2006 Annual Report on Progress on "A Public Health Action Plan to Combat Antimicrobial Resistance"

EXECUTIVE SUMMARY

SURVEILLANCE

Surveillance is the ongoing, systematic collection, analysis, and interpretation of data essential to the planning, implementation, and evaluation of public health practice. Data on patterns and rates of antimicrobial resistance are collected for a variety of microorganisms including over 15 species of bacteria, *Mycobacterium tuberculosis*, yeasts and molds, multiple viruses, and selected parasites through a series of ongoing surveillance systems at the Centers for Disease Control and Prevention (CDC).

These activities address two key Action Items in the Plan, namely:

- Action Item #2: Design and implement a national surveillance plan
- Action Item #5: Develop and implement procedures for monitoring patterns of antimicrobial drug use.

Several reports were of particular interest during the last surveillance period.

- Recent investigations of methicilin-resistant *Staphylococcus aureus* (MRSA) collected through the Active Bacterial Core Surveillance (ABCs) system have revealed the increasing incidence of MRSA infections in community settings in persons that do not have traditional risk factors for MRSA infection or links to the healthcare system. Thus, three categories have been established to describe the epidemiology of MRSA infections: healthcare-associated (formerly classified as nosocomial infections), community-associated, and healthcare-associated with community onset (i.e., with discernable links to the healthcare system, such as recent surgery, dialysis, or indwelling catheters).
- In 2006, the seventh isolate of fully vancomycin-resistant *Staphylococcus aureus* was recovered from a patient in Michigan.
- Rates of antimicrobial resistance to penicillin, erythromycin, cefotaxime, and levofloxacin among invasive *Streptococcus pneumoniae* isolates from children (<5 years of age) have dropped significantly since the introduction of the pneumococcocal vaccine and have remained low. Rates of pneumococcal resistance to penicillin and erythromycin in adults showed more modest declines over the study period (1998-2005).
- Rates of fluoroquinolone resistance (particularly resistance to ciprofloxacin) among *Neisseria gonorrhoeae* isolates continued to increase in 2006 and exceeded 10%. Thus, CDC no longer recommends fluoroquinolones for empiric therapy of primary gonococcal infections in the United States.

- Among non-typhoidal isolates of Salmonella, resistance to nalidixic acid and ceftiofur remained low. These are indicators of increasing resistance to fluoroquinolones and extended-spectrum cephalosporins, respectively.
- Extremely drug resistant strains of *Mycobacterium tuberculosis* [defined as disease caused by *Mycobacterium tuberculosis* that is resistant in vitro to at least isoniazid and rifampin among first-line drugs, and at least three or more of the six main classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicyclic acid)] have been isolated from patients in 10 states; although their overall incidence remains low ($\leq$4 cases in U.S. in last three years).
- The number of multi-drug resistant strains of *M. tuberculosis* (i.e., isolates that are resistant at least to primary therapy drugs – isoniaizid and rifampin) which are more common among foreign-born residents of the United States versus U.S.-born individuals, continued to decline in the United States.
- Antifungal resistance among several *Candida* species recovered from patients undergoing solid organ transplants and as well as other invasive procedures has been under surveillance for several years. Rates of resistance among these organisms remain low for most agents with the exception of species specific resistance problems, such as resistance to fluconazole among *Candida krusei* isolates.
- In the United States, resistance of influenza A viruses to adamantanes (amantadine and rimantadine) reached 96% in 2006. Resistance to a second class of drugs, neuraminidase inhibitors (zanamivir and oseltamivir), remained at approximately 1% among influenza A and B viruses.
- In Alaska, monitoring of resistance of Hepatitis B virus to nucleoside analogues among 32 patients revealed that 8% were resistant on initial therapy and 22% developed resistance on therapy.
- In Central Africa, treatment of 3977 patients with trypanosomiasis (sleeping sickness) with Melarsoprol showed failure rates of 25-55%, depending on the village. Alternate drugs (eflornithine) now being used.

Thus, among the more disturbing trends, MRSA has moved out of its traditional hospital setting, increasing fluoroquinolones resistance among gonococci has severely impacted empiric therapy for these infections, and antiviral resistance has shown dramatic increases.

