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ANTIMICROBIAL RESISTANCE

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

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ANTIMICROBIAL RESISTANCE

WEDNESDAY, SEPTEMBER 20, 2000

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 9:30 a.m., in room SD–124, Dirksen Senate Office Building, Hon. Thad Cochran presiding.

Present: Senator Cochran.

OPENING STATEMENT OF SENATOR THAD COCHRAN

Senator COCHRAN. The subcommittee will please come to order.

This morning we are conducting a hearing on the subject of antimicrobial resistance, a growing national health threat. When penicillin was launched in the early forties, it was touted as a miracle drug capable of countering everything from the common cold to pneumonia and even staph infection.

This antibiotic and others developed since then have enabled us to have a more healthy, productive, and longer living population. These and other antimicrobials have proven to be enormously successful.

But these miracle drugs are producing fewer miracles these days. What we considered easily treatable diseases are now becoming increasingly deadly. As our once invincible pharmaceuticals have begun to lose their ability to kill diseases caused by microbes—to kill disease-causing microbes.

Our extensive use of antimicrobial drugs as well as the remarkable ability of microbes to mutate and develop resistance threatens to return us to the situation we had in the early 1900's, where common infections were often lethal.

Antimicrobial resistance is a threat to the health and safety of countries worldwide, including the United States. All human kind is at risk.

The most susceptible to the threat are the most vulnerable, those who are sick in hospitals and the young in daycare centers. But drug-resistant infections are now occurring in all urban and rural settings and among all populations.

And these are not new unknown microbes. They are such well-known illnesses as tuberculosis, malaria and gonorrhea and such common ailments as sore throats and ear infections.

The threat is real and growing at a time when our society cannot afford the social or financial cost of a drug-resistant outbreak of infectious diseases.

This problem is very serious and I hope we can address it with the urgency that it requires.

At this hearing, I hope we can get suggestions from the experts about how the Federal and State governments, the private sector and academia can work together to deal with the threat.

The Senate has already recognized the problem when it approved an amendment to a Labor HHS appropriations bill this year, which provides funds for pilot projects in antimicrobial resistance surveillance and research.

Another bill that is pending is the—in the legislative committee is S. 2731, the Public Health Threats and Emergencies Act. It also provides new authorization for Federal programs to address antimicrobial resistance surveillance, education and research.

These are good first steps. But they are only the beginning of a full-scale attack we need to solve this serious problem.

A public health action plan to combat antimicrobial resistance has been developed by an interagency task force led by the Centers for Disease Control, the Food and Drug Administration, and the National Institutes of Health. This plan will provide a blueprint for the next decade's fight against resistance. The action plan confirms that we must immediately begin to work on a variety of fronts through a comprehensive and concentrated public, private partnership.

I expect our panelists will testify today that this initiative must include surveillance, prevention, and education as well as research into resistance mechanisms and the development of new and more effective antimicrobial drugs.

We will begin today's hearing with a panel including Dr. Jeffrey Koplan, from the Centers for Disease Control and Prevention; and Dr. Jane Henney, who is Commissioner of the Food and Drug Administration.

Then we will hear from our second panel that will include Dr. Ed Thompson, State Health Director for the State of Mississippi; Dr. Alice Clark, Director of the National Center for the Development of Natural Products; Dr. Merle Sande, Professor and Chairman of the Department of Medicine at the University of Utah School of Medicine; Dr. Martin Rosenberg, Senior Vice President and Director of Anti-Infectives at SmithKline Beecham Pharmaceuticals; and Dr. Mark Nelson, Senior Director of Chemistry at Paratek Pharmaceuticals.

Our witnesses have submitted statements to the committee, which will be made a part of the record in full, and the National Institutes of Health has also submitted a statement, which will be made a part of the record.

STATEMENT OF JEFFREY P. KOPLAN, M.D., DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Senator COCHRAN. Let us begin with Dr. Koplan of the Centers for Disease Control. You may proceed.

Dr. KOPLAN. Thank you, Senator Cochran. Good morning. And thank you for your invitation to testify on the national and global problem of antimicrobial resistance and CDC's response to it.

Incredible changes in infectious diseases have occurred within our own life span. Many of the diseases that threatened our parents are distant history for our children.

In 1942, a 33-year-old woman was hospitalized for a month in Connecticut with a life-threatening streptococcal infection. She was delirious. Her temperature reached almost 107 degrees.

Her doctors gave her an experimental drug called penicillin at Grace New Haven Hospital. Her condition began to improve overnight. She was the first woman American civilian that was saved by penicillin. And she died just this past year at the age of 90.

The typical population of hospital medical wards was very different in the Thirties than it is today. Today wards are filled with patients who have cancer, heart disease, diabetes, complications of high-blood pressure.

In contrast, the wards then were populated by patients with pneumonia, sepsis, typhoid fever, diphtheria and rheumatic fever. There were few effective therapies for most of these conditions. And within a few years, many of these infections became memories of the pre-antimicrobial era.

Unfortunately, the emergence of drug resistance threatens to reverse the progress prompted by the discovery of penicillin and the other miracle antimicrobials that have been developed.

Even with these drugs, infectious diseases remain a leading cause of death worldwide and in the United States. Antimicrobial resistance contributes to this burden as it affects virtually all of the pathogens we have previously considered to be easily treatable.

Here in the 21st century, drug options to treat common infections are becoming increasingly limited and reliance on more expensive options contribute to escalating health-care costs.

Drug resistance is a target plan—is a target area in CDC's plan, "Preventing Emerging Infectious Disease: A Strategy for the 21st Century." Public health priorities in the plan are organized under four broad goals, each of which can be applied to antimicrobial resistance: one, surveillance and response; two, applied research; three, infrastructure and training; and four, prevention and control.

Surveillance data help clinicians know which antimicrobials to prescribe, help researchers focus their efforts and help public health officials mount prevention campaigns.

For many infections, resistance rates vary widely. For example, 15 percent of Streptococcus pneumoniae strains in parts of Maryland are resistant to penicillin, whereas in 5 Tennessee counties, 38 percent are resistant. In Connecticut, the frequency of resistance varies from zero to nearly 40 percent among hospitals. These data highlight the need for such information at all levels—local, State and Federal—in order to guide clinical decisions and target interventions.

With our partners, CDC conducts limited surveillance to monitor resistance for several important pathogens. For example, surveillance for resistance among invasive pneumococcal infections is conducted through nine State health departments involved in CDC's Emerging Infections Program.

Other projects monitor drug-resistance in Helicobacter pylori, typhoid fever, HIV, and malaria, but only in a handful of sites. With

our colleagues in—at the FDA, we monitor food-borne pathogens for antibiotic resistance.

None of these systems is operational in all States, in all hospitals, or covers all organisms for which resistance is a problem. Coordinated national antimicrobial resistance surveillance is needed.

Applied research needs include developing new drugs and vaccines, identifying molecular mechanisms of drug resistance and risk factors associated with its spread, developing improved diagnostic tests and assessing the role of new vaccines and orphan drugs in preventing and controlling the spread of resistant infections.

For example, CDC has entered into a promising research collaboration with a consortium formed by the University of Mississippi, Tulane University, and Xavier University in New Orleans to develop and test new antimalarial drugs.

CDC's ongoing effort to rebuild the U.S. public health infrastructure, to address infectious diseases, is critical in improving the capacity of health departments, health-care delivery organizations, and clinical and public health laboratories to detect and report drug-resistant infections and to implement prevention and control strategies.

Antimicrobial resistance is constantly changing, requiring that laboratory testing methods be kept up to date. For example, a 1998 survey of laboratories found that only 18 percent were actively using appropriate methods to detect emerging resistance in Staphylococcus aureus; only 32 percent were using appropriate methods to find resistance in organisms that typically cause infections in ICU's.

We need to ensure that whenever a doctor sends a specimen to a laboratory, the correct test will be done to detect drug-resistant infections and that the test result will be interpreted correctly and reported. State public health labs will play leading roles in this effort.

CDC's Epidemiology and Laboratory Capacity agreements with State health departments in 43 States and localities provide a mechanism to do this.

Perhaps the most daunting challenge is to develop a coordinated program to prevent the spread of antimicrobial resistance by translating information into public health prevention and control measures. We can all relate to the parent of a sick child who wants his or her child to feel better.

For too long, this has often meant requesting an antibiotic from the child's doctor. We now know that antibiotics are not effective for many conditions for which they have been prescribed.

CDC has conducted focus groups with parents and physicians to better understand the factors behind inappropriate antibiotic use. For example, parents told us that they need an antibiotic in order for their children to return to daycare. Physicians told us that they do not typically have enough time to educate a patient about the problem of antimicrobial resistance and the reasons why antibiotics do not work for viral infections. This reinforced our belief that we must move forward on a nationwide public information campaign.

In cooperation with professional societies, CDC has developed educational materials for physicians and parents, including a prescription pad for physicians to provide patients written instructions for treating symptoms of viral illnesses, for which antibiotics would be inappropriate.

Preliminary data suggests that these approaches are effective. For example, in certain rural Alaskan villages, an education intervention for the public and health-care providers successfully reduced antibiotics prescribing by 31 percent. These data hold promise that we can make a difference.

Combating antimicrobial resistance will require Federal leadership and collaboration among public and private sector partners. Beginning in June 1999, CDC, FDA and NIH joined with seven other Federal agencies to form the Interagency Task Force that you mentioned earlier. It provides a blueprint for specific coordinated Federal actions to address this emerging threat.

CDC's primary role in implementing the plan is in the areas of surveillance and prevention and control, addressing the needs I have detailed already.

PREPARED STATEMENT

In conclusion, recent increases in antimicrobial resistance are cause for serious concern but not pessimism. The rapid spread of resistance demands an immediate and aggressive response. By forming effective partnerships, we can prolong the effectiveness of currently available antimicrobial drugs; accelerate the development of new tools and reduce the threat of antimicrobial resistance for patients today and in future generations. Thank you very much.

Senator COCHRAN. Thank you, Dr. Koplan, for your interesting and provocative statement.

[The statement follows:]

PREPARED STATEMENT OF HON. JEFFREY P. KOPLAN

I am Dr. Jeffrey P. Koplan, Director, Centers for Disease Control and Prevention (CDC). Thank you, Mr. Chairman and members of the Subcommittee, for your invitation to testify today on the emerging national and global problem of antimicrobial resistance and the response by CDC.

ANTIMICROBIAL RESISTANCE AS A PUBLIC HEALTH ISSUE

In March 1942, a 33-year-old woman was hospitalized for a month with a life-threatening streptococcal infection at a New Haven, Connecticut, hospital. She was delirious, and her temperature reached almost 107°F. Treatments with sulfa drugs, blood transfusions, and surgery had no effect. As a last resort, her doctors injected her with a tiny amount of an obscure experimental drug called penicillin. Her hospital chart, now at the Smithsonian Institution, indicates a sharp overnight drop in temperature; by the next day she was no longer delirious. That woman was the first U.S. civilian whose life was saved by penicillin, and she died last year at the age of 90.

The typical medical ward of a large city hospital was very different in the 1930s than it is today. Today's wards are filled with patients with cancer, heart disease, or the complications of diabetes or high blood pressure. In contrast, the wards of the pre-antimicrobial era were populated by patients with pneumonia, meningitis, sepsis, typhoid fever, diphtheria, syphilis, tuberculosis, and rheumatic fever. There were few effective therapies for most of these conditions. Many of the patients were young, and most would die of the disease or its complications. But within a few years, many of these bacterial infections, and particularly their complications, rapidly faded to become memories of the pre-antimicrobial era.

Unfortunately, the emergence of drug resistance threatens to reverse the progress prompted by the discovery of penicillin and other miracle drugs that have been de-

veloped over the last 50 years. Even with these miracle drugs, infectious diseases are a leading cause of death worldwide and the third leading overall cause of death in the United States. Antimicrobial resistance contributes to the burden of infectious diseases domestically and globally including bacterial, fungal, parasitic and viral diseases. Antimicrobial resistance already affects virtually all of the pathogens we have previously considered to be easily treatable. Here in the 21st century, drug options for the treatment of common infections are becoming increasingly limited, and reliance on more expensive options contributes to escalating health care costs. A 1995 Office of Technology Assessment report estimated that the emergence of antimicrobial resistance among six common bacteria in hospitals adds approximately $661 million per year in hospital charges, and this estimate does not include indirect costs. Many other scientific, policy, and government organizations have called attention to this issue, including, in the United States, the American Society for Microbiology, the Infectious Diseases Society of America, the Institute of Medicine, and the General Accounting Office. International organizations that have expressed concern about this issue include the World Health Organization, the European Union, the United Kingdom House of Lords, and Health Canada.

Antimicrobial resistance is a complex and multifaceted public health issue. The use of antimicrobials in agriculture can lead to the development of resistant strains of pathogens that can spread to humans through the food supply or through contact with infected animals. International travel and trade increases the likelihood that drug-resistant pathogens from distant corners of the world can appear in the United States. For example, malaria is frequently brought into our country by U.S. travelers, and is being transmitted domestically at an increasing rate. Because drug-resistant strains of malaria now predominate across the globe, they present a growing problem here. This complexity highlights the importance of a coordinated, overarching multidisciplinary public health approach that involves physicians, epidemiologists, laboratory and behavioral scientists, veterinarians, and health educators. We are all striving to make antimicrobial resistance a manageable problem that does not compromise the availability of safe and effective drugs to treat infectious diseases.

Drug resistance is one of the target areas in CDC's plan, "Preventing Emerging Infectious Diseases: A Strategy for the 21st Century." Public health priorities in the plan are organized under four broad, interdependent goals, each of which can be applied to antimicrobial resistance: improving surveillance and response capacity, addressing applied research priorities, repairing the Nation's public health infrastructure and training programs, and strengthening prevention and control programs. Copies of CDC's plan have been provided to the Subcommittee.

SURVEILLANCE AND RESPONSE

Public health surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of health data that results in public health action. These data are used to detect outbreaks, characterize disease transmission patterns, evaluate prevention and control programs, and project future health care needs. In the case of drug resistance, surveillance data available in a timely manner at national, state, and local levels are needed to help clinicians know which antimicrobials to prescribe, help researchers focus their efforts to develop new drugs and vaccines, and help mount campaigns to improve antimicrobial use and infection control practices.

With the exception of drug-resistant tuberculosis, which is reportable in all 50 states, many states do not require reporting of other drug-resistant infections. In those states where drug-resistant infections are reportable, the extent and type of reporting varies. To obtain more systematic information, CDC, in collaboration with state and local health departments and other partners, conducts limited surveillance in some areas to monitor resistance for several important pathogens. For example, surveillance for resistance among invasive pneumococcal infections is conducted through the nine state health departments involved in CDC's Emerging Infections Program cooperative agreements. Surveillance is also conducted in 300 hospitals for healthcare-acquired infections, in 15 states in collaboration with the Food and Drug Administration (FDA) and the Department of Agriculture for foodborne infections, and in 25 clinics for gonoccocal infections. Other projects monitor drug resistance in *Helicobacter pylori,* typhoid fever, HIV, and malaria, but only in a handful of sites. In many communities, the rates of drug resistance for common, serious infections are based on limited and potentially unreliable data or are simply unknown. Existing systems are not well-coordinated.

For many infections, resistance rates vary widely among communities and among hospitals within communities. As one example, data show that the penicillin resist-

ance of *Streptococcus pneumoniae* can vary considerably by location: 15 percent of strains in parts of Maryland are resistant to penicillin, whereas in five Tennessee counties, 38 percent are resistant. In Connecticut the frequency of resistance varies from zero to 39 percent among hospitals. These data highlight the need for such information at all levels—local, state, and federal—in order to guide clinical decisions and target interventions.

None of these surveillance systems is operational in all 50 states, in all hospitals, or covers all organisms for which antimicrobial resistance is a problem. Coordinated national antimicrobial resistance surveillance is needed to monitor antimicrobial resistance in microorganisms that pose a threat to public health. Core capacities at state and local levels need to be defined. A system to monitor patterns of antimicrobial drug use needs to be developed and implemented. This information is essential to interpret trends and variations in rates of antimicrobial resistance, improve our understanding of the relationship between drug use and resistance, and help identify interventions to prevent and control antimicrobial resistance.

