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Cell

Resistance to Anti-Infective Drugs and the Threat to Public Health

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DOI 10.1016/j.cell.2006.02.009

Increasing resistance of pathogens to anti-infective drugs is an urgent public health problem that must be addressed through more prudent use of these drugs in human medicine and in animal husbandry, agriculture, and aquaculture.

Almost all microbes that infect humans, and for which there are anti-infective drugs, have developed some degree of resistance to these drugs, and at a pace more rapid than anticipated (Table 1). Anti-infective drug resistance costs money and human lives. Infections caused by drug-resistant pathogens are associated with increased morbidity and mortality, prolonged hospital stays, greater direct and indirect costs, prolonged periods during which individuals are infectious, and greater opportunities for the spread of infection to others. Recent estimates of the relationship between resistance of pathogens to anti-infective drugs and health care costs suggest that patients in the United States infected with drug-resistant organisms incur average costs ranging from $6000 to $30,000; and that mortality, morbidity, and length of hospitalization all increase as anti-infective drug resistance continues to develop in staphylococci, enterococci, and gram-negative bacilli (Cosgrove, 2006).

Anti-Infective Drugs and the Microbes They Treat

The microbes that cause infectious diseases are complex, dynamic, and constantly evolving. They reproduce rapidly, mutate frequently, freely exchange genetic material, and adapt with relative ease to new environments and hosts. Through these mechanisms, microbes readily develop resistance to the anti-infective drugs used to treat them. A few years after antimicrobial drugs became widely available post-World War II, warning signs of anti-infective drug resistance began to appear. By the end of the 1940s, for example, soon after the introduction and widespread use of penicillin, the prevalence of penicillin-resistant hospital strains of staphylococcus in the United Kingdom was 14%. By the end of the 1990s, staphylococcal resistance worldwide had risen to levels of 95% or greater, and *Staphylococcus aureus* had accumulated resistance genes to virtually all currently available antimicrobial drugs, with methicillin-resistant infections disseminated in hospital settings and communities (Levy, 1992).

Table 1. Antimicrobial Resistance Rates (2005)

Malaria	0%–82% chloroquine resistance
Tuberculosis	0%–17% primary multi-drug resistance (3% mean worldwide)
HIV	0%–25% primary resistance to at least one antiretroviral drug
Gonorrhea	5%–98% penicillin resistance
Pneumonia and bacterial meningitis	0%–70% penicillin resistance (*Streptococcus pneumoniae*)
Hospital infections	0%–70% resistance to all penicillins and cephalosporins

Source: WHO Policy Perspectives on Medicine, 2005.

These warning signs were largely ignored, however, as new anti-infective drugs continued to be developed, and as the incidence and prevalence of infectious diseases in industrialized countries steadily declined. With the widespread availability of antimalarial drugs and intensified control of its mosquito vector in the early part of the twentieth century, the incidence of malaria rapidly decreased, and in the case of the Southern United States and Southern Europe disappeared. In the 1940s, tuberculosis (TB) hospitals in Europe and the United States started to empty as living conditions improved and effective drugs became available to treat those with acute TB, preventing infection of patient contacts (also see the Essay by D. Young and C. Dye, page 683 of this issue). Simultaneously, a host of hospital-acquired infections that had endangered the lives of hospitalized patients and health workers came under better control, and sexually transmitted infections could easily be cured (Armstrong, Conn, Pinner, 1999).

Despite this progress, more than 14 million humans continue to die each year from infectious diseases, mostly

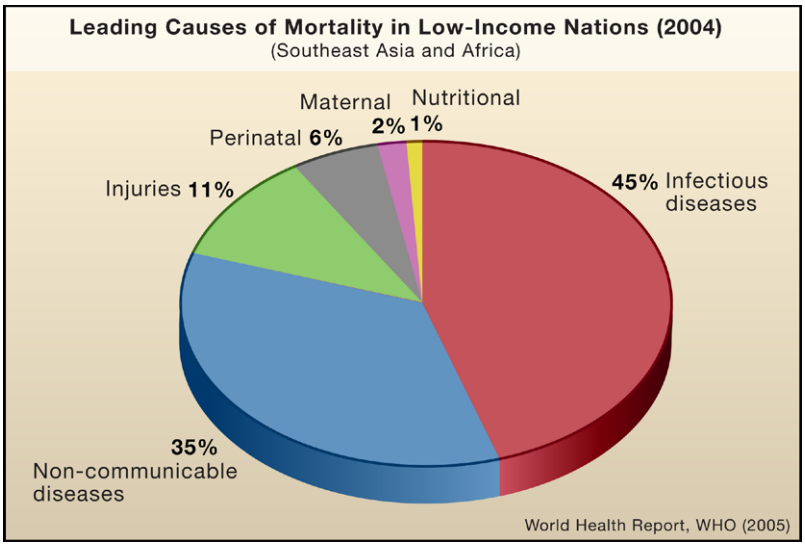

Figure 1. Leading Causes of Mortality in Low-Income Nations (2004)

