need training to carry out the right diagnostic tests, to detect resistance in vitro, and to produce relevant results. Continuing education about antibiotics and resistance is essential to enable laboratory workers to select appropriate "drug-bug" combinations for testing and to interpret results accurately.

Technical developments. Development of simplified diagnostic tests that permit close-to-the-patient testing should be sustained in order to improve the accuracy of diagnoses and provide the prescriber with better information on which to base treatment decisions. The need for affordable diagnostic tests in developing countries is enormous; a similar need exists in the developed world, where hospital managers aim to cut costs. Vaccine development should be sustained.

Surveillance. Information on antibiotic susceptibility that is generated as part of routine microbiological examination of patients' specimens can be a useful source of resistance surveillance data if they can be adequately compared to baseline data. Additional epidemiological and clinical information on patients infected with resistant organisms is particularly valuable and should be gathered wherever possible. Local and national surveillance networks should be established to collate results and use them to update treatment guidelines and lists of essential drugs (*16*). Monitoring of antibiotic usage must be a part of surveillance. For example, Denmark, where rates of antibiotic resistance are very low, has introduced comprehensive monitoring of the consumption of antimicrobial drugs and the occurrence of resistant microbial strains in animals, food, and humans (*17*). The development of a single internationally accepted standard for performance and interpretation of these tests should be encouraged.

Statutory regulation. No amount of education or technical advance will change prescribing patterns if individual or hospital income depends on profit from prescribing. In health care, other sources of income may need to be identified to compensate for the income lost because of reduced prescribing.

Regulation is required to limit the over-the-counter sale of antibiotics and to ensure that the quality of drug manufacture meets the standards of Good Manufacturing Practice (*18*), and providers and prescribers should make every effort to use antibiotics that meet these standards. At the same time, pharmaceutical companies have a responsibility to comply with ethical standards of promotion of their drugs (*19*).

Extending the terms of routine surveillance to include a requirement for statutory notification about pathogens with new or unusual resistance phenotypes is under active discussion in a number of countries. The International Health Regulations, currently undergoing a major revision, will propose a requirement to report a major shift in endemic disease, including the emergence of antibiotic resistance.

Conclusions

WHO recognizes the risks to human health posed by the growing problem of antibiotic resistance and is actively engaged with its member states in many aspects of the strategy outlined above, particularly in strengthening surveillance for resistance; promoting rational use of antibiotics through treatment guidelines and lists of essential drugs; and educating prescribers, pharmacists, health care workers, and the public. Further concerted efforts are needed to implement and evaluate the outcome of this strategy to contain resistance.

Research is needed on a series of issues to improve our chances of dealing with this threat in a more rational and effective manner. It will be necessary to define optimal use of antibiotics to achieve maximum therapeutic effect with minimum selective pressure for resistance. Specificity of standard case management algorithms needs to be increased. Studies should be designed to evaluate the predictive value of in vitro antimicrobial susceptibility tests for clinical outcome. We should also encourage studies of behaviors that encourage misuse and ways to modify them. Finally, it is vital to develop and evaluate specific interventions designed to contain resistance.

Some of the elements of this strategy have been tested in several countries (*2*, *10*, *20*, *21*), but now the environment in which they operate is changing. The relentless increase in the emergence, evolution, and spread of resistance and the lack of new antibiotics that are active against resistant strains have brought the fear that we may truly be entering the post-antibiotic era.

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