APPLIED RESEARCH

Applied research needs include developing new drugs and vaccines; identifying molecular mechanisms of drug resistance and risk factors associated with its development and spread; developing new and improved rapid diagnostic laboratory tests; and, in collaboration with other agencies and private industry, assessing the role of new vaccines and orphan drugs in preventing and controlling the spread of resistant infections. These and related research needs will require collaboration with other agencies and private industry.

CDC has entered into a promising research collaboration with a consortium formed by the University of Mississippi, Tulane University, and Xavier University in New Orleans to develop and test new antimalarial drugs. This work builds on the complementary strengths of the universities. It focuses on the use of computer-assisted drug design and natural products in the development and testing of promising new medicines.

We also need to develop, implement, and evaluate preventive interventions, including infection control strategies, such as those in hospitals, day care centers, long-term care and home health care settings; improve drug-prescribing practices of health care providers; and the use of vaccines to prevent drug-resistant infections. For example, a new conjugate vaccine for children against *Streptococcus pneumoniae,* the leading cause of pneumonia, meningitis, and ear infections, was licensed for use in February 2000. CDC is evaluating the impact of introduction of this vaccine on drug-resistant pneumococcal infections in children. Research is also necessary to evaluate the impact of drug resistance, including clinical outcomes and economic costs of treating resistant infections. Without these kinds of studies, it is extremely difficult to develop and recommend prevention and control measures to institutions and communities.

INFRASTRUCTURE AND TRAINING

CDC's ongoing effort to rebuild the U.S. public health infrastructure to address infectious diseases is critical in improving the capacity of health departments, health care delivery organizations, and clinical and public health laboratories to detect and report drug-resistant infections and to implement prevention and control strategies. Part of this effort includes enhancing capacity to respond to outbreaks and training public health professionals to be able to respond to emerging threats now and in the future. Antimicrobial resistance is a constantly changing challenge requiring that laboratory testing methods be kept up-to-date. For example, a 1998 survey was conducted among laboratories that routinely collaborate with CDC. Only 18 percent were actively using appropriate methods to detect emerging resistance in *Staphylococcus aureus,* and only 32 percent were using appropriate methods to find resistance in organisms that typically cause infections in intensive care units. Thus for two important groups of hospital- acquired infections, less than one-third of laboratories were performing proficiently.

We need to ensure that laboratories remain up-to-date with training and that whenever a doctor sends a specimen for culture to a laboratory, the correct test will be done to detect drug resistant infections, the test result will be interpreted correctly and reported to the doctor in a way that helps to select the appropriate drugs, and, if appropriate, reported to a surveillance system. CDC's Epidemiology and Laboratory Capacity agreements to health departments in 43 states and localities currently help support these types of efforts. In addition, the Emerging Infectious Diseases Laboratory Fellowship Program is a partnership between CDC and the Asso-

ciation of Public Health Laboratories designed to prepare laboratory scientists for careers in public health.

PREVENTION AND CONTROL

Perhaps the most daunting challenge is to develop a coordinated program to prevent the spread of antimicrobial resistance by translating information gleaned from surveillance and research into practical public health prevention and control measures. We can all relate to the parent awake at night with a sick child. All that person wants is for his or her child to feel better. For too long, that has often meant requesting an antibiotic from the child's doctor. Although antibiotics work for bacterial infections, we now know that they are not effective for many conditions for which they have been prescribed including fluid accumulation in the middle ear, colds, and bronchitis.

CDC has conducted focus groups with parents and physicians to better understand the factors behind inappropriate antibiotic use. We learned many things from these conversations. For example, parents told us they need an antibiotic in order for their children to return to daycare. This led us to develop a daycare letter that parents can use to get around this ill-conceived policy. Physicians told us that they do not typically have enough time to educate a patient about the problem of antimicrobial resistance and the reasons why antibiotics do not work for viral infections. This reinforced our belief that we must move forward on a nationwide public information campaign.

A key component of CDC's plan to address antimicrobial resistance is promoting appropriate antimicrobial drug use. CDC is developing a national campaign to improve physician prescribing practices and to educate parents and patients about the proper use of antibiotics. By promoting better communication between the public and the medical community, we are attempting to change the entire culture around which antibiotics are prescribed. We are working towards a day when a patient or parent sees his or her health care provider and rather than requesting an antibiotic, asks for the best treatment available. Where antibiotic use is appropriate, CDC promotes methods to increase adherence to and completion of treatment. For instance, CDC uses directly observed therapy, short-course (DOTS), to ensure patient compliance with tuberculosis treatment. Use of DOTS has increased the proportion of patients completing therapy, lowering the incidence of multidrug-resistant tuberculosis. CDC and FDA have also worked with the American Veterinary Medical Association in its activities to develop prudent-use guidelines for therapeutic veterinary uses of antimicrobials, and CDC strongly supports the new framework articulated by FDA to consider the impact on human drug resistance as part of the approval process for antimicrobials used in food animal production.

In cooperation with professional societies, CDC has developed educational materials for physicians and parents, including a "prescription pad" for physicians to provide patients written instructions for treating symptoms of viral illnesses, for which antibiotics would be inappropriate. In collaboration with AAP and the American Society for Microbiology, CDC has also developed a brochure for parents, "Your Child and Antibiotics," explaining why antibiotics should not be given for most colds, coughs, sore throats, and runny noses. These materials have been distributed widely and are available on the CDC website. Interventions using these materials and behavioral strategies, such as physician-peer discussions, have proved successful in several locations, including managed care settings in Boston and Seattle, rural communities in northern Wisconsin, Alaska Native villages, and on a county-wide basis in Knoxville, Tennessee. Preliminary data suggest that these approaches are effective. For example, in certain rural Alaskan villages, an education intervention for the public and health care providers successfully reduced antibiotic prescribing by 31 percent. No change was seen in communities not receiving the intervention. Although work is ongoing to measure the impact of reduced antibiotic prescriptions on drug-resistance in the community, these data hold promise that we do have the ability to make a difference.

Appropriate drug-use policies should be implemented through a public health education campaign that promotes appropriate antimicrobial drug use as a national health priority. Improved diagnostic practices should be promoted, including the use of rapid diagnostic methods to guide drug prescribing. Reduced infection transmission should be addressed through campaigns that promote vaccination and hygienic practices such as hand washing and safe food handling. Infection control in health care settings should be enhanced by developing new interventions based on rapid diagnosis, improved understanding of the factors that promote cross-infection, and modified medical devices or procedures that reduce the risk of infection.

Comprehensive, multi-faceted programs involving a wide variety of non-federal partners and the public are required to prevent and control antimicrobial resistance. We need to support demonstration projects that use multiple interventions to prevent and control antimicrobial resistance. We need to encourage the incorporation of effective programs into routine practice by implementing model programs in federal health-care systems and promoting the inclusion of antimicrobial resistance prevention and control activities as part of quality assurance and accreditation standards for health care delivery nationwide.

EXAMPLES OF SUCCESSES IN PREVENTING ANTIMICROBIAL RESISTANCE

Although there has been much discussion of how the problem of antimicrobial resistance is increasing, it is also important to note some successes that provide models for future programs. Public health officials in Iowa, in partnership with physicians and health departments in Nebraska and South Dakota, the Indian Health Service, and CDC, recently succeeded in halting an increase in acquisition of vancomycin-resistant enterococci (VRE) among hospitalized patients and residents of long-term care facilities in the tri-state Siouxland region surrounding Sioux City, Iowa.

VRE is a highly resistant organism that is transmitted in health-care settings. Some patients carry the organism without experiencing symptoms, but others develop infections that may be life-threatening. After a rapid increase in VRE was reported in early 1997, a task force was formed by the Siouxland district health department, consisting of local physicians, infection control practitioners, and public health officials.

The VRE task force formulated several interventions, including performing screening cultures on admitted patients, implementing strict infection control policies based on CDC guidelines, and educating health care workers about the epidemiology of VRE and prudent use of antibiotics, especially vancomycin. This strategy was effective. Over a two year period, the overall prevalence of VRE at all the healthcare facilities decreased from 2.5 to 0.5 percent. There was an elimination of VRE from all the hospitals and a significant reduction in VRE at the long-term care facilities. The key to success was the partnership between public health and clinical medicine so that when surveillance data indicated an emerging problem, science-based prevention and control measures could be implemented rapidly to prevent the spread of a serious drug-resistant infection in this community.

Other countries are grappling with problems of drug resistance as well, and we can learn important lessons from their experiences. In the early 1990s, Finland noted a dramatic increase in resistance of Group A streptococci to the antimicrobial drug erythromycin. Use of erythromycin had tripled and drug-resistance rates correlated with the level of use in local areas. A program of public and physician awareness combined with changes in recommendations for prescribing resulted in reduced erythromycin prescribing for minor outpatient infections and a steady decrease in erythromycin resistance rates among Group A streptococci. It was uncertain if this success could be replicated in a country like the United States with a more heterogeneous population and health care system, but preliminary findings from intervention studies sponsored by CDC and others are encouraging.

Another success relies on modern information technology, which can facilitate rapid collection, analysis, and feedback of information to clinicians. A pioneering program of computer-assisted decision support developed at LDS Hospital in Salt Lake City offers antibiotic recommendations to clinicians based upon computerized assessment of the patient's medical record and surveillance data on drug resistance in the health care system. This program was developed with input from local physicians, who view it as a valuable resource. The program is associated with decreased inappropriate antibiotic use, reduced frequency of adverse drug reactions, reduced patient care costs, and a stable rate of drug resistance.

COLLABORATION TO ADDRESS ANTIMICROBIAL RESISTANCE

Combating antimicrobial resistance will require federal leadership and close collaboration among public and private sector partners. Federal agencies need to work together with partners in clinical medicine, laboratory and behavioral science, state and local public health agencies, industry, and the public. International cooperation is also critical. Together, we need to develop public health goals and objectives, along with time frames for implementation.

Beginning in June 1999, CDC, FDA, and the National Institutes of Health joined with seven other federal agencies and departments to form an Interagency Task Force on Antimicrobial Resistance to develop "A Public Health Action Plan to Combat Antimicrobial Resistance." In addition to the three lead agencies, the Task Force

includes members from the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency, and other agencies of the Department of Health and Human Services, including the Agency for Healthcare Research and Quality, the Health Care Financing Administration, and the Health Resources and Services Administration. The Action Plan provides a blueprint for specific, coordinated federal actions to address the emerging threat of antimicrobial resistance. It reflects a broad-based consensus of federal agencies, which was reached with 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. Implementation of this plan will require close collaboration with all of these partners, which is a major goal of the process. This summer, the draft of the Action Plan was provided for public comment. The Interagency Task Force has recently completed reviewing comments received through this process and is now modifying the Action Plan for final publication. This draft plan identifies 11 top priority action items, and overall it has 87 specific action items addressing the important areas of surveillance, prevention and control, research and product development.

The Action Plan includes a summary and a list of issues, goals, and action items and specifies "coordinator" and "collaborator" agencies or departments, and timelines for each. CDC's primary role is in the areas of surveillance and prevention and control, addressing the needs I have detailed already in this testimony. The Interagency Task Force will facilitate coordination among agencies and monitor implementation of the Action Plan. The Task Force plans to produce periodic reports detailing how the plan is being implemented, solicit comments from the public, and update the Plan as new information and issues arise. Copies of this draft plan have been distributed to the Subcommittee members. This document is Part I of the Action Plan, focusing on domestic issues. Since resistance transcends national borders and requires a global approach to its prevention and control, Part II of the plan, to be developed subsequently, will identify actions that address international issues.

CONCLUSIONS

In conclusion, recent increases in antimicrobial resistance are cause for serious concern but not pessimism. The rapid spread of resistance demands an immediate and aggressive response domestically and globally. Preliminary data suggest that antibiotic prescribing practices can be improved. By forming effective partnerships involving clinicians, researchers, public health officials, and patients, we can prolong the effectiveness of currently available antimicrobial drugs; accelerate the development of needed new tools, including rapid diagnostic tests, new antimicrobial agents, and new or improved vaccines; and reduce the threat of antimicrobial resistance for patients today and in future generations.

Thank you very much for your attention. I will be happy to answer any questions you may have.

STATEMENT OF JANE E. HENNEY, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Senator COCHRAN. Dr. Henney is Director of the Food and Drug Administration.

We welcome you to the hearing. You may proceed.

Dr. HENNEY. Mr. Chairman, I am Jane Henney, Commissioner of Food and Drugs.

I am extremely pleased to be here this morning to talk about antimicrobial resistance and FDA's important role in addressing this growing public health problem. I appreciate your including my full written testimony for the record.

As you and Dr. Koplan have already so clearly articulated, antibiotic resistance is well-recognized as a major threat to the health of the U.S. citizens and people around the world.

Although, we have been using antibiotics for more than 50 years, the extent of resistance is much greater than ever before. FDA's goal is to be sure that practitioners have a continuous supply of safe and effective antimicrobials available to protect the health of

humans and animals, and reliable laboratory test products to direct appropriate antibiotics use.

Antibiotics are different from most other drugs approved by FDA, because their effectiveness is so fragile. Another unique characteristic is that these drugs effect not only the patient who receives them, but also their personal contacts, the environment, and the health of the community.

We need to protect the effectiveness of this special class of drug products by using them in a thoughtful way that is based on the best available science.

As with most issues that involve fragile resources, this one has global ramifications. In some countries, antibiotics are available without prescription, and may be impure or sub-potent and many patients cannot afford adequate courses of treatment.

With frequent and wide-ranging air travel and extensive immigration we are able to pass our pathogens to one another with frightening speed.

That means that in order for us to succeed in our efforts to use antibiotics wisely, similar steps must be taken by nations around the world.

In late 1998, an FDA Task Force on Antimicrobial Resistance was established to develop a clear consensus regarding what, given limited resources, should be the key priorities of the agency.

The FDA Task Force Report, completed in draft in October 1999, focuses on four key areas where FDA should and is able to play an important role in achieving specific and practical outcomes. And they are: one, effectively responding to current public health threats; second, facilitating product development; three, facilitating safe and effective use of antimicrobials; and, four, coordinating the FDA's scientific response to antimicrobial resistance.

Details on each of these areas are included in my written statement, but I would like to focus on two of them—product development and education.

There will continue to be a critical need for innovative product development to meet the threat posed by antimicrobial organisms. Desired products include not only new antibiotics but also vaccines to prevent infections and reduce antibiotics use, and improved, more rapid diagnostics to identify pathogens and drug resistance. At each step of the product development process, there is room for improvement and innovations.

We have increased our internal efforts to facilitate development of drugs, vaccines, and medical devices. And these measures include, one, granting a priority review to applications for new antibiotics, which ensures that these applications are acted on in 6 months or less.

Two, working early on with sponsors of critical products and overall product development, clinical trial design and other issues that may arise so that the process can be as effective and efficient as possible.

Three, using different regulatory approaches to provide more rapid development, early consultation and early access, the Subpart E designation, and accelerated approval utilizing a surrogate endpoint, Subpart H, are the tools that are being considered.

Two of the most recent approvals for products to treat highly resistant organisms, Synercid and Zyvox, were developed and reviewed using these approaches. Prior to the approval of these products, patients who were infected with vancomycin-resistant enterococci had no other available therapies. Many of these patients are the most vulnerable and these products are truly lifesaving for these patients.

We are also actively encouraging the development of new vaccines to help reduce the need for antibiotics. Earlier this year, FDA approved the first vaccine to prevent invasive pneumococcal disease in infants and children, Prevnar. Through the provisions provided in the FDA Modernization Act, Prevnar was granted fast track designation and assigned priority review status.

We are also looking at pneumococcal vaccines for the prevention of otitis media and pneumonia, which are often due to pneumocci. The potential contribution of these pneumococcal vaccines in helping to reduce these diseases could further reduce the use of antimicrobials.

Vaccines are also under development that would indirectly affect antimicrobial use. For example, ear infections and respiratory diseases are often treated with antibiotics, but most often caused by viral infections, such as parainfluenza and RSV.

Development of vaccines to prevent these viral infections would also be an important mechanism impacting on unneeded and nonbeneficial antibiotics use.