in developing countries where it is estimated that infectious diseases represent 46% of all deaths (Figure 1). Approximately 90% of these deaths are from six major infections: diarrhoeal diseases; acute respiratory infections; malaria and measles among children less than 5 years of age; and AIDS and tuberculosis, mainly among adults (WHO, 1999). Anti-infective drugs save lives, but as resistance to them continues to emerge in a host of pathogens their effectiveness wanes. Resistance to anti-infective drugs has contributed to recent increases in infectious disease mortality worldwide and is an urgent public health problem.

Anti-Infective Drugs: Rapid Evolution of Resistance

In New York City in the 1990s, multidrug-resistant strains of *Mycobacterium tuberculosis* gained a foothold in hospitals and prisons and among homeless populations. Simultaneously, multidrug-resistant TB emerged in the Russian Federation and its incidence more than doubled in less than seven years, with over 20% of TB patients in prison settings infected with multidrug-resistant strains. In 2000, it was estimated that approximately 3% of all TB infections worldwide were multidrug resistant, and that percentage continues to increase (Dye et al., 2002). Whereas a single six-month course of drug treatment for nonresistant pulmonary TB costs as little as $20, treatment for multidrug-resistant TB can cost well over $2000 because of increased costs for second-line drugs, prolonged hospitalization, and longer treatment regimens. Such high costs put these drugs beyond the realm of many developing countries, and in some TB can no longer be effectively managed, resulting in increased mortality from this disease. Finally, treatment failure in TB patients with multidrug-resistant infections who are then treated with second-line drugs range from 20% to 40%, necessitating additional treatment with even more expensive drugs that often have unpleasant side effects.

By 1976, resistance of the malaria parasite *Plasmodium falciparum* to the cheap and effective frontline drug, chloroquine, was widespread in southeastern Asia; by the mid-1990s resistance to chloroquine was worldwide. Worse yet, the malaria parasite has also developed high-level resistance to two second-level antimalarials, sulfadoxine-pyrimethamine and mefloquine. Currently resistance is developing to antimalarial drugs with increasing rapidity, and it is now recommended that multidrug combinations be used, each with independent modes of action and different biochemical targets, in an effort to slow the development of resistance and better preserve existing antimalarial drugs. This is especially true for the newer antimalarial drugs such as the artemesinin derivatives (Jung et al., 2004). Mortality estimates from public health records in Africa indicate 2- to 11-fold increases in malaria-associated mortality among children when drug resistance develops, with hospital attendance and admissions showing similar increasing trends.

In the 1970s, *Neisseria gonorrhoeae* resistant to the usual doses of penicillin was introduced into Europe and the United States from Southeast Asia, where it is thought to have emerged; by the mid-1990s resistance of this bacterium to penicillin had spread worldwide. Low-cost antibiotics such as penicillin can no longer be used to treat gonorrhea, and gonococcal strains resistant to all major families of antibiotics have now been identified wherever these antibiotics have been widely used. Some countries report that more than 70% of gonococcal infections are caused by bacteria that are resistant to the quinolone ring (the active moiety of many antibiotics).

Nor have antiviral drugs been spared. Resistance to antiretroviral drugs among 96 treatment naive HIV-infected individuals in Mexico, for example, was reported at 6% for delaviridine and nevirapine, 4% for efavirenz, and 2% for almivudine and nelfinavir (Escoto-Delgadillo et al., 2005). Similar levels of resistance have been found among HIV treatment naive patients in the Horn of Africa and elsewhere, necessitating the use of multidrug combinations in order to slow the evolution of HIV strains resistant to current antiretrovirals.

Last year, 91% of influenza infections in the United States—caused by influenza virus A strain H3N2—were found to be resistant to both adamantadine and rimantadine, two drugs regularly used to treat

seasonal influenza (CDC, 2005). Resistance has not yet developed to two other drugs (oseltamivir and zenamivir) used to treat this strain of influenza, but there is great fear that resistance to these two drugs will also eventually develop. In Thailand, low-level resistance to oseltamivir appears to have developed in sporadic human infections caused by the H5N1 avian influenza virus strain (de Jong et al., 2005). This has raised serious concerns given that the H5N1 strain continues to cause sporadic human infections and poses a pandemic threat (see the Commentary by A. Fauci, page 665 of this issue).

