Global antibacterial resistance issues

The clinical use of antimicrobial agents has spawned, as an unwanted consequence, the widespread emergence of bacteria resistant to these valuable drugs. During the past fifty years, resistant organisms have caused problems throughout the world, as will be documented in this brief paper.

Without question, the discovery and clinical application of antibacterial agents represents one of the shining achievements of medical science in the 20th century. Dozens of effective antimicrobial agents have been discovered during the past sixty years. However, with the discovery of each new agent, bacteria have found ways to develop resistance. Indeed, this has been a problem since the dawn of the antibiotic era, but antimicrobial resistance was noted even before this. In the early 20th century, ethylhydrocupreine (optochin) was tried for the treatment of pneumococcal pneumonia and a trial in 1917 was terminated because of drug toxicity; the emergence of resistance to the drug during therapy was also noted. This appears to have been the first documentation of the emergence of resistance to an antimicrobial agent in humans. With the discovery of each new class of antimicrobial agents, beginning with the sulfonamides in the 1930s and penicillin in the 1940s, resistance has developed and has become a truly worldwide problem. Initially, medical scientists overcame the problems of resistance by discovering and developing new classes of antimicrobial agents that were effective against resistant organisms. However, in the past twenty years, that developmental pipeline has been progressively drying up and, with the possible exception of the oxazolidinones, no new classes of agents have been discovered for more than two decades.

In most instances, antimicrobial resistance emerges in response to pressure from clinical, agricultural, aquacultural, or industrial use of antimicrobial agents, but in some instances resistant organisms are found in communities in the absence of the heavy use of antimicrobial agents. In the late 1960s and early 1970s, my colleagues and I obtained stool and other cultures from indigenes of the highlands of Malaita, British Solomon Islands, an area where antibiotics had never been used. Although neither streptomycin nor tetracycline had been used in these communities, we found organisms that already contained plasmids bearing genes mediating resistance to tetracycline and streptomycin. Although difficult to prove, we had assumed that resistance of this type occurs because many of the organisms that produce antibiotics are present in nature and it may provide for exposure of organisms (especially enteric pathogens) to antibiotics in the absence of their clinical use. Subsequent studies have confirmed this and documented a remarkable ability of soil organisms to inactivate antibiotics. In some cases, such as inactivation of daptomycin, this mechanism has not yet been seen among clinical isolates. The recent description of multidrug-resistant bacteria in remote areas of Bolivia appears to be another and even more dramatic example of the fact that the occurrence of multiply-resistant bacteria is not always limited to areas of high antibiotic consumption in the clinical arena.

It is often impossible to pinpoint the origin of antibiotic resistant clones because this is dependent upon the likelihood of a qualified investigator identifying the first resistant clones and then carrying out the appropriate studies to characterize them. In the case of Staphylococcus aureus, some of the earliest studies documenting the explosive emergence of resistance to penicillin in this organism were carried out in the early 1940s by Dr Maxwell Finland at the Boston City Hospital in Boston, Massachusetts. Prior to the use of penicillin, virtually all strains of S. aureus were susceptible to penicillin. Following its introduction for clinical use at the Boston City Hospital in the early 1940s, there was rapid emergence of resistance and by 1947, 32% of S. aureus showed high-level resistance. In 1951, after less than a decade of use of penicillin, 73% of S. aureus were highly resistant to penicillin, virtually all of which were resistant because they produced penicillinase. For a number of years after this, the prevalence of penicillin resistance among hospital acquired strains of S. aureus was noted to be considerably higher in the hospital than among community-acquired strains. However, by 1967 this resistance seemed to have equalised in Boston at about 82–84% for both inpatient and outpatient isolates and this approximate percentage was maintained over the ensuing ten years. These organisms have spread throughout the world, and at present more than 90% of all isolates of S. aureus are penicillin resistant.
Penicillin resistance in *Streptococcus pneumoniae* is not due to the effect of a beta-lactamase like penicillinase, but to alterations in penicillin binding proteins (PBP), leading to ‘mosaic genes’ that have lower affinity for penicillin. The first penicillin resistant pneumococci were described by Australian investigators among a group of indigenous men from the highlands of New Guinea, where the organisms had presumably become resistant because of the administration of long-acting penicillins to this population to prevent pneumococcal respiratory diseases. Penicillin resistant pneumococci were subsequently identified among gold miners in South Africa and, as has been the case with so many other resistant bacteria, they have now spread around the world. There is virtually no part of the world in which these organisms do not presently occur.

Because the greatest pressure from antibiotic use is generated in hospitals (especially intensive care units) it is not surprising that these are the source of some of the most resistant pathogens throughout the world. Multiresistant gram-negative bacteria including *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and other non-fomenterers are classically found in intensive care units. Enteric bacteria (especially *Klebsiella pneumoniae* and *Escherichia coli* [E. coli]) have acquired genes mediating the production of so-called extended-spectrum beta-lactamas (ESBLs), which are able to hydrolyse a broad spectrum of penicillins and extended spectrum cephalosporins. Originally, most of the organisms containing ESBLs remained susceptible to carbapenems but, in recent years, organisms producing a broad variety of chromosomally mediated and transferable carbapenemases have emerged in hospitals throughout the world and this has now become a global problem with interspecies dispersion of these genes. Many of the organisms containing these carbapenemases are literally resistant to all beta-lactamases and in some instances, such as the outbreak of infections due to KPC-2-producing *Klebsiella pneumoniae* in New York City, there have been significant mortality rates since the organisms were resistant to all antimicrobial agents except the polymyxins.