We also want to facilitate the development of new diagnostic tests that can rapidly determine and certainly indicate whether an infection is truly bacterial. The test would also be expected to identify an appropriate antibiotic for treatment.

And finally, in our initiatives geared to new product development, we are committed to developing strategies to overcome economic disincentives for new antimicrobial product development and at the same time balance the need for more restricted appropriate use.

Education is another key component of the FDA's plan. Physicians tell us, as you have also heard from Dr. Koplan, that patients often pressure them to prescribe antibiotics. They may have limited time to explain the rationale for not using an antibiotic, or for using an alternative treatment. Some may not have access to rapid diagnostics or to antibiotic sensitivity testing.

It may be far too tempting to simply prescribe an antibiotic. Since this is often a shot in the dark, because the bacteria have not been identified and susceptibility testing not done, the physician is further tempted to prescribe a new and powerful blockbuster antibiotic that may have the greatest chance of working.

Such antibiotics are often not warranted as many community acquired infections are viral and do not respond to antibiotics or are caused by bacteria still sensitive to older alternative drugs.

And once an antibiotic is prescribed a lack of patient understanding and therefore compliance may also contribute to resistance. Patients, either by omission or commission, often do not take the antibiotic according to directions and frequently fail to take the entire course of antibiotics.

Instead, they stop taking it when they feel better and then save the rest for the next time or share the leftover drugs with a sick friend. The result, inadequate treatment courses, also is a recipe for inducing resistance.

The FDA pledges to work with industry and public health officials using a variety of means to provide better and more consistent information to consumers and health professionals about the judicious use of antibiotics.

We believe it is particularly important to include additional information in the labeling of prescription antibiotics. Yesterday, FDA proposed a regulation that will require statements on prescription antibiotic drug labeling that discusses the appropriate use of antibiotics and how to reduce the development of drug-resistant microorganisms.

The proposal is intended to encourage physicians to prescribe systemic antibacterials more judiciously, and only when clinically necessary, and to encourage physicians to counsel their patients about the proper use of such drugs and the importance of taking them as directed.

The recently approved antimicrobial, Zyvox, reflects some of this language in its package labeling. We believe that this type of information on product labeling will influence prescribing behavior.

The Zyvox labeling is a step in the right direction and we applaud Pharmacia and Upjohn for working with the agency to develop this message.

Let me briefly address our efforts in the area of antimicrobial use in food-producing animals, an area of controversy that has spanned nearly 30 years. Antibiotics have for decades played a key role in ensuring the health of food animals.

Producers have used some of these same products as growth promoters. Such uses have benefits and contribute to the general availability of safe food products at reasonable prices.

At the same time, the potential risks posed by antimicrobial resistance have become of increasing concern.

Although it is not the focus of this hearing, I have provided a summary of the agency's activities in the area of animal drugs and animal health in my written testimony.

I would also note that earlier this week, the Department and the USDA submitted our joint report to Congress on antibiotic resistance in livestock. As you know, this report was requested in fiscal year 2000's appropriations. And the report explains the strategy and includes a timetable and budget for tackling the problem of antimicrobial use and the emergence of antimicrobial resistance.

We recognize at FDA that managing antimicrobial resistance requires coordinated actions and partnerships with many other entities, both within and outside the Federal government.

We are pleased to co-chair with CDC and NIH the Interagency Task Force on Antimicrobial Resistance that has already been mentioned.

I believe that the plan that has been developed reflects a very broad-based consensus of these Federal agencies and others on actions to combat antimicrobial resistance and a very clear blueprint for our Federal actions.

The draft part I of the action plan really focused on domestic issues and was published this past June. It proposes many activities, which FDA will address either as the coordinator or as a partner with other agencies.

Part II of the plan, which will be developed subsequently will follow the development of WHO's approach and identify U.S. agency actions that can more specifically help address international issues.

Mr. Chairman, I would be remiss if I did not take this opportunity to thank you for approving the FDA's antimicrobial resistance increase requested in the fiscal year 2001 Senate Appropriations bill. Both the Senate and the House bills as passed include full funding of FDA's request for antimicrobial resources.

As you know it builds upon 3 years of intense work and cooperation among several key agencies and several State and local health agencies.

We believe that your funding of our Food Safety Initiative has served a key role in establishing a coordinated approach to food safety and antimicrobial resistance. We expect funding for antimicrobial resistance to be a continuing priority of ours.

Let me once again underscore that to adequately address this public health issue, it will take responsible action by more than just the Federal agencies. It is going to take the energy and determination on the part of the medical and veterinary professions, the pharmaceutical and animal health industries and those who grow and care for food-producing animals.

PREPARED STATEMENT

Our highest priority should be to ensure that we have safe and effective antimicrobials to protect human and animal health today and into the future. We are committed to doing our part to ensure that this happens.

And I would be happy to answer any of the questions you may have.

Senator COCHRAN. Thank you very much, Dr. Henney, for your interesting and complete informative statement. We appreciate it very much.

[The statement follows:]

PREPARED STATEMENT OF JANE E. HENNEY

INTRODUCTION

Mr. Chairman and members of the Committee, I am Dr. Jane E. Henney, Commissioner of Food and Drugs, Food and Drug Administration (FDA or Agency). I am pleased to be here this morning to talk about issues related to antimicrobial resistance and FDA's important role in addressing this growing public health problem. While I understand the focus of this hearing is human drugs, my testimony also will include issues related to animal drugs and animal health.

Antibiotic resistance is well recognized as a major threat to the health of U.S. citizens and people around the world. Although we have been using antibiotics for more than 50 years, the extent of resistance is much greater than ever before. Antimicrobial resistance is a natural biological phenomenon that is the result of the rapid replication and evolution of microbes. When a microbial population is exposed to an antibiotic, the more susceptible organisms will succumb, leaving behind only the resistant organisms. Through this selective process, resistant organisms become more predominant throughout the microbial population. Microbes also commonly acquire genes, including those encoding for resistance, by direct transfer from members of their own species or, sometimes, from unrelated microbes. However, the like-

lihood of microbes developing resistance becomes magnified by widespread and often inappropriate antimicrobial use.

In addressing the antimicrobial resistance problem, FDA's goal is to be sure that practitioners have a continuous supply of safe and effective antimicrobials available to protect the health of both humans and animals, as well as reliable laboratory test products to rapidly direct appropriate antibiotic use.

Antibiotics are different from most of the other drugs approved by FDA, because their effectiveness is so fragile. Another unique characteristic is that these drugs affect not only the patient who receives them but also their personal contacts, the environment and the health of the community. We need to protect the effectiveness of this special class of drug products by using them in a thoughtful way that is based on the best available science. If these drugs are overused, or misused, their effectiveness will not be there when patients need them. We already have some infectious diseases where there are either no or few satisfactory therapeutic options because of antibiotic resistance.

We should look at our array of antibiotics as a valuable resource that deserves careful protection. And, as with most issues that involve fragile resources, this one has global ramifications. With frequent and wide-ranging air travel and extensive immigration, we are able to pass our pathogens to one another with frightening speed. That means that in order for us to succeed in our effort to use antibiotics wisely, similar steps must be taken by nations around the world. In some countries, antibiotics are available without prescription and may be impure or subpotent, and many patients cannot afford adequate courses of treatment. Not surprisingly, rates of resistance, particularly to common community acquired and food borne pathogens, are often even higher than in the United States (U.S.). This causes suffering and further demands on already overstretched resources abroad and poses risks to the U.S. through transport of resistant pathogens to our citizens. An example of this type of trans-national threat has been the spread of multi-drug resistant tuberculosis.

FDA TASK FORCE ON ANTIMICROBIAL RESISTANCE

As you know, FDA has key roles in helping facilitate the development of drugs, vaccines, devices and diagnostics as well as ensuring their safe and effective use. In addition, FDA has an important role in informing the public and health professionals of antibiotic resistance and principals of appropriate use through educational outreach, by assuring useful and accurate product labeling, and appropriate marketing. Traditionally, FDA has been active in addressing the resistance problem. However, to further stimulate and coordinate FDA's actions to combat antimicrobial resistance, in late 1998, an internal "FDA Task Force on Antimicrobial Resistance" (Task Force) was established to develop a clear consensus regarding what, given limited resources, should be the key priorities of the Agency.

While FDA saw the need to better coordinate and focus antimicrobial resistance activities within the Agency, it also recognizes that managing antimicrobial resistance requires coordinated actions and partnerships with many other entities, both within and outside the Federal government. FDA is privileged to co-chair with the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) an Interagency Task Force on Antimicrobial Resistance that was formed in 1999 to develop a Public Health Action Plan to Combat Antimicrobial Resistance. The Public Health Action Plan will be briefly discussed later in my testimony.

The internal FDA Task Force Report, completed in draft in October 1999, focuses on issues and areas where FDA should and is able to play an important role in achieving specific and practical outcomes. Recommendations are in four key areas:

1. Promptly and effectively responding to current threats from drug resistance;
2. Facilitating and encouraging development and appropriate use of products which help address the issue;
3. Facilitating the safe and effective use and thus prolonging the life of products by helping improve the quantity and quality of information available to consumers and health professionals regarding antibiotics resistance and principles of appropriate usage; and,
4. Maximizing and coordinating FDA's scientific research to address needs in antimicrobial resistance.

Let me discuss each of these four key areas for addressing the problem of antimicrobial resistance.

1. Effectively Responding to Current Public Health Threats

Therapeutic options for resistant infections have become increasingly limited and, therefore, important to protect and preserve for these critical uses. In particular,

there are agents, including among them both those recently or previously approved and those as yet unlicensed, which are either the only or among the very few available treatments for life threatening resistant infections. This concept of critical "Category I Drugs" is also embodied in the proposed Center for Veterinary Medicine (CVM) Framework. The proposed Framework document, which I will discuss later, outlines the categorization of drugs by their importance to human medicine as well as a risk-based Framework for their use in food animals.

How antibiotics are used could, as it has in the past, be regarded as primarily an issue of "medical practice." However, it is widely acknowledged that the rapidity of development of resistance to an agent is increased with the magnitude of antibiotic use. Thus, use of these precious drugs of last resort for infections easily treated by other medicines is highly likely to ultimately compromise their efficacy, and hence, their safety in treatment of serious infections. FDA plans to partner with and obtain input from others, including other Federal agencies, professional groups and the pharmaceutical industry, in order to assure that important antibiotics are used as wisely as possible.

The development of appropriate public health strategies for managing antimicrobial resistance will require more than sporadic and ad hoc data on the occurrence of resistance. A comprehensive system of antimicrobial resistance surveillance is needed to provide a measure of the resistance patterns, an early warning system for emerging problems, and a baseline to target and evaluate prevention control measures. In addition to establishing baselines and showing trends, early warning of an emerging problem may alert clinicians to a possible problem and have an immediate impact on prescribing decisions and outcome for the patient. There is also a need to improve the understanding of the relationship between drug use and resistance in order to use drugs wisely. This need is pressing with regard to both human and food animal antibiotic use. Again, FDA has important partnerships with CDC and U.S. Department of Agriculture (USDA) addressing surveillance and we are committed to continuing these efforts and broadening our efforts as we consider use issues.

2. Facilitating Product Development

There is and will be a critical need for innovative product development to meet the threat posed by antimicrobial organisms. Desired products include not only new antibiotics, but also vaccines to prevent infections and reduce antibiotic use. We also need improved, more rapid, diagnostics to identify pathogens and drug resistance. At each step of the product development process, there is room for improvement and innovation.

As we address this matter we also need to acknowledge that each new antimicrobial agent represents a major investment by a pharmaceutical company, which must shepherd the product through pre-clinical studies and clinical testing. As is stated in a recent World Health Organization (WHO) report, few breakthroughs in the discovery of antimicrobials have been accidental discoveries, stumbled upon by chance. Instead, they are the result of dedicated scientific effort and vast amounts of money, time, and human labor. This is also true of the development of novel new treatments and of vaccines.

FDA and its partners will continue to consult with representatives of the pharmaceutical industry and other expert parties, such as FDA's Advisory Committee on Anti-Infective Drugs, on strategies to promote the development of new antimicrobial drugs, vaccines, and diagnostic tests. We need to collectively address overcoming economic disincentives to new antimicrobial product development and renewed efforts to promote and expect appropriate use of these important products.

Some examples of what we are doing to facilitate product development for drugs, vaccines, and medical devices follow.

Drugs

During July 1998, FDA's Center for Drug Evaluation and Research (CDER) sponsored a public meeting with industry, academia and other public health agencies to receive input on the topic of antibiotic resistance. This meeting was followed in October 1998, by an Advisory Committee meeting to discuss the issues raised at the July meeting, and included: ways to help speed product development, including approaches to improve clinical trials for studying drugs targeted at resistant organisms; programs that may provide incentives for drug development, such as Orphan Drug designation; and approaches to promote the appropriate use of antibiotics.

As I stated previously, to provide therapeutic options for the treatment of infections due to resistant organisms, critical antibiotics need to be brought to market as expeditiously as possible. The Agency is granting these applications a priority review, which ensures that these applications are acted on in six months or less.

Shortening the development time of these products is also important in bringing these products to market as soon as possible. In this regard, the Agency has worked with sponsors of these products though early discussions on overall product development, clinical trial design, and other issues that may arise so that the process can be as efficient as possible and provide the data that would be necessary to determine the safety and effectiveness of the product. In addition, the use of regulatory approaches to provide more rapid development, such as early consultation and early access (Subpart E designation), and accelerated approval utilizing a surrogate endpoint (Subpart H), has also been discussed.

Two of the most recent approvals for products to treat highly resistant organisms—Synercid® and Zyvox®—were developed and reviewed using these approaches. Prior to the approval of these products, patients who were infected with vancomycin-resistant enterococci had no other available therapies. Many of these patients are immunocompromised or have serious underlying illness requiring care in an intensive care unit and are therefore the most vulnerable. These products are truly "live saving" for these patients.

The development of innovative new products to treat infections due to resistant organisms, especially those for which there are few treatment options, such as multiple resistant gram negative or gram positive organisms, is critically important. CDER has taken the initiative in developing policies regarding the development and the appropriate use of drugs of last resort. This will include developing recommendations that focus the development of these products on the area of need, guidance on the design of clinical trials for these products, the application of regulatory approaches, such as accelerated approval, and the development of policies that will promote the appropriate use of these products. There are a number of issues that will require further refinement and resolution. At present, antibiotics are usually developed for a number of indications (diseases) caused by a variety of organisms, including organisms resistant to other antibiotics. This provides a potentially large market for the sponsor to recoup their research and development costs. This is not a good approach if one wishes to preserve antibiotics that treat resistant organisms. However, the numbers of patients infected with resistant organisms may be sufficiently limited to discourage drug development only for this population. Strategies to overcome these potential economic disincentives to development and to appropriate use will also be considered. The application of existing programs, such as Orphan Drug designation, has been discussed as one potential approach at public meetings in July and October, 1998.

Vaccines

The Agency also is encouraging the development of new vaccines to help reduce the need for antibiotics and, thus, slow the spread of resistance. Pointing to the global importance of vaccines, the WHO refers to prevention through vaccination as the ultimate weapon against infection and drug resistance.

An important vaccine for the prevention of meningitis (a severe infection of the lining of the brain or spinal cord) occurred earlier in the decade. Before the approval of the first *Haemophilus influenzae* type b (Hib) vaccine in 1990 for infants, Hib was the leading cause of bacterial meningitis and was becoming increasingly antibiotic resistant. Today, invasive Hib infection has been virtually eliminated from the U.S. by effective vaccines, reducing not only harm to children but also antibiotic use.

Earlier this year, FDA approved the first vaccine to prevent invasive pneumococcal diseases in infants and children, Prevnar. This vaccine prevents invasive diseases caused by the organism *Streptococcus pneumoniae*, including bacteremia (an infection of the bloodstream) and meningitis, a severe infection of the lining of the brain or spinal cord. *Streptococcus pneumoniae* remains as one of the leading causes of bacterial meningitis, and we are hopeful that vaccines like Prevnar will greatly reduce this threat.

This new vaccine is great news for parents and their children because now, we have a highly effective way to prevent pneumococcal infection, now the major cause of meningitis and serious blood infections in the most susceptible children—those under two years of age.

