DRAFT Wednesday, June 05, 2002
Executive Summary

Progress Report: Implementation of *A Public Health Action Plan to Combat Antimicrobial Resistance* *Part 1: Domestic Issues*

Interagency Task Force on Antimicrobial Resistance

June 2002

INTRODUCTION

This is the first annual progress report on implementation of *A Public Health Action Plan to Combat Antimicrobial Resistance (Part I Domestic Issues)* (1) which was released in January 2001 by the Federal Interagency Task Force on Antimicrobial Resistance. The plan provides a blueprint for federal actions to address the emerging threat of antimicrobial resistance (AR). The Task Force was formed in 1999, after hearings held by Senators Frist and Kennedy, in recognition of the fact that addressing the multifaceted problem of AR required action by multiple agencies and departments. Co-chaired by the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), the Task Force also includes the Agency for Healthcare Research and Quality (AHRQ), the Centers for Medicare and Medicaid Services (CMS), the Health Resources and Services Administration (HRSA), the Department of Agriculture (USDA), the Department of Defense (DoD), the Department of Veterans Affairs (DVA), the Environmental Protection Agency (EPA), and, since 2001, the US Agency for International Development (USAID).

The Action Plan was developed based on input from consultants from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public. It is being implemented incrementally, in collaboration with these and other partners, as resources become available. Part I of the Plan focuses on domestic issues; Part II, under development, will identify federal actions that more specifically address global AR issues in collaboration with the World Health Organization and other partners. The Task Force is continuing to meet to monitor implementation of the Plan and will release annual progress reports and seek additional input at public meetings.

This progress report contains an inventory of projects or activities that are being undertaken by the Task Force agencies to implement action items in the Plan. Like the Plan itself, this report is divided into four major sections: 1) surveillance, 2) prevention and control, 3) research, and 4) product development. Each section contains a brief overview of progress in implementing the top priority action items in that section, followed by an inventory of projects or activities for each action item in the section. Projects applying to more than one action item in the same section are listed once and cross-referenced under the other action items in the section. Projects applying to action items in more than one section are repeated in each section.

This inventory documents progress in implementing the Action Plan, while helping identify gaps and opportunities for increased collaboration among agencies and with nonfederal partners. Many projects in this first progress report were initiated after development of the Plan, and their outcome or impact cannot yet be assessed; however, in future reports, such assessments will be made when possible. Persons wishing more information about particular projects are encouraged to contact the responsible agency. Comments may be provided at a public meeting to be held June 26, 2002 in Bethesda

Maryland (2) or submitted in writing to the pertinent agency or to: Ms. Vickie Garrett, Antimicrobial Resistance, Office of the Director, NCID, CDC, Mail stop C-12, 1600 Clifton Road, NE, Atlanta, GA 30333; telephone 404-639-2603; fax 404-639-4197; or e-mail aractionplan@cdc.gov.

SURVEILLANCE

The surveillance of drug-resistant infections requires coordination of activities by national, regional, state, and local organizations and the accurate detection of AR by clinical and public health laboratories. Because antimicrobial drug use influences the incidence and prevalence of resistance, surveillance for the extent and type of antimicrobial drug use is also needed. A national plan for surveillance of AR must include providing support to states to ensure that local needs for surveillance are met (including clinical laboratory proficiency), that surveillance is conducted for resistant organisms with a significant burden of disease or that pose especially dangerous threats to health, and that new tools are developed for detecting emerging resistance. A national plan must allow different approaches to surveillance of various organisms since it is unlikely that a single, nationwide methodology would be suitable for all pathogens in all settings, or would provide flexibility to meet local needs. However, standards and methods are being promoted that will allow comparison of data among various geographic areas and for national estimates of resistance for certain organisms.

