ANTIMICROBIAL RESISTANCE

Drug-resistant infectious agents—those that are not killed or inhibited by antimicrobial compounds—are an increasingly important public health concern. Antimicrobial resistance has become a significant public health problem because of overuse of antimicrobial drugs and failure to ensure proper diagnosis and adherence to treatment. The most serious cases of resistance have occurred in hospitals and communities and include nosocomial (hospital-acquired) respiratory and blood-borne infections. The impact of antimicrobial resistance includes an increase in the cost of treating infections, the need to use a greater number of broader spectrum and more toxic drugs to clear resistant infections, untreatable infections leading to increased morbidity and mortality, and the spread of resistant infectious agents in hospitals and the outside community.

The phenomenon of antimicrobial resistance is prevalent in developed countries and also is a challenge for developing areas of the world. Factors in the global emergence of resistant malaria parasites, diarrheal pathogens, and sexually transmitted bacteria include incomplete or inadequate antimicrobial therapy, ineffective counterfeit drugs, and lack of access to healthcare. These factors are different from those that influence resistance patterns seen domestically. New prevention and treatment strategies are needed, as well as the effective use of the tools currently available for fighting resistant infectious diseases.

Hospitals are a critical component of the antimicrobial resistance problem. Many factors are believed to contribute to the emergence of drug resistance among nosocomial pathogens, including overuse of broad-spectrum agents, increasing numbers of susceptible and immunocompromised patients, use of invasive procedures and devices, and the breakdown of infection- and disease-control practices. As a result, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased to 66.7 percent in intensive care units (ICUs) in U.S. hospitals, while the prevalence of methicillin-resistant coagulase-negative staphylococci has increased to 89.2 percent. Further, increasing reliance on vancomycin has led to the emergence of vancomycin-resistant enterococci (VRE)—bacteria that infect wounds, the urinary tract, and other sites. The prevalence of VRE has increased to 37.5 percent in U.S. hospital ICUs.[7]

One of the most disturbing trends is the emergence of multidrug-resistant pathogens in the community outside hospitals. MRSA, long a problem in ICUs and nursing homes, is an emerging community-acquired pathogen among patients without history of hospitalization or previous infections. There are increasing reports of MRSA causing serious skin and soft-tissue infections among athletes, prisoners, persons in day care settings, and the homosexual population.

Streptococcus pneumoniae (pneumococci) causes tens of thousands of cases of meningitis and pneumonia and 7 million cases of ear infection in the United States each year, and multidrug-resistant pneumococci are common and increasing. Resistance of *S. pneumoniae* to antimicrobial agents continues to be a major public heath concern.

An estimated 300 million to 500 million people worldwide are newly infected with the parasites that cause malaria, and an estimated

1 million people die every year from this infection. Resistance to chloroquine, once widely used and highly effective for preventing and treating malaria, has emerged in most parts of the world. Resistance to other antimalarial drugs also is widespread and growing.[8]

Multidrug-resistant tuberculosis (MDR-TB) is as contagious as drug-susceptible tuberculosis but requires much more extensive and costly therapy. The incidence of MDR-TB has increased dramatically in the past decade, and strains of the tubercle bacillus that are resistant to one or more drugs are now present on five continents.[9] Accurate and rapid diagnosis of MDR-TB often is not available, resulting in inadequate treatment of patients, who as a result, remain infectious longer and are able to spread MDR-TB to other persons. Because TB is a major cause of death in persons also co-infected with HIV, spread of MDR-TB in this vulnerable population has the potential to dramatically increase the death toll from TB.

Diarrheal diseases cause an estimated 3 million deaths a year—mostly in developing countries where resistant strains of highly pathogenic bacteria, such as *Shigella dysenteriae, Salmonella typhimurium,* and *Vibrio cholerae,* are emerging. Eighty percent of *S. dysenteriae* isolates in Bangladesh, for example, have been found to be resistant to ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX), compared with approximately 40 percent of the other *Shigella* species.[10] Also, resistance is increasing to several critical antimicrobials used to treat invasive *Salmonella* infection, including extended-spectrum cephalosporins and quinolones. In resource-poor countries, drug-resistant *Salmonella* infections could eventually become untreatable.[11] Finally, a recent study in Indonesia found *V. cholerae* O1 strains resistant to ampicillin, TMP-SMX, chloramphenicol, and tetracycline; similar results were obtained for non-O1 *V. cholerae* strains.[12]

In response to the increasingly important public health concerns outlined above, NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens. NIAID-funded projects include basic research into the disease-causing mechanisms of pathogens, host-pathogen interactions, and the molecular mechanisms responsible for drug resistance as well as applied research to develop and evaluate new or improved products for disease diagnosis, intervention, and prevention.