In addition, pneumococcal vaccines are being studied for the prevention of otitis media and pneumonia, which are often due to pneumocci. The potential contribution of pneumococcal vaccines in helping to reduce these diseases could further reduce the use of antimicrobials. Numerous other promising vaccine candidates to protect against organisms for which antimicrobials are typically administered are in various stages of clinical development.

In addition to vaccines that directly impact on pathogens with recognized high rates of resistance, vaccines are also under development that would indirectly affect antimicrobial use. For example, ear infections and respiratory diseases are often

treated with antibiotics, but most are caused by viral infections, such as parainfluenza and respiratory syncytial virus . Therefore, development of vaccines to prevent these viral infections would also be an important mechanism impacting on unneeded and nonbeneficial antibiotic use.

FDA's Center for Biologics Evaluation and Research (CBER) recognizes the importance of expediting clinical development of these products and their public health benefit. CBER has worked with academia, manufacturers, and other government agencies to address the development of new vaccines and therapies as alternative approaches to reduce antimicrobial use. For example, CBER has participated in several workshops addressing key issues related to the development of combination vaccines against multiple childhood diseases. In addition, CBER has expedited the clinical development and approval of these products. For example, through the provisions provided by FDAMA, Prevnar was granted fast track designation and assigned priority review status.

Devices

Another product line that we want to facilitate that will have a significant impact on the appropriate use of antimicrobials is the development of new diagnostic tests that can rapidly determine and certainly indicate whether an infection is bacterial. The test would also then be expected to identify an appropriate antibiotic for treatment. Diagnostic tests that are reliable and whose results are more quickly available have great potential for reducing prescription of antibiotics when they are not necessary and over prescribing a more powerful antibiotic than is clinically necessary. Conversely, rapid identification of resistant infections can lead to earlier use of effective treatments and better outcomes for patients. FDA's Center for Devices and Radiological Health (CDRH) reviews these types of products premarket, assuring that expected performance is reliable for use in patient management and gathering data for surveillance.

3. Facilitating Safe and Effective Use of Antimicrobials

As I stated, antimicrobial resistance is an inevitable consequence of the selective pressure of widespread and often inappropriate antimicrobial use. We all—physicians, patients, pharmaceutical companies, public health professionals, and government agencies—must concede the fact that individually and collectively we are a part of the problem, and acknowledge that it will take all of our efforts to arrive at the solution.

The medical profession plays an important role in this issue. Physicians tell us that patients often pressure them to prescribe antibiotics. They may have limited time to explain the rationale for not using an antibiotic, or for using an alternative treatment. They may not have access to rapid diagnostic tests or to antibiotic sensitivity testing. In addition, there may be financial disincentives to perform these tests. It can be far too tempting to simply prescribe an antibiotic. Since this is often a shot in the dark, because the bacteria have not been identified and susceptibility testing not done, the physician is further tempted to prescribe the latest powerful blockbuster antibiotic. Such antibiotics are often not warranted, as many community acquired infections are viral and do not respond to antibiotics or are caused by bacteria still sensitive to older alternative drugs. A colleague of mine told an interesting story. She was waiting in line at the pharmacy in a hospital in the Washington area. This was just outside the outpatient surgery area. She was the fifth person in line. Now this was shortly after a particular fluoroquinolone was approved. I will not mention the name of the product. The point is that, believe it or not, every single person in the line in front of her was given this new fluoroquinolone. And so was she. It was the blockbuster antibiotic of the day. One might conclude that it was being pushed a little too hard and perhaps used when it was not necessary.

Once an antibiotic is prescribed a lack of patient understanding and, therefore, compliance may also contribute to resistance. Patients, either by omission or commission, often do not take the antibiotic according to directions, and frequently fail to take the entire course of antibiotics. Instead, they stop taking it when they feel better, and then save the rest for the next time or share the leftover drug with a sick friend. The result, inadequate treatment courses, also is a recipe for inducing resistance.

It is not easy to accurately establish the extent of overuse or inappropriate use of antibiotics by the medical profession or patients, but several studies have given estimates that present a picture of substantial overuse of these products. Office-based physicians in the U.S. write more than 100 million antibiotic prescriptions each year. According to CDC, perhaps as many as half of those prescriptions—a total of 50 million—may be unnecessary. They are prescribed for patients who have

the common cold and other viral infections, including influenza. I would like to recognize here the encouraging report last week from CDC that showed that the rate of prescriptions written for children with respiratory illnesses declined between 1989–1990 and 1997–1998. Hopefully, this study is an indication that antibiotics are being used more wisely.

A third component that contributes to antibiotic resistance is the marketing practices of pharmaceutical companies. The messages conveyed are naturally geared to persuading health professionals to buy and use their products. With well over 80,000 detail people and active direct to consumer advertising campaigns, there are effective means to get any marketing message out. An article in USA Today commented that, "Physicians must be honest with themselves and with their patients. Decisions on which prescriptions to write must be made in accordance with the best scientific evidence, not on the best marketing campaign."

However, we have also been remiss at the Federal, State, and Local levels in not aggressively getting out the message about the importance of appropriate antibiotic use and the need to protect these resources.

We need to educate physicians and the public about the resistance problem and encourage more judicious use of antimicrobial drugs. We pledge to do our share with both industry and other public health officials, to provide better and more consistent information to consumers and health care professionals. We believe it is particularly important to include additional information in the labeling of prescription antibiotics.

Yesterday, FDA proposed a regulation that will require statements on prescription antibiotic drug labeling that discuss the appropriate use of antibiotics and how to reduce the development of drug-resistant microorganisms. The proposal is intended to encourage physicians to prescribe systemic antibacterials more judiciously and only when clinically necessary. The proposal also is intended to encourage physicians to counsel their patients about the proper use of such drugs and the importance of taking them as directed.

Specifically, the proposed rule would require that:

—". . . at the beginning of the label, under the product name, the labeling must state that inappropriate use may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of the drug product and related antimicrobial agents, and that the drug product should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms;

—"the 'Clinical Pharmacology' section state that appropriate use of the drug product includes, where applicable, identification of the causative microorganism and determination of its susceptibility profile;

—"the 'Indications and Usage' section state that local epidemiology and susceptibility patterns of the listed microorganisms should direct initial selection of the drug product for the treatment of the listed indications and that because of changing susceptibility patterns, definitive therapy should be guided by the results of susceptibility testing of the isolated pathogens;

—"the 'Precautions' subsection entitled 'General' state that inappropriate use may increase the prevalence of drug resistant microorganisms and may decrease the future effectiveness of the drug product and related antimicrobial agents. This subsection would also include a statement that the drug product should only be used to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms; and,

—"the 'Precautions' subsection entitled 'Information for Patients' state that patients should be counseled that the drug product should be used only to treat bacterial infections and that it does not treat viral infections. The subsection would also advise physicians to counsel patients that the medication should be taken exactly as directed."

The recently approved antimicrobial, Zyvox® (linezolid), has some of this language in its package labeling. Under Indications and Usage, the labeling states, "Due to concerns about inappropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with Zyvox® in the outpatient setting."

It goes on to say, "Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to linezolid [Zyvox®]. Therapy may be instituted empirically while awaiting the results of these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly." The Agency also has issued a request to the sponsor of another drug of last resort asking that they include a statement in the package insert regarding the appropriate use of their product. Discussions with the firm are ongoing.

We believe that having more of this type of information on product labeling will influence prescribing behavior, and that the Zyvox® labeling is a step in the right direction and we applaud Pharmacia and Upjohn for working with the Agency to develop this message.

4. Coordinating FDA's Scientific Response to Antimicrobial Resistance

Lastly, research is an important FDA activity in supporting and filling gaps in the science base of the Agency. Basic and applied research provide the foundation for combating the problem of antimicrobial resistance. Research is essential to support the development of new antimicrobial drugs, vaccines, and diagnostic tests and the development of innovative uses of products. Research also plays an essential role in supporting the science base for regulatory structures and decisions.

Although NIH is the lead government agency focusing on research associated with antimicrobial resistance, FDA research supports strategic goals, such as the development of knowledge bases, and method, agent, or concept driven research. FDA has important scientific resources invested in antimicrobial research and related areas and FDA scientists have made important contributions to the field. The spectrum of such research ranges from the basic, such as mechanisms of resistance induction and transfer related to food animal use of antimicrobials, to the applied, such as improved detection of resistant pathogens in regulated food products.

CVM'S FRAMEWORK DOCUMENT

Let me next briefly address our effort in the area of antimicrobial use in food-producing animals—an area of controversy that has spanned the past 30 years. Antibiotics have, for decades, played a key role in ensuring the health of food animals. And, as you know, producers have used some of these same products as growth promoters. Such uses contribute to the general availability of safe food products at reasonable prices. At the same time, the potential risks posed by antimicrobial resistance have become of increasing concern.

In response, FDA developed in 1999 a discussion document entitled "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals."

The proposed Framework describes the Agency's best thinking on how to evaluate the microbial safety of antimicrobials for use in food animals. The concepts described in the Framework could be used to assess not only new antibiotics, but also previously approved antibiotics. The Agency will take appropriate procedural steps to develop and implement any policies resulting from the concepts.

We believe that the proposed Framework presents a sound science and risk-based approach to the antimicrobial resistance issue, and consistent with guidance issued in December 1999, we are asking companies to assess the microbial safety of all new antimicrobials to be used in food animals.

Depending on the results of this assessment, the drug sponsor may need to conduct pre-approval studies to assess the rate and extent of resistance development in pathogens or commensals of human health concern. We will be issuing a guidance document in the near future to more specifically outline how such studies can be conducted. In addition, we will hold a scientific workshop in January 2001, to outline our approach and seek public input on the establishment of resistance and monitoring thresholds. I would also like to note that the veterinary medical profession and specialty practice organizations of veterinary practitioners are developing judicious use guidelines as well.

As the mechanism for regulating these drugs, the proposed Framework discusses three categories of antimicrobial drugs. The categories would be based on the drug's unique or relative importance to human medicine.

The chain of events that leads to the transfer of antimicrobial resistance from animals to humans is complex. It includes the ability of the drug to induce resistance in bacteria, and the likelihood that use of the drug in food-producing animals will promote resistance. It also includes the likelihood that any resistant bacteria in or on the animal will then be transferred to humans. The final link in this chain of events is the likelihood that such transfer will result in loss of efficacy of human antimicrobial therapies.

The proposed Framework also includes a characterization of the likelihood of human exposure to resistant, foodborne pathogens as HIGH, MEDIUM or LOW. To do this, the drug's attributes—for example, its mechanism and rate of resistance induction, and its induction of cross-resistance to other related or unrelated drugs—would be considered. The proposed Framework also includes an evaluation of how the product is used, and other relevant factors such as animal and manure management practices, environmental contamination, and food processing.

The extent of data required before and after approval of a new antimicrobial drug would depend upon a consideration of the drugs importance to human medicine, the potential for human exposure, and other factors as they may be deemed relevant.

The need for FDA to have additional and more detailed animal drug distribution information is also discussed in the proposed Framework. This information would be most useful if it could be reported by state, species, dosage form, season of use, and an estimate of the antimicrobial activity units sold. Implementation of the concepts articulated in the Framework document would be presented to the public through guidance or notice and comment rulemaking, as appropriate.

National Antimicrobial Resistance Monitoring System: Enteric Bacteria

To make this Framework operational we will depend upon an effective resistance surveillance system and scientifically sound risk assessments. We can now obtain valuable resistance data through the National Antimicrobial Resistance Monitoring System: Enteric Bacteria (NARMS). FDA proposed NARMS in 1995 in response to growing concern about the emergence of untreatable antimicrobial resistance. NARMS was developed in 1996 as a collaborative surveillance effort by FDA's CVM, CDC, and the USDA. This system allows us to prospectively monitor changes in the antimicrobial susceptibility of selected zoonotic, enteric pathogens and commensals.

Currently, NARMS monitors the susceptibility of *Salmonella* and *E. coli* to 17 antimicrobial drugs, including ciprofloxacin, ceftriaxone, ceftiofur, tetracycline, and others. NARMS also monitors susceptibility of *Campylobacter* isolates to eight antimicrobial drugs-among them—azithromycin, ciprofloxacin, clindamycin, erythromycin, and tetracyline.

Seventeen State and Local Health departments submit human clinical isolates of non-typhoid *Salmonella* and *E. coli.* Eight State health departments submit human clinical *Campylobacter* isolates. And four States submit *Campylobacter* isolates from retail poultry. In 1998, NARMS was expanded to include sentinal sites at veterinary diagnostic laboratories.

USDA conducts animal isolate testing which is done at their Agricultural Research Service Russell Research Center. And CDC conducts testing on human isolates at their National Center for Infectious Diseases Foodborne Disease Laboratory.

NARMS is proving to be a valuable source of resistance data, and is helping us characterize the scope of the resistance issue, and monitor changes. NARMS serves as a model surveillance system for other nations establishing their own surveillance systems.

Risk Assessment

Last December, FDA released a draft quantitative risk assessment that modeled the human health impact of fluoroquinolone-resistant *Campylobacter* infections associated with the consumption of chicken. We used data from NARMS, CDC's case control studies, FoodNet, and other sources, for the risk assessment. We'll finalize the results of the risk assessment by early this fall, but the preliminary results did indicate that there is an impact on human health from fluoroquinolone-resistant *Campylobacter* associated with chicken consumption.

And we have initiated a second risk assessment. We are currently conducting a feasibility study to determine whether sufficient data can be obtained to complete a quantitative risk assessment. This one will assess the plausibility of a link between the use of virginiamycin in animals and quinupristin/dalfopristin resistance in humans as well as the human health impact attributable to use of virginiamycin in food-producing animals. This risk assessment will also evaluate risk management options to address the human health impact if it is deemed unacceptable. Ultimately, we want to ensure that significant human antimicrobial therapies are not compromised or lost due to antimicrobial use in animals. At the same time, we want to provide for the use of safe and effective antimicrobials in food animals.

The other major issue related to the use of antimicrobials in food-producing animals is their use for growth promotion in livestock. The Framework approach could also be applied to these products and we will focus our efforts on evaluating those uses that pose the greatest risk to public health. As in all of our decision-making, the best available science will be used to ground and guide our actions.

Antimicrobial Resistance and the Budget

Mr. Chairman, I would be remiss if I did not take this opportunity to thank you for approving FDA's antimicrobial resistance increase request in the fiscal year 2001 Senate Appropriations bill. Both the Senate and the House bills as passed include full funding of FDA's request for antimicrobial resources. The fiscal year 2001 request builds upon three years of intense work and cooperation among several key agencies, FDA, CDC, NIH, USDA and several State and Local Health agencies. FDA believes Congressional funding of the Food Safety Initiative has served a key role

in establishing a coordinated approach to food safety and antimicrobial resistance. We expect funding for antimicrobial resistance to be a continuing priority.

INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE

As I mentioned above, FDA recognizes that managing antimicrobial resistance requires coordinated actions and partnerships with many other entities, both within and outside the Federal government. FDA co-chairs with CDC and NIH an Interagency Task Force on Antimicrobial Resistance that was formed in 1999 to develop a Public Health Action Plan to Combat Antimicrobial Resistance.

The Public Health Action Plan reflects a broad-based consensus of Federal agencies on actions to combat antimicrobial resistance and provides a blueprint for specific, coordinated Federal actions. A draft Part I of the Action Plan focusing on domestic issues was published in late June of this year. Part I includes many proposed activities which FDA will address either as a coordinator or as a partner with other agencies, including priority items to foster product development, to educate professionals and the public, and to develop and implement the concepts outlined in the CVM Framework. Part II of the plan, to be developed subsequently, will follow development of WHO's approach and identify U.S. agency actions that can more specifically help address international issues. Development and implementation of the Public Health Action Plan also has included and will continue to include the participation and efforts of the Agency for Healthcare Research and Quality, USDA, the Department of Defense, the Department of Veteran Affairs, the Environmental Protection Agency, the Health Care Financing Administration, and the Health Resources and Services Administration. These partners are critical given the complex nature of resistance and the need to address the issue in an inclusive and coordinated manner, with consideration of such diverse areas as health care systems, the environment, and agriculture.