Of course, the development of resistance is not limited to intensive care units in developed countries. An excellent illustration of this can be seen in a very large outbreak of dysentery due to *Shigella dysenteriae* type 1 that began in 1968 and was initially caused by antibiotic-susceptible organisms. As the epidemic continued, the *Shigella* acquired a plasmid mediating resistance to streptomycin, tetracycline, chloramphenicol and the sulfonamides. Morbidity and mortality from this epidemic were particularly severe, partly because local health authorities were initially unaware of the fact that they were dealing with antibiotic-resistant *Shigella*. More than 12,500 deaths were recorded in Guatemala during the first year alone. As the epidemic spread northward, the organism acquired new antimicrobial resistance genes and on reaching Mexico City in 1972 it had become resistant to ampicillin, in addition to streptomycin, the sulfonamides, tetracycline, and chloramphenicol.

It was hoped that resistance to sulfonamides could be prevented by the use of the combination of trimethoprim plus sulfamethoxazole since the combination worked on consecutive steps in the same metabolic pathway and provided synergistic inhibition and killing of many organisms, including *Shigella* and *E. coli*. Trimethoprim-sulfamethoxazole (TMP-SMX) was first used clinically in the early 1970s, but by the late 1970s occasional isolates of *Shigella* resistant to TMP-SMX were noted. In the early 1980s in Zaire, an epidemic of diarrhea due to *Shigella dysenteriae* occurred in which the organisms were resistant to chloramphenicol, sulfonamides, tetracycline, streptomycin, ampicillin, and TMP-SMX. Rapid emergence of resistance was also noted in India, Mexico, Brazil, Chile and Thailand. Moreover, in many of these countries, plasmid-mediated resistance to TMP-SMX was also found among *E. coli*. Antimicrobial resistance has also become a problem in other enteric pathogens in the developing world. An epidemic of typhoid fever in 1996 in Tajikistan was related to overflow of sewage, contaminated municipal water and ultimately person-to-person spread. By 1999, more than 24,000 cases of typhoid fever had been reported. More than 90% of the *S. typhi* were multidrug resistant and 82% of the isolates tested were resistant to ciprofloxacin. The possibility of spread of these multiresistant strains of *Salmonella* to other developing countries is of grave concern, since the fluoroquinolones represent the most effective agents we currently have for treating typhoid fever.

More recently, decreased effectiveness of the fluoroquinolones in treating cholera has been documented in Bangladesh. Of even greater concern is a report showing that between September 2004 and March 2005 multiresistant *Vibrio cholerae* 01 emerged in Bangladesh; 79% of fifty-four strains tested were resistant to ciprofloxacin in the earlier *New England Journal of Medicine* study, TMP-SMX, tetracycline, and furazolidine.

An even more dramatic example of the emergence of important multiresistant pathogens in a developing country was related to the discovery of a multiresistant strain of *Yersinia pestis* from a patient in Madagascar with bubonic plague. The strain was resistant to chloramphenicol, tetracycline and streptomycin, as well as to the sulfonamides, ampicillin, kanamycin, spectinomycin and minocycline. All of these resistance genes were carried on a plasmid (presumably from a strain of *Enterobacteriaceae*) that easily could be transferred to other virulent strains of *Yersinia pestis*. Subsequently, other patients from Madagascar infected with this organism have been described. This discovery also
raises the disturbing possibility that such multiresistant strains could be used in bioterrorism attacks throughout the world.

*Neisseria gonorrhoeae* have developed resistance to multiple antimicrobial agents but until recently, the fluoroquinolones could be relied upon for effective oral therapy, at least in most western countries. For a number of years, disturbing reports of a high prevalence of fluoroquinolone resistance have emanated from Asia and the Western Pacific in annual reports from World Health Organization programs (see Figure 1). The prevalence of fluoroquinolone resistance subsequently increased dramatically in Europe in 2007. Although as yet not approaching those in Asia or Europe, more recently the prevalence of these organisms in the United States has risen to a level that has prompted the Centers for Disease Control and Prevention (CDC) to suggest that the fluoroquinolones no longer be used for primary treatment of gonorrhea in the United States. Once again, a problem first described in one part of the world (Asia) has developed into a global problem.

As noted at the onset of this paper, antimicrobial agents are among the most important discoveries of the 20th century, but their utility is constantly being threatened by the emergence of antimicrobial resistance. Although the prevalence of resistance to antimicrobials among various bacterial pathogens varies from place to place, it is truly a worldwide problem and deserves all of the attention that medical science can apply.

**References**