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Antimicrobial resistance

Since their discovery during the 20th century, antimicrobial agents (antibiotics and related medicinal drugs) have substantially reduced the threat posed by infectious diseases. The use of these "wonder drugs", combined with improvements in sanitation, housing, and nutrition, and the advent of widespread immunization programmes, has led to a dramatic drop in deaths from diseases that were previously widespread, untreatable, and frequently fatal. Over the years, antimicrobials have saved the lives and eased the suffering of millions of people. By helping to bring many serious infectious diseases under control, these drugs have also contributed to the major gains in life expectancy experienced during the latter part of the last century.

These gains are now seriously jeopardized by another recent development: the emergence and spread of microbes that are resistant to cheap and effective first-choice, or "first-line" drugs. The bacterial infections which contribute most to human disease are also those in which emerging and microbial resistance is most evident: diarrhoeal diseases, respiratory tract infections, meningitis, sexually transmitted infections, and hospital-acquired infections. Some important examples include penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, multi-resistant salmonellae, and multi-resistant *Mycobacterium tuberculosis.* The development of resistance to drugs commonly used to treat malaria is of particular concern, as is the emerging resistance to anti-HIV drugs.

CONSEQUENCES

The consequences are severe. Infections caused by resistant microbes fail to respond to treatment, resulting in prolonged illness and greater risk of death. Treatment failures also lead to longer periods of infectivity, which increase the numbers of infected people moving in the community and thus expose the general population to the risk of contracting a resistant strain of infection.

When infections become resistant to first-line antimicrobials, treatment has to be switched to second- or third-line drugs, which are nearly always much more expensive and sometimes more toxic as well, e.g. the drugs needed to treat multidrug-resistant forms of tuberculosis are over 100 times more expensive than the first-line drugs used to treat non-resistant forms. In many countries, the high cost of such replacement drugs is prohibitive, with the result that some diseases can no longer be treated in areas where resistance to first-line drugs is widespread. Most alarming of all are diseases where resistance is developing for virtually all currently available drugs, thus raising the spectre of a post-antibiotic era. Even if the pharmaceutical industry were to step up efforts to develop new replacement drugs immediately, current trends suggest that some diseases will have no effective therapies within the next ten years.

CAUSES

Microbes (the collective term for bacteria, fungi, parasites, and viruses) cause infectious diseases, and antimicrobial agents, such as penicillin, streptomycin, and more than 150 others, have been developed to combat the spread and severity of many of these diseases. Resistance to antimicrobials is a natural biological phenomenon that can be amplified or accelerated by a variety of factors, including human practices. The use of an antimicrobial for any infection, real or feared, in any dose and over any time period, forces microbes to either adapt or die in a phenomenon known as "selective pressure". The microbes which adapt and survive carry genes for resistance, which can be passed on.

Bacteria are particularly efficient at enhancing the effects of resistance, not only because of their ability to multiply very rapidly but also because they can transfer their resistance genes, which are passed on when the bacteria replicate. In the medical setting, such resistant microbes will not be killed by an antimicrobial agent during a standard course of treatment. Resistant bacteria can also pass on their resistance genes to other related bacteria through "conjugation", whereby plasmids carrying the genes jump from one organism to another. Resistance to a single drug can thus spread rapidly through a bacterial population. When anti-microbials are used incorrectly - for too short a time, at too low a dose, at inadequate potency; or for the wrong disease - the likelihood that bacteria and other microbes will adapt and replicate rather than be killed is greatly enhanced.

Much evidence supports the view that the total consumption of antimicrobials is the critical factor in selecting resistance. Paradoxically, underuse through lack of access, inadequate dosing, poor adherence, and substandard anti-microbials may play as important a role as overuse. For these reasons, improving use is a priority if the emergence and spread of resistance are to be controlled.