CONCLUSION

Let me once again underscore that to adequately address this public health issue, it will take responsible action by more than just Federal agencies. It is going to take energy and determination on the part of the medical and veterinary professions, the pharmaceutical and animal health industries, and those who grow and care for food-producing animals.

Our highest priority should be to ensure that we have safe and effective antimicrobials to protect human and animal health today and in the future. FDA is committed to doing our part to ensure that this happens. We feel that the internal FDA Task Force Plan and the Interagency Public Health Action Plan are important blueprints to move us forward in a coordinated and effective way.

I would be happy to answer any questions you may have.

PREPARED STATEMENT OF THE NATIONAL INSTITUTES OF HEALTH

ROLE OF NIH IN MEETING THE PUBLIC HEALTH NEEDS IN ANTIMICROBIAL RESISTANCE

NIH has a lead role in coordinating the participating agencies' research efforts to address antimicrobial resistance, and the National Institute of Allergy and Infectious Diseases (NIAID) is the lead Institute at NIH for antimicrobial resistance. Antimicrobial resistance is not one problem, but a whole array of problems spanning microbiology. Basic and clinical research provides the fundamental knowledge necessary to develop appropriate responses to antimicrobial resistance. The broad scope of the U.S. research community as assessed by the NIH and other relevant agencies has a major contribution to make in meeting the diverse challenges such as: new diagnostic tests; new antimicrobial agents (including novel therapeutics); and vaccines and other prevention methods.

NIH CONGRESSIONAL TESTIMONY AND BRIEFINGS ON ANTIMICROBIAL RESISTANCE

On February 25, 1999, Dr. Anthony Fauci, Director, NIAID, testified before the Senate Committee on Health, Education, Labor, and Pensions Subcommittee on Public Health and Safety (see Attachment I), summarizing the Institute's research activities related to antimicrobial resistance (http://www.niaid.nih.gov/director/congress/1999/0225.htm). Many of the activities referenced in this testimony have expanded during the past year; for example, additional genomes have been sequenced. The NIAID website provides updated information on many of these items (see Attachment II, the NIAID website—main link: http://www.niaid.nih.gov/; specific

microbiology and infectious diseases information link: http://www.niaid.nih.gov/research/dmid.htm).

In addition, on June 29, 2000, a briefing for staff to Senator Thad Cochran (R–MS), a member of the Labor/HHS Appropriations Subcommittee, was held to discuss the draft "Public Health Action Plan to Combat Antimicrobial Resistance." Presentations were made by the respective HHS Co-Chairs on the Interagency Task Force on Antimicrobial Resistances: Dr. Dennis M. Dixon, NIH/NIAID; Dr. David Bell, CDC/NCID/OD (Office of the Director, National Center for Infectious Diseases); and Dr. Jesse Goodman, FDA/CBER (Center for Biologics Evaluation and Research, Food and Drug Administration). Also on this same date, a similar briefing was held for House staff that was sponsored by Representative Louise Slaughter (D-NY).

NIAID program officers also have participated in two antimicrobial resistance briefings over the past two years for staff to Senators Edward Kennedy (D-MA) and William Frist (R-TN).

NIH'S ROLE IN THE INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE

The Interagency Task Force on Antimicrobial Resistance, co-chaired by CDC, FDA and NIH and also including HCFA, HRSA, AHRQ, EPA, DOD, USDA, and VA, was initiated by the agencies following the February 1999 congressional hearing on antimicrobial resistance to link the relevant agencies to coordinate the public health response. The initial public activities of this task force were announced in the June 28, 1999, Federal Register in conjunction with a July 1999 meeting organized by the Task Force to involve the scientific and public communities in the development of a Public Health Action Plan to Combat Antimicrobial Resistance. A draft of the plan was posted on the Internet, public comment was received, and the comments are being addressed.

NIH'S ROLE AND ONGOING RESPONSIBILITIES IN THE PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE

Summary of Plan

The plan addresses four key issues: surveillance, prevention and control, research, and product development. NIH took the lead in identifying research areas of need for incorporation into the plan.

Three key challenges facing the public health are central to the mission of the NIH: developing better means of diagnosis, prevention, and treatment of disease. Meeting these challenges has three general requirements: identifying and addressing gaps in the understanding of microbiological processes (basic research); drawing upon and focusing a robust research infrastructure; and establishing a critical pathway for movement of research findings to useful products.

TOP RESEARCH PRIORITY ACTION ITEMS

The research chapter of the Action Plan identifies the responsible agencies and some targeted actions. Representative priority actions (NIH is active in each) include the following:

1. Basic Research: Genomics. Determining the genetic complete genetic code of the individual microbes and deciphering the function of the genes gets at the central operations of the organisms. The NIH will continue to play a leadership role in pathogen genome sequencing and genomics, and in collaborating and coordinating with other agencies and groups to make this vital information publicly available to guide efforts for the three primary challenges: better diagnosis, better treatment, and better prevention of the infections. We have completed numerous microbial genome projects and have launched new systems for managing genome sequencing and genome information. The NIAID has demonstrated the ability to devise and implement a priority setting process that includes community involvement to address the complex issues. For genomics, these include the selection of organisms; the public availability of data, and meeting the public health need. This is a cross cutting activity, of interest to many agencies. The USDA has embarked upon a similar priority setting process for agriculturally important organisms.

2. Clinical Research: Clinical trials of antimicrobial resistance issues that are difficult to resolve in the industrial sector.

—Novel therapies in need of a proof of principle

—Existing antimicrobials used in novel ways

—Combinations of antimicrobials

NIAID has had good success with trial groups for viruses (Collaborative Antiviral Study Group), and for fungi (Mycoses Study Group). These examples include partnering with industry. There is no strictly analogous multi-center antibacterial

study group with a focus on antimicrobial resistance that is currently in existence. The Task Force and the developing Action Plan already have contributed to shaping one new activity that NIAID is currently soliciting with existing resources.

ATTACHMENT I.—DR. ANTHONY S. FAUCI'S FEBRUARY 25, 1999 TESTIMONY BEFORE THE SENATE COMMITTEE ON EDUCATION, LABOR, AND PENSIONS SUBCOMMITTEE ON PUBLIC HEALTH AND SAFETY

Senator Frist and members of the Subcommittee, I am pleased to appear before you today to discuss the role of the National Institutes of Health (NIH) in combatting the problem of antimicrobial resistance, and the recent progress and initiatives in addressing this enormous problem.

As you are aware, many diseases are increasingly difficult to treat because of the emergence of drug-resistant organisms, including HIV and other viruses; bacteria such as staphylococci, enterococci, and *E. coli* which cause serious infections in hospitalized patients; bacteria that cause respiratory diseases such as pneumonia and tuberculosis; food-borne pathogens such as *Salmonella* and *Campylobacter*; sexually transmitted organisms such as *Neisseria gonorrhoeae*; *Candida* and other fungi; and parasites such as *Plasmodium falciparum*, the cause of malaria. According to the Institute of Medicine (IOM), the total cost of treating antimicrobial-resistant infections may be as high as $5 billion annually in the United States.

Because of antimicrobial resistance, some infections have become untreatable in certain circumstances. Patients in our best hospitals have died with strains of the tuberculosis (TB) bacterium resistant to the entire armamentarium of anti-TB drugs. Some strains of *Pseudomonas aeruginosa*, a bacterium that causes septicemia and pneumonia in cystic fibrosis and immunocompromised patients, are becoming difficult to treat with currently available antimicrobial agents. Enterococcal infections are increasingly resistant to vancomycin, a drug which is often a physician's "ace-in-the-hole" when treating bacterial infections that do not respond to other drugs. In the past two years, strains of *Staphylococcus aureus* with reduced susceptibility to vancomycin have emerged, threatening to return us to the pre-antimicrobial era, when *S. aureus* infections were untreatable and frequently resulted in the death of previously healthy children and adults in the prime of life.

Treating antimicrobial-resistant infections often requires the use of more expensive or more toxic drugs and can result in longer hospital stays. For example, many isolates of *Streptococcus pneumoniae*, a leading cause of earaches, pneumonia, and meningitis, are resistant not only to penicillin but to the second and third-line antimicrobials as well. Alternatives are expensive and in some cases not licensed for children, making the management of this common infection increasingly difficult.

The emergence of antimicrobial resistance is not a new phenomenon, nor an unexpected one. In fact, resistance pre-dates the discovery of antibiotics and is an inevitable result of the rapid replication and evolution of microbes. A single random gene mutation can have a large impact on an organism's disease-causing properties. A mutation that helps a microbe survive in the presence of an antimicrobial agent will quickly become predominant throughout the microbial population. Microbes also commonly acquire genes, including those encoding for resistance, by direct transfer from members of their own species or from unrelated microbes. Once established in a microbial population, resistance is virtually impossible to eradicate.

The innate adaptability of microbes is accelerated by the selective pressure of widespread and often inappropriate use of antimicrobial agents. The Centers for Disease Control and Prevention (CDC) has estimated that one-half of the more than 100 million courses of antibiotics prescribed annually by U.S. office-based physicians are unnecessary—that is, they are prescribed for colds and other viral infections which they do not affect. Hospitals provide a fertile environment for drug-resistant pathogens. Patients at increased risk for development of infections (surgical, trauma, chemotherapy and transplant), a high density of very sick people and extensive use of antimicrobials are circumstances associated with resistance.

It is underappreciated that all major groups of microorganisms—viruses, fungi, and parasites as well as bacteria—become resistant to antimicrobials. For example, strains of HIV resistant to multiple antiretroviral drugs are now commonplace, and can be transmitted from an infected individual to an uninfected one. Although treatments that combine new drugs called protease inhibitors with other anti-HIV medications often effectively suppress HIV production in infected individuals, studies suggest that many treatment failures occur due to the development of resistance by the virus. Fungal pathogens account for a growing proportion of nosocomial infections, and clinicians are concerned that the increasing use of antifungal drugs will lead to drug-resistant fungi. Recent studies have documented resistance of Candida species to fluconazole, a drug used widely to treat patients with systemic fungal dis-

eases. Parasitic diseases such as malaria are also becoming more difficult to treat. Resistance to chloroquine, a drug once widely used and highly effective for preventing and treating malaria, has emerged in most parts of the world, and resistance to other antimalarial drugs also is widespread and growing. The impact of chloroquine resistance is profound, especially in resource-poor settings. For example, in Nigeria it costs 75 cents to treat a chloroquine-sensitive case of malaria, but $25 to treat a resistant infection.

A broad consensus has emerged that decreasing the incidence of infections resistant to antimicrobials will require the cooperation of many individuals and organizations worldwide, including health care providers; patients and their families; local, state and territorial health departments; U.S. federal agencies (e.g. CDC, NIH, Food and Drug Administration); professional and non-profit organizations; the World Health Organization and its member states; industry; and academia. In the past few years, most if not all of these groups have been represented in major meetings and reports on antimicrobial resistance, including one from the Institute of Medicine's Forum on Emerging Infections. The Forum was created in response to a request by CDC and NIH, and has conducted a series of workshops, including one concerning antimicrobial resistance in July, 1997.

The IOM and other organizations have emphasized the need for improved systems for monitoring outbreaks of drug-resistant infections and a more judicious use of antimicrobial drugs, in both human medicine and agriculture. They also underscore the critical role that basic and applied research plays in combatting the problem of antibiotic resistance. It is in this latter capacity that NIH is predominantly involved.

NIH funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens. The National Institute of Allergy and Infectious Disease (NIAID) has a lead role in many of these activities, but numerous other Institutes and Centers at NIH also support and participate in research related to antibiotic resistance.

NIH-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. Numerous genome projects seek to identify new gene targets for the development of drugs and vaccines. Other NIH sponsored activities with relevance to antimicrobial resistance include physician and researcher training and education. In addition, NIH supports a number of clinical trials networks with the capacity to assess new antimicrobials and vaccines with relevance to drug-resistant infections. Among these are the AIDS Clinical Trials Groups, the Mycoses Study Group, the Collaborative Antiviral Study Group, and Vaccine and Treatment Evaluation Units.

Basic research funded by NIH has yielded extraordinary results. For example, NIAID intramural scientists recently illuminated one way in which the anti-TB drug isoniazid blocks the TB bacterium, information which previously had eluded researchers. They found that isoniazid disables a protein of the bacterium involved in cell wall synthesis called KasA, and also found mutations in the KasA gene that contribute to isoniazid resistance. With the knowledge that KasA is important to mycobacterial growth, it may be possible to develop other drugs that specifically target this molecule. The finding also opens the door to the development of new tests to detect isoniazid resistance, and assays to quickly screen new anti-TB drugs for their ability to target KasA.

Research into the molecular basis of drug resistance in parasites has led to the development of molecular tools to identify drug-resistant parasites; the identification of the genetic basis of resistance and resulting biochemical alterations in several parasite species; the identification of methods to reverse resistance; and the synthesis of drugs that are effective against drug-resistant strains of malaria. In an important technical achievement, NIAID-supported researchers recently determined the complete genetic sequence of chromosome 2 of *Plasmodium falciparum*, the parasite that causes the most severe form of malaria. This new information promises to help identify virulence factors and proteins involved in the parasite's lifecycle that may eventually serve as targets for the development of drugs and vaccines. Other researchers have determined the complete genomic sequence of two strains of *M. tuberculosis*, which promises to facilitate identification of new targets for TB vaccine development, and provide insights relevant to drug design and a better understanding of TB pathogenesis.

Indeed, the remarkably rapid and accurate methods now available for sequencing the genomes of disease-causing microbes promises to revolutionize the study of microbial pathogenesis and drug resistance. In addition to *M. tuberculosis and P. falciparum*, NIH supports the genetic sequencing of many other pathogens with high

levels of drug resistance, including HIV, *Enterococcus faecalis*, *S. pneumoniae*, *Neisseria gonorrhoeae*, *Salmonella typhimurium*, *Streptococcus pyogenes*, *Candida albicans*, and, as noted below, both drug-resistant and drug-susceptible strains of *S. aureus*.

Over the past two fiscal years, NIH and NIAID have been adding funds for antimicrobial resistance research. With this increased support, NIH has been able to accelerate research in this area. Among many initiatives undertaken in consultation with the research community, NIH developed a plan for *S. aureus* that may serve as a model for addressing drug resistance. This strategy includes the funding of grants to sequence the genomes of two strains of the pathogen (one resistant to methicillin and one susceptible), a workshop to facilitate the use of emerging data from the genome projects, and a Request for Proposals (RFP) entitled "Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA)." An award for the network will be made in the next few months; we anticipate that this project will give basic and clinical investigators a common reference for discussing the organisms and access to the same research strains. Another outgrowth of this effort and NIAID grant support is the recent discovery of a potential novel therapeutic target to block the disease-causing mechanisms of *S. aureus*.

These new projects build on significant initiatives in each of the previous two years. In 1996, NIH encouraged the scientific community with a Program Announcement to submit grant applications to support basic and applied research on emerging infectious diseases, including fungal diseases and those due to bacteria that are resistant to antibiotics. In 1997, NIAID released a Program Announcement to encourage basic research on the molecular biology and genetics of resistance among bacteria and fungi, development of new tests for detecting resistance, identification of new classes of antimicrobial agents, and evaluation of alternative treatments of drug-resistant infections.

Vaccine research is a key to preventing infections caused by drug-resistant organisms. The NIH vaccine research portfolio includes projects to develop and test new and improved candidate vaccines against many infectious organisms with high levels of resistance. A notable success story was the development of vaccines against *Haemophilus influenzae* type b (Hib), a bacterium which can lead to life-threatening meningitis, pneumonia and other complications, especially in young children. In the 1970s and 1980s, widespread *H. influenzae* resistance to penicillin-like drugs began to appear, making patient care increasingly difficult. Working with partners in industry and academia, NIH-supported researchers developed a Hib vaccine that protected children older than two years; this vaccine reached the market in 1985. Subsequently, researchers developed conjugated vaccines to protect children under two years of age from Hib; previous versions of the Hib vaccine were not immunogenic in young infants. The success of Hib conjugate vaccines has been extraordinary: more than 35 countries have followed the lead of the United States and adopted these vaccines into their immunization programs, cutting the incidence of invasive Hib disease to negligible levels wherever the vaccine has been used. In the United States only 258 cases of invasive Hib disease among children younger than 5 years were reported in 1997, a 97 percent reduction from 1987.