The surveillance of antimicrobial agent usage in the United States from ambulatory care visits (an ambulatory care visit is defined as a visit to a physician's office, hospital outpatient department, or hospital emergency department) also showed several interesting trends:

- From 1993/94 through 2005, the prescribing rate at ambulatory care visits increased for azithromycin/clarithromycin (up 250%), quinolones (up 130%), and amoxicillin/clavulanate (up 25%).

- From 1993/94 through 2005, the prescribing rate at ambulatory care visits decreased for erythromycins (down 88%), amoxicillin/ampicillin (down 49%), and cephalosporins (down 32%).
- From 1993/94 through 2005, the prescribing rate at ambulatory care visits decreased for penicillins (down 63%), trimethoprim-sulfamethoxazole (down 46%), and tetracyclines (down 36%).

Thus, there has been a decrease in the use of older, less expensive antimicrobial agents, and a substantial increase in the prescribing of newer, more expensive antimicrobial agents in the outpatient setting. To date, there is no systematic reporting of veterinary drug use so the Task Force has been unable to monitor the usage in animals.

PREVENTION AND CONTROL

The prevention and control of antimicrobial resistant infections requires interventions to promote the appropriate use of antimicrobial agents and prevent the transmission of infections in community and healthcare settings. Top Priority Action Items in this focus area include the following:

- Action Item #25: Conduct a national public health education campaign to promote appropriate antimicrobial drug use as a national health priority.

- Action Item #26: Develop and facilitate the implementation of educational and behavioral interventions that will assist clinicians in appropriate antimicrobial prescribing.

- Action Item #39: Evaluate the effectiveness (including cost-effectiveness) of current and novel infection-control practices for healthcare and extended care settings and in the community.

- Action Item #58: In consultation with stakeholders, finalize and implement the proposed FDA guidance and for re-evaluating currently approved veterinary antimicrobial drugs.

- Action Item #63: Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote appropriate drug use and reduce infection rates, in order to assess how interventions found effective in research studies can be applied routinely and most cost-effectively on a large scale.

Appropriate Use of Antimicrobial Agents

Appropriate antimicrobial agent use policies are being promoted in programs targeting both the public and physicians.

- CDC expanded its National Campaign for Appropriate Antibiotic Use in the Community "Get Smart Know When Antibiotics Work" and funded a number of state health departments to develop state-based coalitions to emphasize the importance of judicious antimicrobial use.
- CDC worked with the Coalition for Affordable Quality Healthcare to develop intervention programs for healthcare delivery organizations focused on judicious antimicrobial use. It also expanded its medical curriculum and pharmacy initiative, and extended it focus on appropriate prescribing practices to adults with upper respiratory infections.
- CDC expanded its *Prevent Antimicrobial Resistance in Healthcare Settings* campaign to improve prescribing in a variety of healthcare institutions. This campaign involves working with partners to emphasize 12 evidence-based steps for diagnosis of infection, appropriate treatment, appropriate use of antibiotics, and prevention of infection transmission.
- The Agency for Healthcare Research and Quality (AHRQ), through its network of Centers for Education and Research on Therapeutics, sponsored education and research projects to evaluate and improve antimicrobial agent use. This included a diagnostic decision aid for pediatric sinusitis, a program on reducing antimicrobial prophylaxis errors, and materials for reducing the use of antimicrobial agents for acute otitis media.
- The Department of Defense (DoD) implemented an intervention program to enhance the communication skills of primary care providers on the prudent use of antimicrobial agents in DoD settings.
- The Department of Veterans Affairs (DVA) introduced guidelines and training programs regarding appropriate antimicrobial drug use for staff and trainees in its large network of healthcare facilities. The success of programs to improve use in outpatients has been demonstrated by data from the National Ambulatory Medical Care Survey, which indicate that antimicrobial agent prescribing rates for children seen in physician offices have declined in recent years.
- Center for Medicare and Medicaid Services (CMS) used the Medicare quality improvement organizations in all 50 states to promote optimal antimicrobial agent use for inpatient pneumonia treatment and surgical infection prevention.
- CMS implemented a web-based decision support system targeting improved antimicrobial agent therapy in rural hospitals. CMS also developed interventions to improve the use of antimicrobial agents in long-term care facilities and physicians' offices.
- FDA approved a new labeling rule intended to educate physicians and the public about the resistance problem and to encourage physicians to prescribe systemic antibacterial drugs only when clinically necessary.