Top Priority Action Items in this focus area include the following:

- With partners, design and implement a national AR surveillance plan that defines national, regional, state, and local surveillance activities and the roles of clinical, reference, public health, and veterinary laboratories. The plan should be consistent with local and national surveillance methodology and infrastructure that currently exist or are being developed. (Action Item #2)

- Develop and implement procedures for monitoring patterns of antimicrobial drug use in human medicine, agriculture, veterinary medicine, and consumer products. (Action Item #5)

NATIONAL SURVEILLANCE PLAN

National surveillance of AR in microorganisms that pose a threat to public health is being developed and implemented by coordinating existing projects and addressing unmet needs in collaboration with partners. Standards and methods such as the National Electronic Diseases Surveillance System (NEDSS) are being promoted in healthcare settings, large national laboratory companies, and in public health reporting by state health departments. In addition, when focused surveillance for critical pathogens (e.g., *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus*) is conducted, methods are being developed that can be used by state health departments and healthcare

facilities (e.g., National Healthcare Safety Network) not currently involved in federally-sponsored systems. When surveillance methods have not been well established (e.g., antiretroviral resistance in HIV infection), smaller scale surveillance is being evaluated to determine appropriate standards, methods, and utility of the data. For some organisms, available laboratory tests are not optimal to detect resistance (e.g., *Chlamydia, trichomonas*, lice). For these organisms, research is helping to develop methods of detection, and in turn, tools to conduct surveillance. For rare patterns of resistance in common pathogens of which widespread dissemination would be a major health threat (e.g., vancomycin-tolerant and vancomycin-resistant *Streptococcus pneumoniae*, vancomycin-intermediate *S. aureus*) sentinel or pilot surveillance is being conducted to ensure timely and accurate detection of these infections. Well-established, national surveillance for drug-resistant pathogens (e.g., *Mycobacterium tuberculosis*) continues. Each of these programs for surveillance clearly specifies activities that may be conducted at national, state, and local levels, which are often dependent on resources. AR surveillance is also being expanded to new organisms of concern in consultation with state health departments and healthcare institutions.

Standardized methods are being promoted by CDC to ensure comparability of results among geographical and institutional systems (e.g., NEDSS, cumulative antimicrobial susceptibility data). Public health officials, clinicians, and researchers are involved with many of the surveillance programs and provide for timely dissemination of data to interested parties. Necessary core capacities at state and local levels are being supported through grants. National AR surveillance has been built upon existing disease surveillance infrastructure. Methods and standards from current projects are either being expanded to encompass greater geographic areas or are being modified so they can be exported to areas that are not currently conducting surveillance. This is particularly true in the areas of healthcare associated infections, surveillance for *Streptococcus pneumoniae* infections, and surveillance for AR among foodborne pathogens and infections. Surveillance is also being conducted where possible through microbiology laboratories in large healthcare networks (e.g., DVA Emerging Pathogens Initiative, DoD AR Surveillance Network).

Improved surveillance for AR in agricultural settings will allow early detection of resistance trends in pathogens that pose a risk to animal and plant health, as well as in bacteria that enter the food supply. This task is being accomplished in various ways, e.g., expanding and enhancing the National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria to all 50 states (in FY2003) and launching a study of antimicrobial resistant pathogens found on retail foods.

Surveillance data will also help improve understanding of the relationship between antimicrobial drugs and pesticides used on plants and the emergence of drug resistance. The first steps in this regard for antimicrobial pesticide products are being taken by EPA, which is reviewing current scientific data on whether use of antimicrobial pesticide products results in the development of resistance to either the pesticide products themselves or to human or animal drugs.

As in the past, all surveillance activities are being conducted with respect for patient and institutional confidentiality.

Available, reliable drug susceptibility data are essential for AR surveillance. Examples of activities to improve accuracy of AR detection and reporting includes training and proficiency testing programs for diagnostic laboratories through development of a CDC Web site which deals with current antimicrobial susceptibility testing issues in clinical microbiology laboratory practice, a CD-ROM which provides materials necessary for training laboratory workers to test bacterial isolates for resistance to antimicrobial agents and issue accurate reports to physicians, training of laboratorians through the National Laboratory Training Network, and by promoting and further refining standardized methods for detecting drug resistance in important pathogens, including programs supported by CDC that include *chlamydia*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, HIV and influenza. Public and private sector partners have started to address barriers to AR testing and reporting, e.g., barriers due to changes in healthcare delivery.