UNPRECEDENTED TRENDS

In the past, medicine and science were able to stay ahead of this natural phenomenon through the discovery of potent new classes of antimicrobials, a process that flourished from 1930-1970 and has since slowed to a virtual standstill, partly because of misplaced confidence that infectious diseases had been conquered, at least in the industrialized world. In just the past few decades, the development of resistant microbes has been greatly accelerated by several concurrent trends. These have worked to increase the number of infections and thus expand both the need for antimicrobials and the opportunities for their misuse. Such trends include:

- urbanization with its associated overcrowding and poor sanitation, which greatly facilitate the spread of such diseases as typhoid, tuberculosis, respiratory infections, and pneumonia;
- pollution, environmental degradation, and changing weather patterns, which can affect the incidence and distribution of infectious diseases, especially those, such as malaria, that are spread by insects and other vectors;
- demographic changes, which have resulted in a growing proportion of elderly people needing hospital-based interventions and thus at risk of exposure to highly resistant pathogens found in hospital settings;
- the AIDS epidemic, which has greatly enlarged the population of immunocompromised patients at risk of numerous infections, many of which were previously rare;
- the resurgence of old foes, such as malaria and tuberculosis, which are now responsible for many millions of infections each year;
- the enormous growth of global trade and travel which have increased the speed and facility with which both infectious diseases and resistant microorganisms can spread between continents.

As the number of infections and the corresponding use of antimicrobials have increased, so has the prevalence of resistance. In addition, the enhanced food requirements of an expanding world

population have led to the widespread routine use of antimicrobials as growth promoters or preventive agents in food-producing animals and poultry flocks. Such practices have likewise contributed to the rise in resistant microbes, which can be transmitted from animals to man.

FACTORS THAT ENCOURAGE THE SPREAD OF RESISTANCE

The emergence and spread of antimicrobial resistance are complex problems driven by numerous interconnected factors, many of which are linked to the misuse of antimicrobials and thus amenable to change. In turn, antimicrobial use is influenced by an interplay of the knowledge, expectations, and interactions of prescribers and patients, economic incentives, characteristics of a country's health system, and the regulatory environment.

Patient-related factors are major drivers of inappropriate antimicrobial use. For example, many patients believe that new and expensive medications are more efficacious than older agents. In addition to causing unnecessary health care expenditure, this perception encourages the selection of resistance to these newer agents as well as to older agents in their class.

Self-medication with antimicrobials is another major factor contributing to resistance. Self-medicated antimicrobials may be unnecessary, are often inadequately dosed, or may not contain adequate amounts of active drug, especially if they are counterfeit drugs. In many developing countries, antimicrobials are purchased in single doses and taken only until the patient feels better, which may occur before the pathogen has been eliminated. Inappropriate demand can also be stimulated by marketing practices. Direct-to-consumer advertising allows pharmaceutical manufacturers to market medicines directly to the public via television, radio, print media, and the Internet. In particular, advertising on the Internet is gaining market penetration, yet it is difficult to control with legislation due to poor enforceability.

Prescribers' perceptions regarding patient expectations and demands substantially influence prescribing practice. Physicians can be pressured by patient expectations to prescribe antimicrobials even in the absence of appropriate indications. In some cultural settings, antimicrobials given by injection are considered more efficacious than oral formulations. Such perceptions tend to be associated with the over-prescribing of broad-spectrum injectable agents when a narrow-spectrum oral agent would be more appropriate. Prescribing “just to be on the safe side" increases when there is diagnostic uncertainty, lack of prescriber knowledge regarding optimal diagnostic approaches, lack of opportunity for patient follow-up, or fear of possible litigation. In many countries, antimicrobials can be easily obtained in pharmacies and markets without a prescription.

Patient compliance with recommended treatment is another major problem. Patients forget to take medication, interrupt their treatment when they begin to feel better, or may be unable to afford a full course, thereby creating an ideal environment for microbes to adapt rather than be killed. In some countries, low quality antibiotics (poorly formulated or manufactured, counterfeited or expired) are still sold and used for self-medication or prophylaxis.