Preventing Transmission of Infections

- CDC data from ongoing population-based surveillance of invasive pneumococcal disease in 7 geographic areas indicated that introduction of pneumococcal conjugate vaccine in 2000 led to a large decrease in resistant infections, but

strains not covered by the vaccine are emerging and are often resistant to multiple antibiotics.

- CDC data suggested that vaccination reduced the racial disparity in disease rates, with rates for both white and black children falling below the Healthy People 2010 target of 46 cases/100,000 population. The number of cases of invasive disease in adults also declined, suggesting that vaccine use may have helped to decrease transmission of pneumococci to unvaccinated persons. Five of the seven-pneumococcal serotypes in the vaccine account for most of the pneumococcal strains that are resistant to penicillin and other antibiotics.
- CMS promoted pneumococcal and influenza vaccinations for Medicare beneficiaries. CMS's ongoing Healthy People 2010 has a goal of increasing targeted adult immunization rates to 90%. The campaign is focused on improving immunization rates among minorities and other vulnerable populations.
- CDC's network of Centers of Excellence in Healthcare Epidemiology evaluated the effectiveness of current and novel infection control practices at multiple academic medical centers..
- DVA's program to evaluate the outcome of infection control interventions for serious infectious diseases is continuing. Improved infection control practices reduced the spread of infections in healthcare settings and thus also decrease the use antimicrobial drugs.

FDA Regulatory Framework for Approving Antimicrobial Drugs for Use in Food Animal Production

- FDA draft guidance document for industry was published in September 2002 and a public meeting held October 2, 2002 to explain the guidance and solicit additional comments. An approach for evaluation of drugs according to their importance in human medicine has been incorporated into the pre-approval assessment strategy and is fully explained in the draft guidance document. That portion of the document was taken to a FDA Anti-Infective Drugs Advisory Committee in January 2003.
- FDA evaluated comments from the Anti-Infective Drugs Advisory Committee as well as comments received at the public meeting in October and all written comments have been evaluated. The FDA published the final guidance document titled "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern" (6) in October 2003. This document outlines a pathway drug sponsors can use to address concerns about antimicrobial resistance prior to approval of their drug. The guidance balances the need for antimicrobials to treat livestock and poultry with the need to protect human health by considering the importance of drugs in human medicine.
- FDA risk assessment analysis of the relationship between the emergence of quinupristin-dalfopristin resistant *Enterococcus faecium* in humans and the use of virginiamycin in food animals was published in 2004. A risk assessment of the use of fluoroquinolones in poultry was completed; given its conclusions, the Center for Veterinary Medicine in October 2000 began the legal process to

withdraw approval of fluoroquinolones for use in poultry. One of the two affected drug manufacturers withdrew its fluoroquinolone product, and the other requested a hearing. The Administrative Law Judge filed an initial decision in early 2004 agreeing with the Center for Veterinary Medicine and stating that the poultry fluoroquinolone product should be removed from the market. On July 28, 2005, the FDA Commissioner announced the Agency's final decision to withdraw the approval. The final rule withdrawing approval of enrofloxacin for use in poultry was effective on September 12, 2005.

Comprehensive Demonstration Projects

- CDC provided technical assistance to hospitals in Pittsburgh and surrounding areas of Southwestern Pennsylvania to reduce catheter-associated bloodstream infections and infections caused by MRSA.
- CDC's Bloodstream Infection Initiative resulted in a 68% reduction in the rate of catheter-associated bloodstream infections. The initial MRSA interventions have led to reductions in MRSA infection rates of >60% in several intervention units, including the Pittsburgh VA Medical Center.

RESEARCH

Knowledge and understanding of the growing problem of antimicrobial resistance is a prerequisite for a planned and coordinated federal response to this problem. The NIH has the lead in this area, but increasingly, federal agencies are collaborating and pooling resources to accomplish the action items in the Plan. Research accomplishments in the following areas will be highlighted:

- Action Item #67: Supporting additional research, including high risk and high payoff research in nontraditional fields that will lead to an increased understanding broadly of: microbial physiology, ecology, genetics, mechanisms of resistance, host factors; and the impact of variable antimicrobial use patterns, preventive, therapeutic, and growth promoting agents, and environmental residues on the emergence and spread of resistant organisms and resistance factors.
- Action Item #69: Work with the appropriate peer review structures to ensure that the requisite expertise is applied to the review process to facilitate funding of quality antimicrobial resistance research.
- Action Item #70: Providing to the research community genomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostics methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens.
- Action Item #75: In consultation with academia and the private sector, identify and conduct human clinical studies addressing antimicrobial resistance issues of public health significance that are unlikely to be studied in the private sector.