In addition, NIAID supports a number of clinical trial networks with the capacity to assess new antimicrobials and vaccines with relevance to drug-resistant infections. Among these networks are the AIDS Clinical Trials Group, the Collaborative Antiviral Study Group, the Tuberculosis Research Unit, the Vaccine and Treatment Evaluation Unit, and the Bacteriology and Mycology Study Group, with one unit directed toward serious resistant bacterial infections. A study protocol, "Infection-Control Strategies to Reduce Colonization and Infection Caused by Antimicrobial-Resistant Bacteria in Adult ICUs," is under development.

In recent years, NIAID has launched several projects to accelerate research on antimicrobial resistance, to develop products to address this challenge, and to support new clinical trial activities in this area. The Network on Antimicrobial Resistance in

Staphylococcus aureus provides a repository of resistant bacteria, a registry of case information, and a network of investigators to support and stimulate research in the area of resistant bacterial infections. In fiscal year 2002, NIAID announced an initiative called Partnerships for Novel Therapeutics and Vector-Control Strategies in Infectious Diseases, with the goal of supporting partnerships to develop new drugs and diagnostics in areas that are not currently a high priority for industry but are likely to have a high impact on public health. In 2003, NIAID awarded 18 grants under a new initiative designed to encourage the submission of grant applications on "Innovative Approaches for Combating Antimicrobial Resistance" (RFA-02-009).

NIAID cochairs the Interagency Task Force on Antimicrobial Resistance with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration; eight other Government agencies also are represented on the task force. In June 2002 and June 2003, public meetings were held to provide an annual summary of accomplishments associated with *A Public Health Action Plan to Combat Antimicrobial Resistance, Part 1: Domestic Issues.* First published in January 2001, the action plan reflects a broad-based consensus of Federal agencies on actions needed to address antimicrobial resistance, which is based on input from constituents and stakeholders and serves as a blueprint for specific coordinated Federal actions. The action plan is available online at CDC's antimicrobial resistance Web site, *www.cdc.gov/drugresistance.*

NIAID also investigates antimicrobial resistance in its Division of Intramural Research (DIR). In laboratory and clinical studies, DIR scientists study the microbe and the host to elucidate the factors contributing to resistance to a variety of antimicrobial drugs. For example, to respond to the growing threat to TB-control programs posed by the emergence of MDR-TB, DIR scientists are studying the development of resistance to specific anti-TB drugs (such as pyrazinamide and isoniazid) as well as the larger issue of whether specific factors exist that predispose some patients to develop multiple drug resistance. These scientists, in collaboration with South African colleagues, recently identified the key role played by an unusual DNA polymerase enzyme in the generation of the genetic mutations that confer drug resistance in *Mycobacterium tuberculosis.* This finding may lead to the development of anti-TB drugs that target this enzyme.[13]

In addition, intramural scientists, in collaboration with colleagues from Yonsei University and Masan National Tuberculosis Hospital in Busan, South Korea, are establishing a center of excellence for the study of MDR-TB. The center will address the basic biology underlying the development of drug resistance and serve as a clinical site for the evaluation of novel anti-TB agents.

DIR scientists also are studying the contribution of biofilms—communities of microorganisms embedded in a mucoidal (slime) matrix—to drug resistance. A bacterium often associated with biofilms, *Staphylococcus epidermidis,* is the most common pathogen in hospital-acquired infections and is responsible for healthcare costs of more than $1 billion per year. Although usually a harmless bacterium of human skin, *S. epidermidis* may cause septicemia or endocarditis in patients undergoing immunosuppressive therapy, in

premature newborns, or in injection drug users. However, most infections occur after the insertion of indwelling devices such as catheters or prosthetic heart valves. In these cases, the ability of *S. epidermidis* to form biofilms represents the most important virulence determinant. In a biofilm, the bacteria are dramatically less susceptible to antibiotic treatment and to attacks by human immune defenses. For these reasons, *S. epidermidis* infections are very difficult to eradicate. DIR scientists propose that drugs preventing and/or targeting biofilm formation will be of extraordinary use in antistaphylococcal therapy because they will enable the immune system to cope with an infection and increase the efficiency of common antibiotics. To provide the scientific basis for the development of drugs interfering with biofilm formation, DIR scientists are investigating the molecular biology, biochemistry, and epidemiology of biofilm formation. This investigation includes studying specific factors contributing to biofilm formation, their regulation, and the interaction of biofilm-forming *S. epidermidis* strains with the host.