MONITORING DRUG USE PATTERNS

Methods for monitoring patterns of antimicrobial drug use are being developed and implemented as a component of the national AR surveillance plan. CDC is supporting projects that collect data through new and existing healthcare data systems, through surveys of outpatient physicians, and through other databases (e.g., marketing surveys). Analysis of antimicrobial use databases has proven to be complex, requiring sophisticated statistical methods and linkage with appropriate clinical information and potentially with databases on resistant infections. This is being done for the healthcare and community settings. This information is essential for interpreting trends and variations in rates of AR, improving our understanding of the relationship between drug use and resistance, identifying and anticipate gaps in availability of existing drugs, and for identifying interventions to prevent and control AR.

PREVENTION AND CONTROL

The prevention and control of drug-resistant infections requires measures to promote the appropriate use of antimicrobial drugs and prevent the transmission of infections (whether drug-resistant or not). Top Priority Action Items in this focus area include the following:

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

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

- Evaluate the effectiveness (including cost-effectiveness) of current and novel infection-control practices for healthcare and extended care settings and in the community. Promote adherence to practices proven to be effective. (Action Item #39)

- In consultation with stakeholders, refine and implement the proposed FDA framework for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for re-evaluating currently approved veterinary antimicrobial drugs.
  (Action Item #58)

- 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. (Action Item #63)

APPROPRIATE DRUG USE

Appropriate drug-use policies are being promoted in programs for the public and clinicians. AHRQ, through its network of Centers for Education and Research on Therapeutics, has sponsored education and research projects to evaluate and improve antimicrobial drug use; e.g., in a network of managed care organizations. CDC expanded its National Campaign for Appropriate Antibiotic Use in the Community by increasing (to 18) the number of state health departments funded to develop state-based coalitions of partners. CDC also worked with partners (e.g., the Coalition for Affordable Quality Healthcare) to develop intervention programs for healthcare delivery organizations, developed a medical curriculum, and extended a previous focus on pediatric prescribing to adults through development of prescribing principles for upper respiratory infections and patient education materials, in collaboration with professional societies. The DoD is developing an intervention program to enhance the communication skills of primary care providers on the prudent use of antimicrobial agents in DoD settings. The DVA has 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 encouraging data from the National Ambulatory Medical Care Survey, which indicate that antibiotic prescribing rates for children seen in physician offices have declined in recent years (3).

To improve prescribing in healthcare settings (primarily affecting inpatients), CDC launched a national campaign *Prevent Antimicrobial Resistance* in March 2002, focusing on hospital

care of adults. 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. CDC also worked with the National Committee for Clinical Laboratory Standards to develop guidelines for clinical microbiology laboratories on how to compile and report summaries of cumulative antimicrobial susceptibility data in a standardized manner to aid in clinical decisions. CMS is using the Medicare quality improvement organizations in all 50 states to promote optimal antibiotic use for inpatient pneumonia treatment and surgical infection prevention. A CMS Web-based decision support system targets improved antibiotic therapy in rural hospitals. CMS is also developing interventions to improve the use of antibiotics in long-term care facilities and physicians' offices.

FDA proposed a new labeling rule for antibiotics that is intended to educate physicians and the public about drug resistance and to encourage physicians to prescribe systemic antibacterial drugs only when clinically necessary. These actions to decrease the overuse and misuse of antimicrobial agents will decrease the selective pressure favoring the spread of AR. Public comments were solicited, and FDA has drafted revisions to the rule.