- Action Item #78: Encouraging basic and clinical research in support of novel approaches for preventing and treating infections with resistant organisms that occur in humans and animals by partnering with academia and the private sector.

Expanding the Research Base

- NIH initiatives have extended grant and funding opportunities related to or including antimicrobial resistance to new groups of investigators and are stimulating research in this area. Representative initiatives include basic, applied, and product-oriented research areas and have been directed at academicians and industrial researchers.
- NIH's Small Research Grant and the Exploratory/Developmental Research Grant announcements continue to fund awards focused on antimicrobial resistance and drug development. These funding mechanisms join the long-standing investigator-initiated R01 and the Small Business Innovation Research award mechanisms in providing meaningful platforms for advancing antimicrobial drug development and resistance research as evidenced by an accumulating spectrum of funded projects. The cumulative listing of funded awards can be searched at http://crisp.cit.nih.gov/ using various key words of interest.
- NIH continued to encourage research applications involving partnering with the industrial sector in 2005 and 2006 through the "Cooperative Research Partnerships for Biodefense" initiatives. Through these initiatives the development of new antimicrobials is an important goal and one that could help address the problems of resistance by increasing the number of available antimicrobial drug candidates when compounds under study have broad spectrum of action against multiple microorganisms. Also, it is anticipated that the knowledge gained from advancing diagnostic and vaccination approaches to the target organisms will have benefit to these disciplines overall.
- NIH's 2006 initiative, "Partnerships to Improve Diagnosis and Treatment of Selected Drug-Resistant Healthcare-Associated Infections", funded projects directly targeted to several important, but less researched health associated bacterial pathogens.
- CDC awarded four extramural grants addressing the development of new methods to prevent the transmission of antimicrobial resistant pathogens.
- USDA funded projects addressing antimicrobial resistance and microbial ecology focusing on resistance in commensal bacteria of livestock and commensals that enter the food supply.

Science and Technology Support

- NIH and other federal agencies made significant investments in 90 large scale DNA sequencing projects, including the genomes of microbial pathogens and invertebrate vectors of infectious diseases, which are now complete. Coordination of these activities across federal agencies occurs through the Microbe Project Interagency Working Group (http://www.microbeproject.gov/) including NIH, USDA, NSF, DOE, DOD and FDA. The ultimate goal is to advance the field of pathogen genomics, which continues to uncover clues to

microbial functioning that holds promise for the prediction of disease progression, patient care, and treatment.

- NIAID's Pathogen Functional Genomics Resource Center (http://www.niaid.nih.gov/dmid/genomes/pfgrc/default.htm) provided microarray slides, Gateway clone sets, computational tools, and training to researchers to study organisms that pose important public health challenges. Functional genomics research reagents are available or are in development for a number of organisms at the Resource Center web site (http://pfgrc.tigr.org/resources.shtml).
- NIAID Bioinformatics Resource Centers (BRCs) established relational databases to collect, integrate, and update a variety of data types, such as genome sequences, comparative genomics, genome polymorphisms, gene expression, proteomics, host/pathogen interactions and pathways. Access to these data and their interpretation is facilitated by a user-friendly web interfaces and state of the art analysis tools.
- NIH's Center for Scientific Review (CSR) established a new Study Section, Drug Discovery and Mechanisms of Antimicrobial Resistance (DDR), within the new Infectious Diseases and Microbiology Integrated Review Group (IRG). It reviews grant applications that are concerned with the identification of novel antimicrobial agents, including agents that could be used in bioterrorism, for the prevention and treatment of infectious diseases and the study of the evolution, mechanisms, and transmission of resistance.