Many in the public health community are optimistic that the Hib vaccine success story can be repeated with a new conjugated vaccine against another important respiratory pathogen widely resistant to antimicrobials, i.e. *Streptococcus pneumoniae*. More than one-third of *S. pneumoniae* isolates have intermediate or high-level resistance to penicillin. The burden of this pathogen is enormous; S. pneumoniae is the leading cause of morbidity and mortality in infants and young children worldwide, resulting in 1.2 million child deaths each year. In this country, pneumococcal disease is responsible for 40,000 deaths, 500,000 cases of pneumonia, and 7 million cases of otitis media.

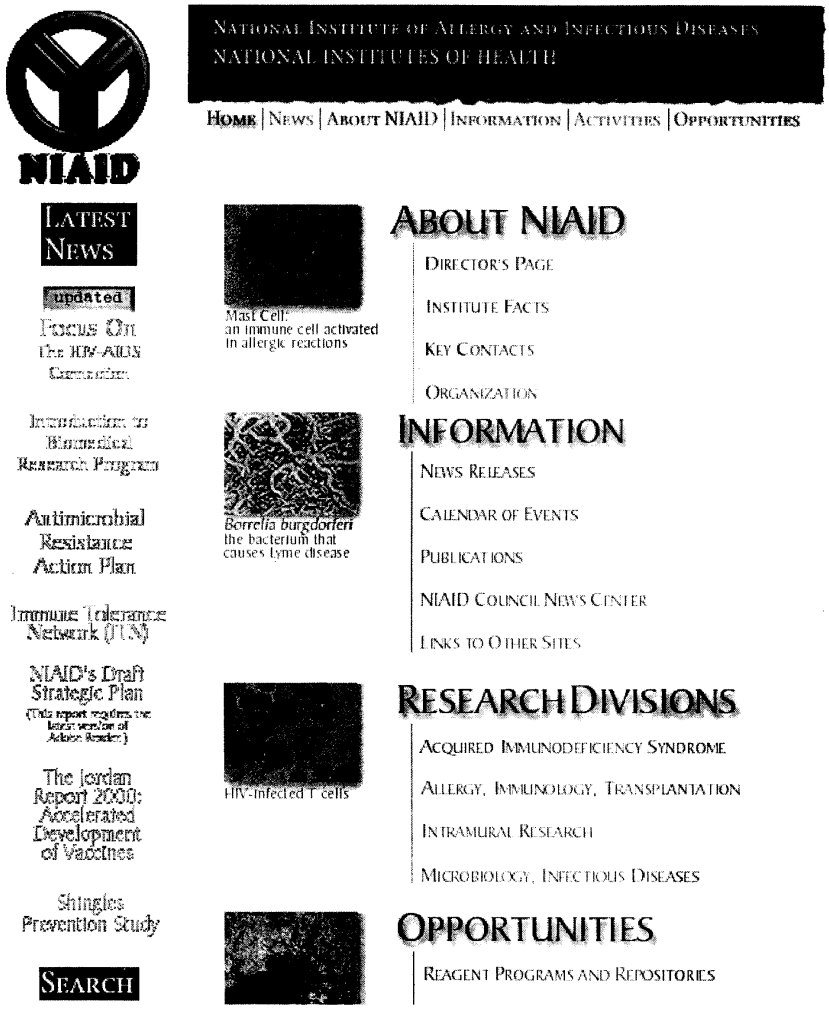
The current pneumococcal vaccine is not immunogenic in young children and only moderately efficacious in the elderly, another group at risk of severe pneumococcal disease. New conjugated pneumococcal vaccines, developed with the help of NIAID funding and tested in the Institute's Vaccine and Treatment Evaluation Units, promise to be significantly more effective. For example, a recent report from a three-year study of more than 38,000 infants in California found that a 7-valent conjugated pneumococcal vaccine was 100 percent efficacious in preventing meningitis and bacteremia in young infants. NIH-supported vaccine development is underway for other resistance problems such as malaria, gonorrhea, and TB.

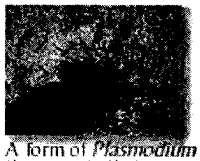
The recent IOM report on antimicrobial resistance asserts: "What is needed now is sustained, sufficient support—for basic pioneering research, for the clinical research required to move truly new products from the laboratory to the pharmacy, and for the infrastructure underpinning both." With our current and planned initia-

tives, NIH is well-positioned to play a pivotal role in combatting the many drug-resistant pathogens that threaten human health.

ATTACHMENT II

NIAID Website





A form of *Plasmodium* the parasite that causes malaria

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Last updated Sept. 14, 2000 (jls)

A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE

[June 2000 Draft]

EXECUTIVE SUMMARY

This Public Health Action Plan to Combat Antimicrobial Resistance (Action Plan) was developed by an interagency Task Force on Antimicrobial Resistance that was created in 1999. The Task Force is co-chaired by the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health, and also includes the Agency for Healthcare Research and Quality, the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency, the Health Care Financing Administration, and the Health Resources and Services Administration.

The Action Plan reflects a broad-based consensus of federal agencies on actions needed to address antimicrobial resistance (AR), which was reached 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. While some actions

are already underway, complete implementation of this plan will require close collaboration with all of these partners, a major goal of the process. The plan will be implemented incrementally, dependent on the availability of resources.

The Action Plan provides a blueprint for specific, coordinated federal actions to address the emerging threat of antimicrobial resistance. This document is Part I of the Action Plan, focusing on domestic issues. Since AR transcends national borders and requires a global approach to its prevention and control, Part II of the plan, to be developed subsequently, will identify actions that more specifically address international issues. The Action Plan, Part I (Domestic Issues), includes four focus areas: Surveillance, Prevention and Control, Research, and Product Development. A summary of the Priority Goals and Action Items in each Focus Area follows below. A complete list is found in pages 12–38.

Surveillance

Unless AR problems are detected as they emerge—and actions are taken quickly to contain them—the world may soon be faced with previously treatable diseases which have again become untreatable, as in the pre-antibiotic era. Priority Goals and Action Items in this focus area address ways to:

—Develop and implement a coordinated national plan for AR surveillance
—Ensure the availability of reliable drug susceptibility data for surveillance
—Monitor patterns of antimicrobial drug use
—Monitor AR in agricultural settings to protect the public's health by ensuring a safe food supply as well as animal and plant health

A coordinated national AR surveillance plan for monitoring AR in microorganisms that pose a threat to public health will be developed and implemented. The plan will specify activities to be conducted at national, state, and local levels, define the roles of participants, promote the use of standardized methods, and provide for timely dissemination of data to interested parties, e.g., public health officials, clinicians, and researchers. Needed core capacities at state and local levels will be defined and supported. When possible, the plan will coordinate, integrate, and build upon existing disease surveillance infrastructure. All surveillance activities will be conducted with respect for patient and institutional confidentiality.

The availability of reliable drug susceptibility data is essential for AR surveillance. The accuracy of AR detection and reporting will be improved through training and proficiency testing programs for diagnostic laboratories and by promoting and further refining standardized methods for detecting drug resistance in important pathogens, including bacteria, parasites, fungi, and viruses. Public and private sector partners will address barriers to AR testing and reporting, e.g., barriers due to changes in healthcare delivery.

A plan to monitor patterns of antimicrobial drug use will be developed and implemented as an important component of the national AR surveillance plan. This information is essential to interpret trends and variations in rates of AR, improve our understanding of the relationship between drug use and resistance, and help identify interventions to prevent and control AR.

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. Agricultural surveillance data will also help improve understanding of the relationship between antimicrobial drug and pesticide use and the emergence of drug resistance.

Prevention and Control

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

—Extend the useful life of antimicrobial drugs through prudent use policies that discourage overuse and misuse
—Improve diagnostic testing practices
—Prevent infection transmission through improved infection control methods and use of vaccines
—Prevent and control emerging AR problems in agriculture
—Ensure that comprehensive programs to prevent and control AR involve a wide variety of non-federal partners and the public and become a part of routine practice nationwide

Prudent drug-use policies will be implemented through a public health education campaign that promotes prudent antimicrobial drug use as a national health priority. Other actions in support of prudent drug use will include reducing inappropriate prescribing through development of guidelines, computer-assisted decision

support, consideration of regulatory changes, and other interventions that promote education and behavior change among clinicians, and informing consumers about the uses and limitations of antimicrobial drugs.

Improved diagnostic practices will be promoted, including the use of rapid diagnostic methods to guide drug prescribing, the appropriate use of clinical laboratories, and appropriate testing methods by those laboratories. Improved diagnostic practices will be promoted through guidelines, training, and regulatory and reimbursement policies.

Reduced infection transmission will be addressed through public health campaigns that promote vaccination and hygienic practices such as hand hygiene and safe food handling. Infection control in health care settings will be enhanced by developing new interventions based on rapid diagnosis, improved understanding of the factors that promote cross-infection, and modified medical devices or procedures that reduce the risk of infection.

The prevention and control of AR in agriculture requires (1) improved understanding of the risks and benefits of antimicrobial use and ways to prevent the emergence and spread of resistance; (2) development and implementation of principles for prudent antimicrobial drug use in the production of food animals and plants; (3) improved animal husbandry and food-production practices to reduce the spread of infection; and (4) a regulatory framework to address to need for antimicrobial drug use in agriculture while ensuring that such use does not pose a risk to human health.

Comprehensive, multi-faceted programs involving a wide variety of non-federal partners and the public are required to prevent and control AR. The AR Task Force agencies will ensure ongoing input and review and collaboration with non-federal partners. The appropriate agencies will support demonstration projects that use multiple interventions to prevent and control AR (e.g., through surveillance, judicious drug use, optimized diagnostic testing, immunization practice, and infection control). The Task Force agencies will encourage the incorporation of effective programs into routine practice by implementing model programs in federal health-care systems and promoting the inclusion of AR prevention and control activities as part of quality assurance and accreditation standards for health care delivery nationwide.

Research

Understanding of the fundamental processes involved in antimicrobial resistance within microbes and the resulting impact on humans, animals, and the environment forms an important basis for influencing and changing these very processes and outcomes. Basic and clinical research provides the fundamental knowledge necessary to develop appropriate responses to antimicrobial resistance emerging and spreading in hospitals, communities, farms, and the food supply. Priority Goals and Action Items in this focus area address ways to:

—Increase understanding of microbial physiology, ecology, genetics and mechanisms of resistance

—Augment the existing research infrastructure to support a critical mass of researchers in AR and related fields

—Translate research findings into clinically useful products, such as novel approaches to detecting, preventing, and treating antimicrobial resistant infections

Needs in the field of AR research will be identified and addressed through a government-wide external program review. Additional research is needed, for example, on the epidemiology of resistance genes; on mechanisms of AR emergence, acquisition, spread, and persistence; and on the effects of antibiotics used as agricultural growth promotants on microbes that live in animals, humans, plants, soil and water. Further study is also required to determine whether variations in drug use regimens may stimulate or reduce AR emergence and spread. Improved understanding of the causes of AR emergence will lead to the development of tools for reducing microbial resistance, as well as for predicting where AR problems are likely to arise.

A comprehensive research infrastructure will help ensure a critical mass of AR researchers who will interact, exchange information, and stimulate new discoveries. This will be achieved through the appropriate mechanisms and scientific conferences that promote research on AR. The AR Task Force agencies will work with the academic and industrial research communities to attract AR researchers, prioritize needs, identify key opportunities, and optimize the utilization of resources to address AR problems.

The translation of research findings into innovative clinical products to treat, prevent, or diagnose drug-resistant infections is an area in which the government can play an important role, focusing on gaps not filled by the pharmaceutical industry or by other non-governmental groups. Special efforts will be placed on the identifica-

tion, development and testing of rapid, inexpensive, point-of-care diagnostic methods to facilitate judicious use of antimicrobials. The AR Task Force agencies will also encourage basic research and clinical testing of diagnostic methods, novel treatment approaches, new vaccines and other prevention approaches for resistant infections.

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 this focus area address ways to:

—Ensure that researchers and drug manufacturers are informed of current and projected gaps in the arsenal of antimicrobial drugs, vaccines, and diagnostics, and of potential markets for these products (designated here as "AR products")

—Stimulate the development of priority AR products for which market incentives are inadequate, while fostering their appropriate use

—Optimize the development and use of veterinary drugs and related agricultural products that reduce the transfer of resistance to pathogens that can infect humans

Current and projected gaps in the arsenal of AR products and potential markets for these products will be reported to researchers and drug manufacturers through an interagency working group convened to identify and publicize priority public health needs.

The development of urgently needed AR products will be stimulated from drug discovery through licensing. The regulatory process for AR products will continue to be streamlined, and incentives that promote the production and appropriate use of priority AR products will be evaluated in pilot programs that monitor costs and assess the return on the public investment.

The production of veterinary AR products that reduce the risk of development and transfer of resistance to drugs used in human clinical medicine will be expedited through a streamlined regulatory and approval process. As with drugs for the treatment of human infections, pilot programs will be initiated to evaluate incentives to encourage the development and appropriate use of priority products that meet critical animal and plant health needs.

Private and public partners will also evaluate ways to improve or reduce the agricultural use of particular antimicrobial drugs, as well as ways to prevent infection, such as the use of veterinary vaccines, changes in animal husbandry, and the use of competitive exclusion products (i.e., treatments that affect the intestinal flora of food animals).

TOP PRIORITY ACTION ITEMS TO COMBAT ANTIMICROBIAL RESISTANCE

(All 11 items have top priority, regardless of their order in the list)

Surveillance

With partners, design and implement a national AR surveillance plan that defines national, regional, state, and local surveillance activities; the roles of clinical, reference, public health, and veterinary laboratories; and is 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, in agriculture, and in consumer products. (Action Item #5)

Prevention and Control

Develop and implement a public health education campaign to promote judicious antimicrobial use as a national health priority. (Action Item #27)

In collaboration with professional societies and other stakeholders, develop, disseminate, and evaluate clinical guidelines that address judicious antimicrobial use. (Action Item #29)

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 #61)

Support demonstration projects to evaluate comprehensive strategies that use multiple interventions to promote judicious drug use and reduce infection rates, in order to assess how interventions found effective in research studies can be applied effectively on a routine basis and on a large scale and how this application can be done most cost-effectively. (Action Item #66)

Research

Provide 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 #73)

Develop a human clinical trials network, involving medical research and healthcare institutions, to coordinate and conduct clinical trials addressing AR issues that are difficult to resolve in industry-sponsored studies (e.g., novel therapies, new treatment regimens, and other products and practices). (Action Item #78)

Identify, develop, test, and evaluate the impact of new rapid diagnostic methods (e.g., tests for resistance genes including nonculture specimens, point of care diagnostics for patients with respiratory infections and syndromes, and diagnostics for drug resistance in microbial pathogens). (Action Item #79)

Product Development

Create an Interagency AR Product Development Working Group to identify and publicize priority public health needs for new AR products (e.g., innovative drugs, targeted spectrum antibiotics, point-of-care diagnostics, vaccines, anti-infective medical devices, and biologics). (Action Item #82)

In consultation with stakeholders, economic consultants, and the AR Product Development Working Group, identify ways (e.g. financial and/or other incentives or investments) to promote the development and/or judicious use of priority AR products for which market incentives are inadequate. (Action Item #83)

INTRODUCTION AND OVERVIEW

Background

In the 1940s, the widespread availability of penicillin and the subsequent discovery of streptomycin led to a dramatic reduction in illness and death from infectious diseases. However, bacteria and other disease-causing organisms—viruses, fungi, and parasites—have a remarkable ability to mutate and acquire resistant genes from other organisms and thereby develop resistance to antimicrobial drugs. When an antimicrobial drug is used, the selective pressure exerted by the drug favors the growth of organisms with mutations that allow them to resist the drug's action. The extensive use of antimicrobial drugs has resulted in the emergence of drug resistance that threatens to reverse the miracles of the last half century.

