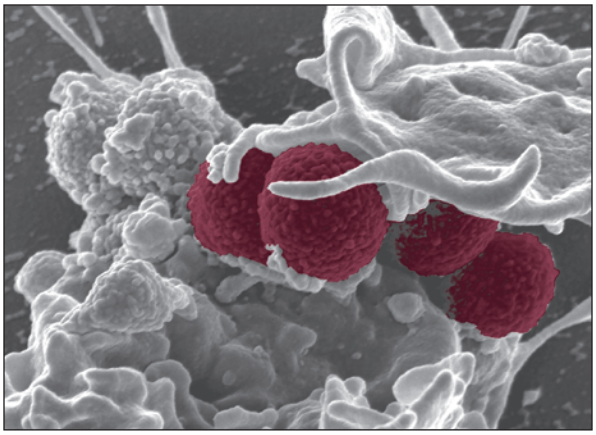
ANTIMICROBIAL RESISTANCE

Antimicrobial resistance has become an increasingly important public health problem because of the overuse of antimicrobial drugs and failure to ensure proper diagnosis and adherence to treatment. Drug-resistant infectious agents include those that are not killed or inhibited by antimicrobial compounds. Serious cases of resistance have occurred in hospitals and communities and include nosocomial (hospital-acquired) respiratory and bloodborne infections. Due to the emergence and spread of antimicrobial resistance, several bacterial infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus*, vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *Mycobacterium tuberculosis*, and penicillin-resistant *Streptococcus pneumoniae* are difficult to treat and have negative clinical outcomes. 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, the development of 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 health care. 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.



MRSA. Methicillin-resistant *Staphylococcus aureus*.

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. Currently 5 to 10 percent of patients admitted to acute care hospitals acquire health care-associated infections, and the risks have increased steadily during the recent decades.[4, 5] Approximately 2 million patients in the United States acquire an infection as a result of receiving health care in a hospital, and overall 70 percent of the bacteria causing such infections are resistant to at least one of the drugs most commonly used to treat these infections.[6]

Antimicrobial resistance negatively affects patient clinical outcome and cost to the healthcare system. Several studies utilizing different methodologies have concluded that MRSA infections are more frequently fatal than are methicillin-sensitive infections. One retrospective cohort analysis revealed a 22 percent difference between mortality in MRSA bacteremia (35.3 percent) compared with methicillin-sensitive bacteria (8.8 percent). Another study, which evaluated the health and economic impact of VRE infections, showed increases in case fatality

rates and hospital costs in the VRE group as compared to matched controls, respectively.[7, 8, 9]

One of the most disturbing trends is the emergence of multidrug-resistant pathogens in facilities other than hospitals. MRSA, long a problem in intensive care units (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 daycare settings, and injection drug users.

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. Multidrug-resistant pneumococci are common and increasing. Resistance of *S. pneumoniae* to antimicrobial agents continues to be a major public health concern.[10]

Group A streptococci (GAS, *Streptococcus pyogenes*) are the most frequent and important cause of bacterial pharyngitis in children and adults. Macrolide antibiotics are prescribed increasingly for treatment of pharyngitis due to GAS. A high prevalence of macrolide resistance has been recognized in Europe and Southeast Asia for many years. Recently, the emergence of erythromycin resistance in GAS in the United States, Canada, and Argentina has been reported.

Group B streptococci (GBS) remain a leading cause of serous neonatal infections resulting from the transfer of GBS from a colonized mother to her infant during labor and delivery. The number of GBS infections in infants has been reduced by intrapartum administration of antibiotics during labor, with penicillin as the agent of choice. However, recommended strategies for women who are allergic to penicillin have been updated to include cefazolin because of the increased resistance to erythromycin and clindamycin and reports of cefoxitin resistance.[11]

An estimated 300 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.[12] 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.

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 in all regions of the world.[13] 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, the 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.[14] 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.[15]

Finally, a 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.[16]

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 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 Units, and the Bacteriology and Mycology Study Group, with one area of emphasis directed toward serious resistant bacterial infections. A study protocol, "Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Intensive Care Units (STAR-ICU)" was initiated in FY 2005, and others are 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 FY 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."

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 2005, a public meeting was held to discuss progress in implementing "A Public Health Action Plan to Combat Antimicrobial Resistance Part 1: Domestic Issues" and obtain feedback from stakeholders. The action plan, which was created in 1999, reflects a broad-based consensus of Federal agencies on actions needed to address antimicrobial resistance, and is based on input from a wide variety of constituents and collaborators. The action plan is available online at CDC's Antimicrobial/Antibiotic Resistance Web site, *www.cdc.gov/drugresistance*.

A research initiative, "Sepsis and CAP: Partnerships for Diagnostics Development," was announced in August 2004. The purpose of this initiative is to support industry development of broad diagnostic technologies that provide early detection of select major causes of septicemia, bacteremia, candidemia, and community-acquired pneumonia. Nine awards were made. Also, a protocol for evaluating an anti-endotoxin vaccine for human use is in early phase studies. Preliminary results show that the anti-endotoxin vaccine appears to be safe and well-tolerated in humans. Studies to further evaluate safety, functional activity, and immunogenicity are underway.

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 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 collaborating with colleagues from Yonsei University and National Masan Tuberculosis Hospital in Busan, South Korea, who established a center of excellence for the study of MDR-TB. The center is addressing the basic biology underlying the development of drug resistance and serving as a clinical site for a natural history clinical research protocol and for 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* can 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 is 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.

In 2005, DIR scientists found that a molecule called PGA (for poly-gamma-DL-glutamic acid) protects *S. epidermidis* from innate immune defenses, human antibiotic compounds, and salt concentrations similar to levels found on human skin. They used mice fitted with catheters to demonstrate that an *S. epidermidis* strain deficient of PGA was unable to cause infection while strains containing PGA did.[17] If a vaccine can be developed to negate the effect of the PGA, it could be useful against all pathogens in which PGA is a basis for disease development, such as *S. epidermidis* and *B. anthracis*, which causes anthrax.

DIR scientists investigating the molecular basis of community-acquired MRSA infections recently found that MRSA strains causing community infections in the United States are more virulent than an MRSA strain common in hospitals. Their work further suggested that enhanced community-acquired MRSA virulence is linked to (or results from) evasion of killing by neutrophils, which likely underlies the ability of prominent community-acquired MRSA strains to cause disease in individuals without known risk factors. The study also revealed potential vaccine antigens and targets for therapeutics designed to control *S. aureus* infections.[18]

NIAID will continue collaborating with industry in order to stimulate and augment research into antimicrobial resistance and continue the development of novel products to address resistant bacterial infections in healthcare settings.