Identify and Conduct Human Clinical Studies Addressing Antimicrobial Resistance Issues of Public Health Significance and Novel Therapeutics

- NIH's Bacteriology and Mycology Study Group and associated Bacteriology and Mycology Biostatistical and Operations Unit continue to support clinical trials involving resistant bacterial and fungal infections. A reserve fund was created to support orphan studies that could not be funded through industrial sponsors to enable the group to undertake more independent, innovative, and public health-oriented clinical studies.
- NIH and CDC research partnerships are advancing the development and testing of novel products to address resistant pathogens, such as *Mycobacterium tuberculosis*. Tuberculosis has a major impact on health through out the world, with the emergence of resistance seriously complicating therapy.
- The search for new antimicrobials in unusual settings is being carried out through the International Cooperative Biodiversity Groups Program in collaboration with other NIH Institutes and Centers, the National Science Foundation and the USDA. Six awards have been made to multidisciplinary research groups that also include researchers outside the US, to explore natural products as a source of pharmaceuticals. Through these activities and others described in the Task Force Inventory of Projects, NIH and the other federal partners are investing in target discovery and moving promising products down the developmental pathway.

PRODUCT DEVELOPMENT

As antimicrobial drugs lose their effectiveness, new products must be developed to prevent, rapidly diagnose, and treat infections. The Priority Goals and Action Items in the Product Development focus area include:

- Action Item #79: Create an Interagency AR Product Development Working Group to identify and publicize priority public health needs in human and animal medicine for new AR products
- Action Item #80: Identify ways to promote the development and/or appropriate use of priority AR products, such as novel compounds and approaches, for human and veterinary medicine for which market incentives are inadequate.

To address these issues and other Action Plan issues, three strategies were embraced. First, to ensure researchers and drug developers are informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, and diagnostics, and of potential markets for these products; second, stimulate development of priority antimicrobial resistance products for which market incentives are inadequate, while fostering their appropriate use; and third, optimize the development and use of veterinary drugs and related agricultural products that reduce the transfer of resistance to pathogens that can infect humans.

- FDA sponsored several public workshops to encourage product development and address regulatory questions that have been raised since the publication of the Action Plan. These have included workshops on antimicrobial drug development, including clinical trial design issues; conferences on tuberculosis drug development; novel therapeutics for enteric infections; a workshop on the development of broad spectrum therapeutics; a National Academy of Sciences workshop on new classes of antimicrobials; and a workshop on research priorities for vaccine development.
- The Global Alliance for TB Drug Development is a public-private partnership to stimulate new drug development against tuberculosis. NIAID and CDC are involved in this collaboration with private partners, who contribute to the development of new drugs to shorten the treatment of tuberculosis and facilitate its control in the poorest countries. Over 30 organizations are stakeholders in this partnership, including the Bill & Melinda Gates Foundation, USAID, the World Bank, and WHO.
- CDC completed a project on biofilm formation by *Candida* species and an evaluation of a novel antifungal drug catheter lock technique to eradicate or prevent catheter-associated *Candida* biofilms. Key outcomes of this work include establishment of laboratory capacity to study *Candida* biofilms and response to antifungal treatment.
- FDA continued its regulatory review of novel therapeutic approaches using immunoglobulin for prevention of serious lower respiratory tract diseases caused by respiratory syncytial virus.

- FDA's biodefense program has expanded to include study of the spread of antimicrobial resistance, the mechanisms of resistance, and development of strategies to recover use of existing antimicrobial agents.
- FDA has held meetings with the Professional In-Vitro Diagnostics Roundtable (a group representing all major professional laboratory groups) to clarify regulatory requirements for antimicrobial testing devices. To further discussion on obstacles and issues that might exist in technology transfer; FDA Center for Devices and Radiological Health assisted device manufacturers in the most efficient way to get an alternative method for detecting vancomycin resistance in *Staphylococcus aureus* to market by offering protocol advice and providing an expedited review option.
- FDA published a guidance document to ensure the safe and effective use of in vitro diagnostics for detecting novel influenza A (or A/B) viruses (such as H5N1, H9N2, and H7N7) from human specimens. The guidance also included recommendations and information for assessing the clinical performance of these devices.
- FDA cleared a new assay submitted by CDC for the detection of human infection with H5 Avian Flu virus. Other recent approvals include: MASTALEX-MRSA, a rapid test for confirming methicillin-resistant *Staphylococcus aureus*; the Smart GBS Dx System, a rapid DNA test for detecting Group B beta-hemolytic streptococci in pregnant women; and ImmunoCard STAT EHEC, a rapid test for detecting Shiga toxins 1 and 2 produced by enterohemorrhogic *Escherichia col*i in stool specimens to aid in the diagnosis of severe diarrheal disease.