Anti-Infective Drug Resistance: Its Impact and Evolution in Humans

The natural phenomena that cause the development of drug resistance—mutation at anti-infective target sites, the acquisition of resistance mechanisms by genetic transfer—are exacerbated and amplified by events that increase the selective pressure on anti-infective drugs. These include the misuse of anti-infective drugs in the treatment of human and animal illnesses and indiscriminate use in animal husbandry, aquaculture, and agriculture.

It is paradoxical that selective pressure due to misuse of anti-infective drugs can be increased by either under use or over use. In developing countries, it is inadequate or inconsistent access to drugs leading to truncated treatment, or a failure to take the full course of therapy, that increase selective pressure. This is compounded by self-prescription and purchase of anti-infective drugs on the open market due to lack of enforcement of legislation or the sale of counterfeit drugs with substandard or insufficient active ingredients. Between January 1999 and October 2000 alone, among 46 confidential reports of counterfeit drugs from 20 countries, 32% contained no active ingredient, and the rest either had incorrect quantities of active ingredients, extraneous ingredients, or impurities. In many developing countries, the higher cost and limited availability of the few remaining second-line anti-infective drugs makes them an unrealistic choice where they are most needed.

In industrialized countries, it is often the overprescribing of antibiotics by health workers and excessive demand for antibiotics by the general population that increase selective pressure and amplify the selection and survival of resistant microbes. Antibiotics are often prescribed empirically in the absence of laboratory confirmation of infection. In a study on the management of tonsillitis in 17 European countries, for example, between 68% and 100% of patients were prescribed antibiotics, and in more than 40% of these cases prescription was empirical. In Canada, as many as half of the 26 million antibiotic prescriptions dispensed annually are estimated to be unnecessary (Kondro, 1997), and during a recent year in the United States, 12 million antibiotic prescriptions were provided to adults for upper respiratory tract infections where they have little or no effect.

Over-use and under-use of antibiotics occurs simultaneously in most countries, however, and is linked to economic status and the ability to pay for healthcare. In Thailand, over the course of a year, 60% of viral infections were improperly treated with an antibiotic, and 89% of bacterial infections were correctly treated with an antibiotic, most often amoxicillin (Suttajit et al., 2005). Those receiving antibiotics were young, male, and could afford to pay, whereas significantly fewer antibiotics were used to treat non-paying patients.

Indiscriminate Use in Animal Husbandry, Aquaculture, and Agriculture

Anti-infective drugs are vital in the treatment of infections in animals. In many countries, 50% of all anti-infective drug production each year is for animal husbandry. Antibiotics are added to animal feed (particularly that of pigs and poultry) for mass prophylaxis against infections or for growth promotion, and to water to treat fish diseases. Anti-infective drugs are considered important for sustainable livestock production and for the control of animal infections that can be passed on to humans as zoonoses.

Certain anti-infective drugs administered to animals are also used for disease control in humans resulting in selection for crossresistance in microbes that are important in human medicine or for resistant organisms that can be passed from animals to humans. The relationship between the increase in prevalence and distribution of drug-resistant infections and the use of antibiotics in animals is poorly understood, but they are clearly related.

Anti-infective drugs are often used as pesticides for treating fruit trees and other agricultural products ranging from rice to orchids. In the United States, about 300,000 pounds of oxytetracycline and streptomycin are sprayed on fruit trees each year to prevent infection with *Erwinia amylovora*, the bacterial cause of fire blight (NAS, 1998). Development and transfer of drug resistance to other organisms may be caused by such agricultural use. There is, however, little hard evidence to show the importance that anti-infective use in agriculture has on the environment and on human infections, principally because of the difficulty in attributing risk to practice.

International Spread of Anti-Infective Drug Resistance

Drug-resistant organisms are not only a problem locally, they can also spread rapidly throughout the world in humans, animals, vectors, or food (WHO, 2001). In 1997, the multidrug-resistant serotype 23F of *Streptococcus pneumoniae*, which caused an outbreak of infection in a daycare center in South Africa, was found to be identical to a clone isolated in Spain and also to strains circulating in Korea. Meanwhile, multidrug-resistant salmonella isolates arrived in Denmark through importing infected boar from Canada; such isolates have spread internationally via livestock including horses.