Hospitals are a critical component of the antimicrobial resistance problem worldwide. The combination of highly susceptible patients, intensive and prolonged antimicrobial use, and cross-infection has resulted in nosocomial infections with highly resistant bacterial pathogens. Resistant hospital-acquired infections are expensive to control and extremely difficult to eradicate. Failure to implement simple infection control practices, such as handwashing and changing gloves before and after contact with patients, is a common cause of infection spread in hospitals throughout the world. Hospitals are also the eventual site of treatment for many patients with severe infections due to resistant pathogens acquired in the community. In the wake of the AIDS epidemic, the prevalence of such infections can be expected to increase.

Veterinary prescription of antimicrobials also contributes to the problem of resistance. In North America and Europe, an estimated 50% in tonnage of all antimicrobial production is used in food-producing animals and poultry. The largest quantities are used as regular supplements for prophylaxis or growth promotion, thus exposing a large number of animals, irrespective of their health status, to frequently subtherapeutic concentrations of antimicrobials. Such widespread use of antimicrobials for disease control and growth promotion in animals has been paralleled by an increase in resistance in those bacteria (such as *Salmonella* and *Campylobacter*) that can spread from animals, often through food, to cause infections in humans.

THE NEED FOR A GLOBAL RESPONSE

In September 2001, WHO launched the first global strategy for combating the serious problems caused by the emergence and spread of antimicrobial resistance. Known as the WHO Global Strategy for Containment of Antimicrobial Resistance, the strategy recognizes that antimicrobial resistance is a global problem that must be addressed in all countries. No single nation, however effective it is at containing resistance within its borders, can protect itself from the importation of resistant pathogens through travel and trade. Poor prescribing practices in any country now threaten to undermine the potency of vital antimicrobials everywhere.

The strategy recommends interventions that can be used to slow the emergence and reduce the spread of resistance in a diverse range of settings. The interventions are organized according to groups of people whose practices and behaviours contribute to resistance and where changes are judged likely to have a significant impact at both national and international levels. These include consumers, prescribers and dispensers, veterinarians, and managers of hospitals and diagnostic laboratories as well as national governments, the pharmaceutical industry, professional societies, and international agencies. Global principles for the containment of antimicrobial resistance in food-producing animals were issued by WHO in June 2000.

As much of the responsibility for containing resistance rests with national governments, the strategy gives particular attention to interventions involving the introduction of legislation and policies governing the development, licensing, distribution, and sale of antimicrobial agents. The strategy is sufficiently flexible to be applied in poor and wealthy nations alike. The process for selecting the necessary interventions to limit emerging antimicrobial resistance can be based on the diseases most prevalent in a given country. In advocating widespread adoption of this strategy, WHO aims to encourage the urgent actions needed to reverse or at least curtail trends which have major economic as well as health implications. Moreover, in view of the global nature of the antimicrobial resistance problem, the efforts of any nation to implement the WHO Global Strategy are likely to be felt worldwide.

The strategy builds on a number of WHO activities aimed at both monitoring the global emergence and spread of antimicrobial resistance and extending direct support to countries. WHO helps countries establish laboratory-based networks for the surveillance of resistance. Specific activities include staff training, support in methods for the quality assurance of laboratory tests, and provision of laboratory reagents. In addition, WHO distributes a computer software program, WHONET. Microbiologists, clinicians, and infection control workers may use this software to improve the systematic monitoring of drug resistance in their hospitals and communities and to share their data in a common format among national networks.

Since 1977, WHO has produced Model Lists of Essential Drugs in order to help governments select the most effective and appropriate drugs in line with priority needs. The lists, which are regularly revised, also contribute to the rational purchasing and use of drugs. Studies have demonstrated that in those areas in which an essential drugs programme is in operation, significantly more essential

drugs are available, significantly fewer injections and antimicrobials are utilized, and drug stocks last about three times longer than in regions without such a programme. At present over 120 countries have implemented an essential drugs list. With the first global strategy for containment of antimicrobial resistance now available, WHO is also in a position to advise health policy-makers and managers on the specific interventions needed to safeguard the effectiveness of vital drugs and thus ensure that their life-saving capacity remains available to future generations.

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