PREVENTING INFECTION TRANSMISSION

Widespread use of a new pneumococcal vaccine for children was temporally associated with unprecedented declines in cases of invasive pneumococcal disease and in the proportion of cases resistant to antimicrobial drugs. Preliminary CDC data from ongoing population-based surveillance of invasive pneumococcal disease in 7 states indicate that the number of cases in children under 5 years of age declined by 57% in 2001. The number of cases of invasive disease in persons older than 5 years of age 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. For the first time since pneumococcal resistance surveillance was re-instituted by CDC in 1991, the percentage of invasive pneumococcal infections not susceptible to penicillin declined - from 27% in 2000 to 25% in 2001(CDC Active Bacterial Core Surveillance, unpublished data). CDC contracts for 52% of the national market share for pediatric vaccines and provides funds and technical assistance to 64 state, territorial, and local health departments for immunization programs. CMS promotes and pays for pneumococcal and influenza vaccination of Medicare beneficiaries in all settings.

The effectiveness of current and novel infection control practices is being evaluated in CDCs network of Centers of Excellence in Healthcare Epidemiology, a program in which prevention research to improve infection control practices is conducted at 7 academic medical centers. Infection control is also a major element of the campaign *Prevent Antimicrobial Resistance*, outlined above, and of the comprehensive demonstration programs outlined below. DVA has an ongoing program to evaluate the outcome of infection control interventions for serious infectious diseases. Improved infection control practices reduce the spread of infections in healthcare settings and thus also decrease the use antimicrobial drugs.

FDA REGULATORY FRAMEWORK FOR ANTIMICROBIAL DRUGS IN FOOD ANIMAL PRODUCTION

A regulatory framework for antimicrobial drugs used in food-animal production, proposed by FDA, was discussed extensively with stakeholders, and the concepts were refined on the basis of comments received. A guidance document for industry is currently being developed as the next step in implementing this framework. An approach for evaluation of drugs according to their importance in human medicine has been incorporated into the pre-approval assessment strategy. Approaches to developing thresholds and evaluating antimicrobial drug effects on pathogen load were discussed at public meetings. A proposed rule and guidance is under development for requiring annual reports of use and quantity of antimicrobial drugs marketed for food animals. An analysis (risk assessment) of the relationship between the emergence of quinupristin-dalfopristin resistant *Enterococcus faecium* in humans and the use of virginiamycin in food animals is in progress. A risk assessment of the use of fluoroquinolones in poultry was completed; given its conclusions, FDA proposed withdrawing approval of fluoroquinolones for use in poultry. One of the two affected drug manufacturers withdrew its fluoroquinolone product, and the other requested a hearing; preparations for the hearing are in progress. These FDA actions address the need for antimicrobial drug use in agriculture and veterinary medicine, while ensuring that such use does not pose a risk to human health.

COMPREHENSIVE DEMONSTRATION PROJECTS

Comprehensive demonstration projects involving a wide variety of nonfederal partners were implemented to prevent and control AR through multiple interventions (e.g., surveillance, appropriate drug use, optimized diagnostic testing, immunization practice, and infection control). CDC-sponsored projects included a regional approach involving a coalition of healthcare facilities and business and community leaders in Pittsburgh, a statewide program in Wisconsin, a group of healthcare institutions in Chicago, and an integrated approach in rural communities in Utah and Idaho. The success of comprehensive regional approaches such as these is illustrated by the successful control of vancomycin-resistant enterococci in the Sioux City, Iowa area, with leadership from the Sioux City Health Department and support from the Iowa, South Dakota, and Nebraska State Health Departments, and CDC. (4)

RESEARCH

Understanding the fundamental processes involved in AR within microbes and the resulting impact on humans, animals, and the environment forms an important basis for influencing and changing these processes and outcomes. Basic and clinical research provides the fundamental knowledge necessary for developing appropriate responses to the AR that is emerging and spreading in hospitals, communities, farms, and the food supply. Top Priority Action Items in the research focus area address ways to

- Provide the research community access to 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 #70)