Drug-resistant pathogens are a growing menace to all people, regardless of age, gender, or socioeconomic background. They endanger people in affluent, industrial societies like the United States, as well as in less developed nations. Examples of clinically important microbes that are rapidly developing resistance to available antimicrobials include bacteria that cause pneumonia, ear infections, and meningitis (e.g., *Streptococcus pneumoniae* [1]), skin, bone, lung, and bloodstream infections (e.g., *Staphylococcus aureus* [2][3]), urinary tract infections (e.g., *Escherichia coli* [4]), foodborne infections (e.g., *Salmonella* [5]), and infections transmitted in health care settings (e.g., *enterococci* [6] and *Klebsiella* [7]).

For example, up to 30 percent of *S. pneumoniae* found in some areas of the United States are no longer susceptible to penicillin, and multi-drug resistance is common. Approximately 11 percent of *S. pneumoniae* are resistant to "third generation" cephalosporin antibiotics, and resistance to the newest fluoroquinolone antimicrobials has already been reported. [8] Nearly all strains of *Staphylococcus aureus* in the United States are resistant to penicillin, and many are resistant to newer methicillin-related drugs.[2] Until 1997, vancomycin was the only uniformly effective treatment for *S. aureus* infections. Since 1997, however, strains of *S. aureus* with decreased susceptibility to vancomycin have been reported. [9][10]

Many other pathogens—including the bacteria that cause tuberculosis [11] and gonorrhea, [12] the virus that causes AIDS, [13] the fungi that cause yeast infections, [14] and the parasites that cause malaria [15]—are also becoming resistant to standard therapies. If we do not act to address the problem of AR, we may loose quick and reliable treatment of infections that have been a manageable problem in the United States since the 1940s. Drug choices for the treatment of common infections will become increasingly limited and expensive—and, in some cases, nonexistent.

Who is at risk?

While anyone may acquire a drug-resistant infection, certain people are at increased risk, including patients in hospitals and children in daycare centers. Drug-resistant infections may be acquired in health care settings (e.g., staphylococcal infections in intensive care units), in the community (e.g. pneumococci acquired from

a classmate) and through the food supply (e.g., salmonella acquired from meat or eggs), both domestically and overseas. However, resistant microbes are increasingly appearing in new settings. Methicillin-resistant S. aureus, which for 30 years with few exceptions was a problem only in hospitals, is now occurring in the community.[3][16]

Financial costs.—The costs of treating AR infections place a significant burden on society—a burden that is likely to grow larger as the number of cases of drug-resistant illness increase. Individuals infected with drug resistant organisms are more likely to require hospitalization, to remain in the hospital for a longer time, and to have a poor prognosis. For example, it has been estimated that the in-hospital cost of hospital-acquired infections caused by just six common kinds of resistant bacteria are at least $1.3 billion per year, in 1992 dollars.[17] This estimate does not include the costs of infections caused by other pathogens, the costs of lost workdays, post-hospital care, or resistant infections in the outpatient or extended care facility settings.

SOLUTIONS: WHAT SHOULD BE DONE? AR will always be with us. The challenge before us is to transform this increasingly urgent threat into a manageable problem. Over the past ten years, the Institute of Medicine,[18] the American Society for Microbiology,[19] other panels of distinguished experts, the Congressional Office of Technology Assessment,[17] and the General Accounting Office[20][21] have provided recommendations and options for government action to address the dangers posed by AR. The experts agree that we need to improve surveillance for emerging AR problems, to prolong the useful life of antimicrobial drugs, to develop new drugs, and to utilize other measures, e.g., improved vaccines, diagnostics, and infection control measures to prevent and control AR.

Despite the urgency of the problem, the achievement of these goals has not been simple or straightforward, and accomplishments to date have been insufficient. Monitoring, preventing, and controlling AR requires sustained effort, commitment, and collaboration among many groups in the public and private sectors, and involvement of the general public. It also requires support and leadership from the Federal Government and a willingness to address complex and sometimes controversial scientific, medical, and economic issues.

A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE

This "Public Health Action Plan to Combat Antimicrobial Resistance" provides a blueprint for specific, coordinated federal actions to address this emerging threat. The Plan builds upon reports prepared by expert panels in recent years. This document is Part I of the Plan, focusing on domestic issues. Since AR transcends national borders and requires a global approach to its prevention and control, Part II of the plan, to be developed subsequently, will identify actions that more specifically address international issues. A National Action Plan to Combat Multi-drug Resistant Tuberculosis has been published previously.[22]

Partnerships and Implementation

This plan was developed by an Interagency Task Force on Antimicrobial Resistance that was created in 1999. The Task Force is co-chaired by the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), and also includes the Agency for Healthcare Research and Quality (AHRQ), the Department of Agriculture (USDA), the Department of Defense (DOD), the Department of Veterans Affairs (DVA), the Environmental Protection Agency (EPA), the Health Care Financing Administration (HCFA), and the Health Resources and Services Administration (HRSA).

The Plan reflects a broadly-based consensus of federal agencies on actions to combat AR. The Plan is based in part on input from a public meeting held in Atlanta, Georgia, in July 1999.[23] Present at the meeting were consultants from a wide variety of groups, including state and local health agencies, universities, professional societies, pharmaceutical and biotechnology companies, health care delivery organizations, agricultural producers, consumer groups, and the public. Implementation of this plan will require collaboration with all of these partners. The plan will be implemented incrementally, as resources and, where needed, new appropriations, become available. The agencies recognize that a number of the items may require either new statutory authority or the adoptions of changes in regulatory requirements. The extent to which such measures may be needed to implement a given action item will be considered by the coordinators and collaborators assigned to each item.

The Plan includes a summary and a list of issues, goals, and action items addressing surveillance, prevention and control, research, and product development. Except where specified, these issues, goals, and action items apply to human AR issues and

not to non-human (e.g., agricultural) issues. Agricultural issues refer to the production of animals and plants, as well as fish and other species (aquaculture). For each action item, "coordinator" and "collaborator" agencies/departments are specified. Contingent on available resources, the coordinators will assume the primary responsibility of carrying out the specified action items and the collaborators will assist and/or carry out part of the specified action. The Interagency Task Force will monitor and, if necessary, update the Plan, during the coming years.

THE FOCUS AREAS

I. SURVEILLANCE

INTRODUCTION

Surveillance of AR is critical to provide early warning of emerging problems, monitor changing patterns of resistance, and target and evaluate prevention and control measures.[1] Timely surveillance information is also necessary to assist researchers in developing new drugs and for good patient care. For example, clinicians should be informed of drug resistance problems in their communities that may influence their prescribing decisions and help them avoid treatment failures. In addition, monitoring patterns of antimicrobial drug use is needed to interpret trends and variations in rates of AR, improve understanding of the relationship between drug use and resistance, and help identify preventive interventions.

At present, the United States lacks a coordinated national plan for AR surveillance. Creating a national plan requires collaboration with partners in the public and private sectors. Improved AR surveillance depends upon enhanced epidemiologic and laboratory capabilities at local, state, and national levels, use of standardized and reliable laboratory testing methods, and enhanced use of informatics.

A. Issue.—The United States lacks a coordinated national plan for surveillance of:

—AR emergence in organism-drug combinations of public health importance

—Antimicrobial drug use in human and non-human settings

1. Goal.—Collaborate with appropriate partners to develop procedures and methods for nationwide surveillance of AR emergence in organism-drug combinations of public health importance

a. Action Items

(1) Determine which organisms and susceptibility to specific antimicrobial drugs should be under surveillance and create a mechanism for periodic updating of this list.

Coordinators: CDC, FDA, USDA, EPA
Timeline: Initiated

(2) TOP PRIORITY ACTION ITEM.—Identify the components of a national AR surveillance plan and the roles of partners in its design and implementation.

—Determine which surveillance activities should be conducted routinely at national, regional, state, or local levels and which may require specialized projects.
Cordinators: CDC, FDA, USDA

—Define the roles of clinical, reference, public health, and veterinary laboratories at federal, state, and local levels in AR surveillance.
Coordinator: CDC; Collaborators: DOD, DVA, FDA, USDA, HCFA

—Improve coordination of AR surveillance systems at CDC, FDA, and USDA (e.g., identify components for integration).
Coordinators: CDC, FDA, USDA

—Ensure that the national AR surveillance plan is consistent with local and national surveillance methodology and infrastructure that currently exist or are being developed.
Coordinators: CDC, USDA, FDA
Timeline: For entire action item 2, begin within one to two years

(3) Develop standards and methodologies.

—Develop standards and methodologies for monitoring drug-resistant infections in humans and animals, as well as for monitoring drug-resistant microbes in food products and environmental samples.

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[1] Public health surveillance is the ongoing, systematic collection, analysis, and interpretation of data for use in the planning, implementation, and evaluation of public health practice. desirable qualities of any system include simplicity, flexibility, acceptability, sensitivity, and representativeness. a surveillance system also includes the timely dissemination of these data to persons who can undertake effective prevention and control activities, including clinicians, researchers, laboratorians and public health personnel. MMWR, guidelines of evaluating surveillance systems, May 6, 1988/37(s5); 118.

Coordinators: CDC, UDSA, FDA, EPA

—Develop standardized laboratory methodologies and data elements that allow susceptibility test results and AR surveillance data to be compared across geographic jurisdictions.

Coordinators: CDC, UDSA, FDA, EPA

—Similarity, use standardized definitions and methodology (Related Action Item: Surveillance #5) to create an electronic surveillance system that health care institutions can use to compare AR data from other local facilities.

Coordinator: CDC; Collaborators: HCFA, DVA, DOD, HRSA

—Develop standards for reporting quantitative resistance data (e.g., MICs or zone diameters) in ways that will detect decreased susceptibility. This is necessary because numerical AR test results reported non-quantitatively (e.g., as susceptible, intermediate, or resistant) as″susceptible" may mask an emerging AR problem (i.e, microbes with a small decrease in susceptibility may still be classified as susceptible).

Coordinators: CDC, USDA, FDA

—Assess how current policies on maintaining the confidentiality of medical and veterinary data collected for other purposes relate to procedures for gathering data on antimicrobial resistance. If necessary, develop a comprehensive national confidentiality policy on human and agricultural AR surveillance that includes both patient and institutional confidentiality, is consistent with confidentiality policies applied to other forms of surveillance and research data, and that recognizes the differences in human and animal agriculture surveillance programs.

Coordinator: CDC; Collaborators: DVA, HCFA, DOD, FDA, USDA

Timeline: For entire action item 3, initiated

(4) Address additional surveillance issues unique to AR.

—Conduct post-marketing surveillance for the development of resistance to critical antimicrobial drugs. Surveillance should be linked to information on drug use, and criteria should be developed to allow a prompt response to a finding of increased resistance related to a specific pattern of use (e.g. consumer and professional alerts, enhanced education, labeling changes, or restrictions on use).

Coordinators: FDA, CDC, USDA

—Facilitate the collection on AR surveillance data on pathogens for which cultures are not routinely obtained, either because the infections are empirically treated without laboratory diagnosis or because they are diagnosed with non-culture tests.

Coordinator: CDC

Timeline: For entire action item 4, begin within one to two years

2. Goal.—Collaborate with appropriate partners to develop procedures and methods for nationwide surveillance of antimicrobial drug use in human and non-human settings

a. Action Item

(5) TOP PRIORITY ACTION ITEM.—Develop and implement procedures for monitoring antimicrobial drug use in human medicine, in agriculture, and in consumer products.

—Incorporate appropriate confidentiality protections in these procedures

—Link human drug-use data to clinical information (e.g., diagnosis, severity of illness, and outcome)

—Link agricultural drug-use data to species and usage patterns.

—Assess geographic variations in drug use

Coordinators: CDC, FDA, USDA; Collaborators: EPA, DVA, DOD

Timeline: For entire action item 5, begin within one to two years

(6) Identify and evaluate methods for collecting (e.g., optimal sampling methods) and disseminating the surveillance data on antimicrobial drug use:

—Ientify inexpensive sources of drug use data (e.g., the National Ambulatory Medical Care Survey [NAMCS], the National Hospital Ambulatory Medical Care Survey [NHAMCS], and databases in some health care delivery systems and pharmacies) and evaluate their usefulness for surveillance purposes

Coordinators: CDC, FDA

—Consider ways that results of periodic drug use surveys could be made available to food animal producers and veterinarians to encourage participation in data collection

Coordinators: CDC, FDA, USDA

Timeline: For entire action item 6, begin within one to two years

(7) Work with accrediting agencies to address antimicrobial drug-use monitoring as part of quality assurance in health care delivery systems. (Related Action Item: Prevention and Control #67)

Coordinators: CDC, HCFA

Timeline: Begin within one to two years

(8) Convene a working group to assess the possible need for additional federal regulations to facilitate and protect confidentiality in antimicrobial drug use monitoring programs.

Coordinators: CDC, USDA, FDA

Timeline: Begin within one to two years

B. Issue.—Implementation of the national plan for AR surveillance will require:

—Reliable drug susceptibility data

—Adequate capacity and resources at state and local health and agricultural agencies

—An accessible, centralized source of AR data

1. Goal.—Promote the consistent and appropriate use of reliable laboratory tests for antimicrobial drug susceptibility

a. Action Items

(9) Ensure that clinical laboratories that provide data for AR surveillance purposes have clinical access to and routinely participate in pertinent training and applicable proficiency testing programs with good performance and indicate AR testing methodologies in their surveillance reports (e.g., specific automated methods or manual techniques).

Coordinator: CDC; Collaborator: HCFA

Timeline: Initiated

(10) Evaluate the performance of licensed, automated AR testing devices in context of changing resistance patterns and update their labeling where appropriate (e.g., changes in quantitative resistance that may make a test result invalid).

Coordinators: FDA, CDC

Timeline: Begin within one to two years

(11) Work with the National Committee for Clinical Laboratory Standards (NCCLS) further to refine antifungal susceptibility testing methods for yeasts and molds.

Coordinators: CDC, USDA, HCFA

Timeline: Initiated

(12) Develop and promote standardized clinical, epidemiologic, and laboratory methods for documenting drug resistance among parasites (e.g., lice, Trichomonas, Giardia).

Coordinators: CDC, NIH

Timeline: Begin within three to five years

(13) Identify ways to overcome economic, legal, and other barriers to appropriate AR testing and to the reporting of results (e.g., reimbursement policies, managed-care practices, cost considerations, empiric treatment recommendations, etc.). (Related Action Item: Prevention and Control #37)

Coordinators: HCFA, HRSA, CDC, AHRQ

Timeline: Begin within one to two years

(14) Identify a legal mechanism for manufacturers to provide otherwise unavailable drugs to government reference laboratories for the sole purpose of antimicrobial drug susceptibility testing (as part of surveillance) with the understanding that these drugs will not be used for drug discovery purposes.

Coordinator: CDC

Timeline: Begin within one to two years

2. Goal.—Ensure that state and local health and agricultural agencies have the capacity to conduct surveillance of drug-resistant organisms of public health importance

a. Action Items

(15) With state health and agriculture departments and other stakeholders, define needed core capacity (the minimum needed in human, laboratory, and electronic resources) at the state and local level to ensure that basic AR surveillance is conducted in these jurisdictions. As part of this effort, ensure that state public health and veterinary diagnostic laboratories maintain the capacity to test the drug-susceptibility patterns of resistant organisms of public health importance, especially for drug-microorganism combinations for which testing methods are not routinely available at hospital and commercial laboratories.

Coordinators: CDC, USDA, FDA

Timeline: Begin within one to two years

(16) Provide resources to assist in meeting state and local core capacity needs for AR surveillance. Strive to prove consistent funding from year to year to state and local public health and veterinary diagnostic laboratories that meet quality assurance standards.

Coordinators: CDC, USDA, FDA

Timeline: Initiated

3. Goal.—Disseminate surveillance data in a timely manner to public health officials, clinicians, and others who may make decisions based on an analysis of the data

a. Action Items

(17) Provide an accessible, centralized source of AR data from major surveillance systems involving animal and human populations. In consultation with stakeholders, determine how to report AR data in a way that is useful to interested parties (e.g., clinicians, public health officials, veterinarians, and researchers). Include sufficient detail in surveillance reports to permit local analysis and comparison with trends in drug use and medical and agricultural practices.

Coordinators: CDC, USDA, FDA, HCFA

Timeline: Begin within one to two years

(18) Provide health-care system administrators and other decision makers with data on the impact of drug-resistant organisms (e.g., outcome, treatment costs) and on effective prevention and control measures.