Improved Use of Anti-Infective Drugs

Greater efforts must be made to reduce selective pressure on anti-infective drugs. There is a lack of scientific and medical evidence to indicate how this can be done, but all aspects of anti-infective drug use in humans, animals, and agriculture must be addressed. It is not clear how to prioritize interventions, and so a broad strategy is required. This strategy necessitates more prudent use of antibiotics in human medicine, in animal medicine, and in animal husbandry/agriculture and measures to prevent the spread of drug-resistant organisms, including better surveillance because border controls are difficult to enforce and are not effective. Although these measures apply to both developed and developing countries, the balance between activities must be tailored to the quantity and patterns of anti-infective drug use.

Many infections can be prevented and transmission reduced through simple, cheap, and effective measures such as hand washing, the use of bed nets, condoms, and vaccination, and avoidance of unnecessary injections, especially where syringes and needles are re-used. The general population can be educated through targeted campaigns with a clear message that emphasizes when anti-infective drugs should be used and when they should not, as well as the dangers of their overuse. In Singapore, hand washing during the 2004 outbreak of severe acute respiratory infection (SARS) was shown to be protective in preventing transmission of SARS within hospitals (Curtis, Cairncross, 2003), and a meta-analysis of seven intervention studies suggests that hand washing in the community can reduce the risk of diarrhoeal disease by up to 47%. Current television campaigns in France emphasize the correct use of anti-infective drugs, and similar campaigns in Canada during the 1990s were shown to markedly decrease requests for antibiotics.

Healthcare providers should be taught about the importance of accurate diagnosis and management of common infections, infection control, and disease prevention throughout their training as well as through in-service education. The development and use of clinical guidelines at each level of care containing currently recommended doses and duration of treatment (as well as the maximum use of the recommended drug combinations for treating HIV, TB, and malaria) are also strongly recommended.

Other measures include stronger and more rapid diagnosis of infectious diseases and restricting availability to prescriptions to licensed outlets, establishment of infection control programs in hospitals, and vigilance against counterfeit drugs by restricting marketing authorization to those anti-infective drugs meeting international standards of quality, safety, and efficacy. Finally, the development of simple diagnostic tests and technologies that facilitate accurate diagnosis would permit more sparing use of anti-infective drugs.

Farmers and policy-makers should be educated about the appropriate use of anti-infective drugs in animal husbandry, aquaculture, and farming. In particular, they should understand the importance of anti-infective drugs in human health, the need to prevent infection by vaccinating animals when possible, and the need to stop using anti-infective drugs for promoting growth of livestock. It is often those working in human public health who are most able to convince those in the animal and agricultural industries about the importance of safe anti-infective drug use. In addition, safe levels of residues from anti-infective drugs in animal and plant products for human consumption should be established, and regulation of the bulk use of anti-infective drugs should be enforced through legislation at the national level.

The Future

Resistance to anti-infective drugs is an urgent public health problem threatening the treatment and control of infectious diseases ranging from those that have long been endemic in human populations—malaria, TB, and sexually transmitted infections—to those that have recently emerged and become endemic such as HIV. Drug resistance is also a threat to the control of seasonally occurring infections such as meningitis and influenza, and to those that pose pandemic threats such as the H5N1 strain of avian influenza A. Drug-resistant pathogens—whether parasites, bacteria, or viruses—can no longer be effectively treated with common anti-infective drugs. The risk is great that because of drug resistance many more people will die from infectious diseases, and infections associated with major surgery and invasive hospital procedures will become more dangerous.

One of the major responses of medical workers to the problem of drug resistance has been to switch patients from older to newer drugs. Although effective initially, this strategy has resulted in the emergence of resistance to the newer drugs. This, combined with a declining investment in research and development of new classes of anti-infective drugs, has serious consequences for public health.

The ultimate solution to anti-infective drug resistance is prevention of infection through vaccination, and continued research and development of vaccines is an important part of any strategy to address drug resistance. Smallpox, which killed approximately 3 million persons each year as recently as 1967, has been eradicated using an effective and widely available vaccine (Fenner et al., 1988), and poliomyelitis also appears in line for eradication because of an effective vaccine (Heymann and Aylward, 2004). Eradication of these viral diseases has pre-empted the need for antiviral drugs, and resistance has therefore not been an issue. Effective use of vaccines has, in fact, shifted infectious disease morbidity and mortality away from those diseases for which vaccines exist to those infectious diseases for which there are no preventive vaccines, and for which anti-infective drug resistance is now a major risk.

The urgent need to combat drug resistance demands three major responses: conservation of existing anti-infective drugs through prudent use and investment in research and development both for new anti-infective drugs and for vaccines, which are the ultimate solution to infection and drug resistance.

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