- In consultation with academia and the private sector, identify and conduct human clinical studies addressing AR issues of public health significance that are unlikely to be studied in the private sector (e.g. novel therapies, new treatment regimens, and other products and practices). (Action Item #75)

- Identify, develop, test, and evaluate new rapid diagnostic methods for human and veterinary uses with partners, including academia and the private sector. (Action Item #76)

- . Encourage basic and clinical research supporting the development and appropriate use of vaccines in human and veterinary medicine in partnership with academia and the private sector. (Action Item #77)

SCIENCE AND TECHNOLOGY

Science and technology are advancing at an inordinate rate. It is critical that investigators have the most up-to-date tools necessary to conduct pivotal studies. NIH has provided the research community with the genomic sequences of over 40 important pathogens, including those that challenge our ability to treat infections. In addition, a functional genomics center has been developed and is providing relational databases, computational tools, micro arrays and proteomics, reagents, and training to scientists and researchers to optimize the use of genomic information to understand the disease-causing characteristics of pathogens and their vectors. Other NIH and FDA resources, including reference laboratories, bacterial repositories, Web sites, and grants programs, are providing needed materials and extending important technologies to scientists. USDA is sponsoring research, through university grants and the Agricultural Research Service, to investigate the linkage between the use of antimicrobials in food animal production and the development of antimicrobial resistant foodborne pathogens. The projects will identify methods and develop educational materials for animal producers on ways to minimize potential risks.

TRANSLATING RESEARCH FINDINGS INTO INNOVATIVE CLINICAL PRODUCTS

Translating research findings into innovative clinical products for public health priorities, including drug-resistant infections, is a priority of the federal agencies which have focused resources on a gap currently not filled by the pharmaceutical industry. For the first time, clinical trials directed at preventing, diagnosing, or treating serious drug-resistant bacterial infections in the intensive care setting will be conducted by the NIH Bacteriology and Mycology Study Group. Safety and efficacy trials of vaccines and

therapies with relevance to drug-resistant infections continue within the Tuberculosis Research Unit, the Vaccine and Treatment Evaluation Units, and other NIH clinical trial networks. Collaborations are ongoing between the DVA and the NIH AIDS Clinical Trials Group to assess intermittent and chronic HIV regimens that minimize development of resistance to antiretroviral therapies.

NEW RAPID DIAGNOSTIC METHODS

New rapid diagnostic methods are needed at the point of patient care to optimize use of antimicrobial drugs and minimize resistance development. Several new NIH grants activities, the Challenge Grant Program and the Partnerships Initiative, seek to promote the research and development of new rapid diagnostic methods and novel products through collaborations and partnerships with the private sector and academia. The DoD evaluated two rapid diagnostic tests for their ability to identify influenza as the cause of respiratory outbreaks. If proven successful, these tests will reduce unnecessary antimicrobial use and help slow the emergence of AR in bacterial respiratory pathogens. USDA-ARS is currently evaluating new methods for detecting antimicrobial resistance in Enterococci and Campylobacter.

VACCINE DEVELOPMENT

The development and appropriate use of vaccines in human and veterinary medicine is critical to preventing infections, reducing the rate of infection transmission, and minimizing the need for antimicrobial therapy. CDC, DoD, FDA, and NIH all conducted studies to assess the effectiveness of a variety of licensed and candidate pneumococcal vaccines in children and adults, including members of the military. Several of these studies resulted in licensure of products; others are likely to result in new indications for use of these products. A study conducted by NIH showed that an acellular pertussis vaccine given to adolescents and adults would be safe and effective in reducing the burden of disease in this population, and in reducing secondary transmission to infants. NIH scientists identified a new group B streptococcal surface antigen for use as a vaccine candidate or as a carrier protein, and in separate studies have characterized conserved outer membrane proteins of *Neisseria* that play a role in disease progression. TB vaccine candidates to prevent colonization, infection, and transmission were investigated in independent projects supported by FDA and NIH.

As suggested in the IOM 1998 Report, through these activities NIH and the other federal partners are providing, "… sustained, sufficient support - for basic pioneering research, for the clinical research required to move truly new products from the laboratory to the pharmacy, and for the infrastructure underpinning both."

PRODUCT DEVELOPMENT

New products are not being developed fast enough to address the increase in microbial resistance to drugs used to treat infections in human medicine. Not only do we need to develop new classes of antimicrobial agents that are able to kill otherwise resistant organisms, but we need to develop vaccines and anti-infective devices with the potential to prevent infections. In addition, develop better diagnostic tools are needed to aid in appropriate use of therapeutics.

Product development is also an important issue for veterinary medicine and agriculture. U.S. agencies and private sector partners must intensify efforts to encourage the development and use of veterinary drugs and agricultural practices that are unlikely to stimulate resistance to important human drugs or spread resistant pathogens to humans. In addition, we need to focus more attention on developing strategies to prevent animal infections (e.g., vaccines, changes in husbandry) and on existing and new products more effectively.

Pertinent issues include:

- Researchers and manufacturers need to be better informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, and diagnostics and of potential markets for these products.

- Market incentives and regulatory processes need to be adequate to stimulate the development of certain priority AR products or enforce their appropriate use.

- The development and use of antimicrobial drugs and related products in agriculture and veterinary medicine need to be optimized to reduce the development and transfer of resistance to pathogens that can infect animals and humans.

Top priority action items in this focus area include:

- 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 #79)

- 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. (Action Item #80)

ASSESSMENT OF FUTURE NEEDS FOR AR PRODUCTS

To provide a systematic assessment of the current status and projected future needs for AR products, a cooperative interagency effort involving stakeholders including regulated industry is intended to identify and publicize priority public health needs in human and animal medicine for new AR products. FDA has chosen to perform these cooperative

activities within an existing framework (i.e., preexisting advisory committees) to enhance the efficiency and the applicability of the results of such discussions. FDA has begun this process through meetings with industry stakeholders and through a public advisory committee meeting on February 19 and 20, 2002, and has identified the following essential components of ongoing activities:

- Involvement of experts in the nonmedical disciplines.

- Modeling future resistance trends, product needs and potential markets, considering AR surveillance data and numbers of patients at high risk of developing drug resistant infections.

- Involvement of experts from a range of disciplines who can provide input on issues such as modeling future resistance trends, identifying product needs and potential markets, considering AR surveillance data and numbers of patients at high risk of developing drug resistant infections.

- Evaluation of current market incentives for the development of priority AR products.

- Reassessment of AR product priorities regularly.

- Evaluation of the availability of currently approved, critical products when shortages or the potential for shortages exists and develop an approach to ensure that the supply of these products meets the public health needs.

- Coordination of the information and priorities developed through cooperative efforts with other agencies and stakeholders to inform and allow coordination with planning and action efforts in research, prevention and control, and product development.

- Consideration (in consultation with academia and industry) of whether the government has a constructive role to play in the discovery of drugs and other products targeted to address areas in which market incentives are limited and unmet needs exist. This role could use intramural, extramural or partnership-type mechanisms. The products developed under such mechanisms could be licensed commercially either with or without specific stipulations about use.

PROMOTING DEVELOPMENT OF AR PRODUCTS

FDA is developing guidance on the development of antimicrobial drugs for resistant indications and has held meetings with industry stakeholders, made presentations at scientific meetings, and convened a public advisory committee meeting on February 19, and 20, 2002. FDA is also developing guidance documents to promote the development of several novel types of AR products (e.g., topical antimicrobicides, plant-based vaccines). Finally, FDA has begun internal meetings to consider economic incentives

and is developing guidance on non-economic incentives based upon existing regulatory tools. These approaches are planned to include:

- Consultation with outside stakeholders, economic consultants and development of cooperative interagency efforts.

- Careful economic modeling and analysis, and assessing these pilot programs for return on public investment.

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