Coordinators: CDC, AHRQ

Timeline: Begin within one to two years

C. Issue.—Monitoring AR in agricultural settings is essential to ensure animal and plant health and a safe food supply

1. Goal.—Monitor AR in animal and plant pathogens and in bacteria that can be transmitted to humans through the food supply

a. Action Items

(19) Expand and enhance coordination of surveillance for drug-resistance in enteric bacteria in sick and healthy humans, and sick and healthy animals on farms, at slaughter, and at retail. This effort may include:

—Expanding the National Antimicrobial Resistance Monitoring System: Enteric Bacteria (NARMS:EB)

—Comparing AR data on pathogenic and non-pathogenic organisms detected on farms (in sick and healthy animals), at slaughter, and in commercial food products

—Utilizing these data to monitor the transmission of resistant infections and assess the effectiveness of prevention measures

Coordinators: CDC, FDA, USDA

Timeline: Initiated

(20) Evaluate the usefulness of monitoring sentinel human populations (e.g., farm, abattoir, fruit and vegetable, and food processing plant workers) and persons in the general community for infection or colonization with resistant enteric bacteria.

Coordinators: CDC, USDA, FDA

Timeline: Begin within three to five years

(21) Conduct pilot studies to assess the extent and impact of environmental contamination by antimicrobial drug residues and drug-resistant organisms that enter the soil or water from human and animal waste. If appreciable contamination is detected, conduct routine or sentinel surveillance in waste, in surface and ground water, and in soil from agricultural areas in which waste is used for fertilizer. (Related Action Item: Prevention and Control #58)

Coordinators: EPA, CDC, USDA

Timeline: Begin within three to five years

(22) Gather information on the relationship between antimicrobial pesticide and herbicide use and the emergence of drug-resistance, by monitoring:

—The prevalence and incidence of drug-resistant organisms in agricultural areas where antimicrobial pesticides are and are not used

—The prevalence of colonization or infection with resistant bacteria in human or animal populations who live or work near orchards or who consume fruit products sprayed (or treated) with antimicrobial pesticides (Related Action Item: Prevention and Control #64)

Coordinators: EPA, CDC, USDA

Timeline: Begin within three to five years

II. Prevention and Control

INTRODUCTION

Prevention and control of drug-resistant infections requires measures to promote the prudent use of antimicrobial drugs (i.e., maximizing their therapeutic effect while minimizing the potential for development of resistance). Prudent antimicrobial drug use can be facilitated by promoting appropriate prescribing by clinicians, informing consumers about the uses and limitations of antimicrobial drugs, and improving diagnostic techniques. Measures to prevent transmission of infection, whether drug-resistant or not, are also important in controlling AR. These include the appropriate use of vaccines and infection control, sanitation, and hygiene measures. Efforts to control drug-resistant infections must become part of everyday practice in health-care settings across the nation, as well as in other settings (e.g., agriculture) in which antimicrobial drugs are used. Partners in many sectors of society, as well as the general public, will need to be involved in this effort.

A. Issue.—Overuse and misuse of antimicrobial drugs can hasten the development of resistance and shorten the drug's useful life.

1. Goal.—Identify methods for promoting judicious antimicrobial use

a. Action Items

(23) Identify factors that promote or impede judicious drug use in hospitals, extended care facilities, and outpatient settings, working in collaboration with health policy researchers and organizations that can help implement AR prevention and control strategies.

Coordinator: CDC; Collaborators: FDA, AHRQ, DVA, DOD
Timeline: Initiated

(24) Develop judicious drug use policies and evaluate the effectiveness (including cost-effectiveness) of implementing these policies in hospitals and other health-care delivery settings. Identify ways to increase adherence to judicious use policies proven to be effective.

Coordinator: CDC; Collaborators: AHRQ, FDA, DVA, DOD, HCFA
Timeline: Initiated

(25) Evaluate the relationship between prescribing behavior and specific antimicrobial drug marketing and promotional practices. Assess the public health effects of these practices.

Coordinators: CDC, FDA
Timeline: Begin within three to five years

(26) Help individual hospitals and health care systems analyze how the availability of AR data and computer-assisted decision support systems influences prescriber behavior, health outcomes, and costs. This may include the provision of computer software and the establishment of projects that involve the Medicare Peer Review Organizations (PROs).

Coordinator: CDC; Collaborators: HCFA, DVA, DOD
Timeline: Begin within three to five years

2. Goal.—Promote judicious antimicrobial use through educational and behavioral interventions found to be effective

a. Action Item

(27) TOP PRIORITY ACTION ITEM.—Develop and implement a public health education strategy to promote judicious antimicrobial use as a national health priority. The strategy should involve patients, clinicians, educators, industry, and policy makers. Elements of this campaign may include:

—Culturally appropriate educational and behavioral interventions implemented through community-based programs that target
  —Patients and selected populations and communities, such as daycare centers and schools
  —Prescribing clinicians
  —Health care delivery-systems
—A clearinghouse for educational materials (e.g., booklets and CD–ROM presentations) on judicious drug use and AR prevention
—A periodically updated priority list of drug-resistant microorganisms in humans and animals
—A glossary disseminated through CDC Website that defines technical words commonly used in discussions of AR issues

Coordinator: CDC; Collaborators: USDA, FDA, HCFA
Timeline: Begin within one to two years

(28) Work with pharmaceutical manufacturers to implement programs directed at clinicians and the public that promote judicious antimicrobial drug use for priority drug-pathogen combinations. Consider providing incentives to participating companies. (Related Action Item: Product Development #83)

Collaborator: CDC; Collaborators: USDA, FDA, HCFA

Timeline: Begin within one to two years

3. Goal.—Promote judicious antimicrobial use through guidelines, regulatory changes, and public policy actions

a. Action Items

(29) TOP PRIORITY ACTION ITEM.—In collaboration with professional societies and other stakeholders, develop, disseminate, and evaluate clinical guidelines that address:

—Judicious antimicrobial use

—Self-care and symptomatic treatment for common viral infections

—Advice to patients on how to help prevent the emergence of AR infections through appropriate use of antimicrobial drugs

Coordinators: CDC, FDA; Collaborator: NIH

Timeline: Initiated

(30) Explore ways to integrate judicious use information into antimicrobial package inserts and promotional materials, to provide such information to patients with each prescription, and to provide clear guidance to industry to ensure that promotion of antimicrobials directed towards consumers does not encourage inappropriate or unneeded use.

Coordinator: FDA; Collaborator: CDC

Timeline: Begin within one to two years

(31) Articulate factors that support the current approach of requiring prescription-only dispensing for all systemic (i.e., non-topical) antimicrobial drugs used in clinical medicine.

Coordinator: FDA; Collaborator: CDC

Timeline: Begin within three to five years

(32) Periodically review and update antimicrobial drug susceptibility information included in drug labeling, in coordination with the National Committee for Clinical Laboratory Standards (NCCLS).

Coordinator: FDA; Collaborator: CDC

Timeline: Begin within one to two years

(33) Convene an advisory panel or other expert group to consider the management of drugs of last resort for the treatment of resistant infections. Issues for discussion might include:

—Promoting early and wide adoption of prudent use guidelines

—Establishing intensive surveillance of drugs of last resort, with mechanisms for triggering changes in product labeling and use when increased resistance is detected

—Labeling drugs of last resort with the recommendation that they be preferentially used for the treatment of conditions associated with organisms that are resistant to other drugs

Coordinator: FDA; Collaborator: CDC

Timeline: Begin within one to two years

(34) Convene a working group to examine the impact of federal reimbursement policies for home parenteral antimicrobial treatment on judicious antimicrobial use. Where needed, the working group will make recommendations for modifying these policies.

Coordinator: HCFA; Collaborators: CDC, HRSA

Timeline: Begin within one to two years

(35) Develop and submit measures for appropriate antimicrobial use to the National Committee for Quality Assurance for inclusion in Health Plan Employer Data and Information Set (HEDIS), which provides comparative data on managed care organizations.

Coordinator: CDC; Collaborator: HCFA

Timeline: Initiated

B. Issue.—Improve diagnostic practices can enhance antimicrobial use and patient care.

1. Goal.—Identify and promote the widespread use of diagnostic testing and reporting strategies that effectively facilitate judicious use of antimicrobial drugs in routine practice

a. Action Items

(36) Evaluate the potential impact of improved diagnostic tests, including rapid point-of-care tests on antimicrobial drug use and patient care, and assess their financial implications. Take into account tests that distinguish between bacterial and viral infections; tests that identify resistant pathogens; and tests that distinguish common clinical syndromes such as bacterial sinusitis and acute bacterial otitis media from illnesses with similar manifestations for which antimicrobials are not beneficial. (Related Action Item: Research #79)

Coordinator: CDC; Collaborators: DVA, DOD

Timeline: Begin within one to two years

(37) Identify economic and other barriers in the health care system (e.g., reimbursement policies by third-party payers, managed care practices, cost considerations, empiric treatment recommendations, etc.) to diagnostic testing that promotes appropriate use of antimicrobials. Develop recommendations that remove disincentives or promote incentives to such testing.

Coordinator: HCFA; Collaborators: CDC, HRSA

Timeline: Begin within three to five years

(38) In collaboration with professional societies, industry, and other stakeholders, develop guidelines for use by clinicians and clinical microbiology laboratories that address:

—Appropriate specimen collection

—Performance, interpretation, and reporting of antimicrobial (including antifungal) susceptibility tests performed on clinical specimens

—Use of in-office (point-of-care) tests for infection, including AR infections

Coordinator: CDC; Collaborator: FDA

Timeline: Begin within three to five years

(39) In collaboration with professional societies, industry, and other stakeholders, develop guidelines for use by health-care-delivery organizations that address the use of clinical microbiology laboratories. The guidelines will:

—Promote access to clinical microbiology services by clinicians

—Promote access to appropriate on-site microbiology services in acute care facilities

—Allow physicians to submit specimens to clinical laboratories other than those designated by their health care delivery organization or the patient's insurance company, with appropriate justifications

Coordinator: CDC; Collaborator: HCFA for bullet 2.

Timeline: Begin within three to five years

(40) Promote the increased performance of direct examination of microbiological specimens (e.g., by Gram stain or other rapid method), in circumstances where appropriate clinically relevant and reliable information can be garnered, as a readily available point-of-care diagnostic test. This will require working within the framework of the Clinical Laboratory Improvement Amendment (CLIA) regulations and involving medical education and health care delivery organizations.

Coordinator: CDC; Collaborator: HCFA

Timeline: Begin within one to two years

C. Issue.—Preventing infection transmission through improved infection control and use of vaccines can help prevent the spread of antimicrobial resistance.

1. Goal.—Identify ways to reduce disease transmission in health-care settings and in the community

a. Action Items

(41) Identify factors that promote transmission of drug-resistant pathogens in health-care facilities, in extended care facilities, and in community settings such as daycare centers. These may include characteristics of the facilities and of the populations that they serve.

Coordinator: CDC; Collaborators: DVA, DOD

Timeline: Initiated

(42) Evaluate the effectiveness (including cost-effectiveness) of current and novel infection-control strategies used in hospitals and other health-care delivery settings.

Coordinator: CDC; Collaborators: DOD, DVA

Timeline: Initiated

(43) Identify ways to increase adherence to infection-control practices proven to be effective in previous studies.

Coordinator: CDC; Collaborators: DOD, DVA

Timeline: Initiated

(44) Evaluate the cost-effectiveness and impact on patient care and drug resistance of medical devices that incorporate anti-infective compounds to prevent infection (e.g., anti-infective urinary catheters and prosthetic heart valves). Where appropriate, encourage the clinical use of these devices. (Related Action Item: Product Development #85)

Coordinator: CDC; Collaborators: AHRQ, DOD, DVA, FDA, HRSA, HCFA

Timeline: Begin within three to five years

(45) Encourage the development of clinical alternatives to those invasive medical procedures and devices that increase the risk of infection in hospitals and other health care setting, e.g., substitution of transcutaneous monitoring of blood oxygen levels of indwelling catheters.

Coordinator: CDC; Collaborators: FDA, DVA

Timeline: Begin within three to five years

(46) Evaluate the benefits and risks of incorporating antimicrobial, disinfectants, or antiseptic chemicals into consumer products (e.g., soap, toys, kitchen utensils, clothes, paints, plastics, and film preservatives). Consider whether they:

—Have any efficacy in reducing infection

—May play a role in promoting drug resistance

Coordinators: CDC, EPA; Collaborator: FDA

Timeline: Begin within three to five years

2. Goal.—Promote infection control through behavioral and educational interventions

a. Action Items

(47) Conduct a public health campaign to promote hand hygiene and other hygienic practices that prevent the transmission of infectious organisms, in collaboration with professional societies and stakeholders. This campaign may be coordinated with the public health education strategy to promote judicious antimicrobial use described in Action Item #27: Prevention and Control. Components will include:

—Evaluating the curricula of school hygiene courses

—Funding school-based and other programs that promote hand hygiene and other behaviors that prevent infection

—Building on previous campaigns (e.g., ASM's Operation Clean Hands)

Coordinator: CDC

Timeline: Begin within one to two years

(48) Support ongoing public health education campaigns on food-safety such as FDA and USDA's Fight BAC program,[24] whose aim is to educate food producers, suppliers, retailers, and consumers about food safety practices that reduce foodborne infections (including AR infections)[25]

Coordinators: USDA, CDC, FDA

Timeline: Initiated

(49) Educate the public about the merits and safety of irradiation as one tool to reduce bacterial contamination of food.

Coordinator: CDC

Timeline: Begin within one to two years

3. Goal.—Optimize the use of vaccines to prevent drug-resistant infections and reduce antibiotic use

a. Action Items

(50) Support community-based programs that promote and facilitate availability of recommended vaccinations for adults and children.

Coordinator: CDC

Timeline: Initiated

(51) Identify vaccines useful in reducing drug-resistant infections and evaluate novel methods for improving coverage with these vaccines. For example:

—Evaluate the risks and benefits of allowing certain vaccines for adults (e.g., for pneumococci and influenza virus) to be dispensed by pharmacists without prescription

—Review and evaluate methods to promote administration of pneumococcal vaccines (e.g., offering vaccination when patients are discharged from the hospital), and encourage the use of methods found to be effective

Coordinator: CDC; Collaborators: DVA, FDA, HCFA

Timeline: Begin within three to five years

D. Issue.—Prevention and control of drug resistance in agriculture is important to promote animal and plant health, as well as to prevent AR transmission to humans through the food supply or through contact with infected animals.

1. Goal.—Improve understanding of the risks and benefits of antimicrobial use, and ways to prevent the emergence and spread of drug resistance, in agricultural settings

a. Action Items

(52) Evaluate the nature and magnitude of the impact of using various antimicrobial drugs as growth promotants in different species, using current animal husbandry practices. Use this information to assist in risk-benefit assessments of such use.

Coordinator: USDA; Collaborators: CDC, FDA

Timeline: Begin within one to two years

(53) Conduct additional research to further define the effects of using various veterinary drugs on the emergence of resistant bacteria that infect or colonize food animals of different species, using various animal husbandry practices. Identify risk factors and preventive measures. Assess the associated risk of:

—Transmission of AR infections to humans

—Clinical disease in humans

—Transfer of resistance factors from animal flora to human flora

Coordinators: CDC, USDA, FDA

Timeline: Initiated

(54) Conduct epidemiologic and laboratory studies to assess the risk of development and transfer of resistance related to the use of antimicrobial drugs in food and non-food plants, and identify risk factors and potential preventive measures.

Coordinator: USDA; Collaborators: CDC, FDA, EPA

Timeline: Initiated

(55) Develop rapid tests for inspecting fresh commodities like fruit for evidence of contamination with bacteria that are resistant to antibiotics.

Coordinator: USDA; Collaborators: EPA, FDA, CDC

Timeline: Begin within one to two years

(56) Evaluate the effect of current food processing and distribution methods on the emergence and spread of drug-resistant organisms.

Coordinator: USDA; Collaborators: CDC, FDA

Timeline: Begin within one to two years

(57) Identify and evaluate new food pasteurization strategies.

Coordinator: USDA; Collaborators: FDA, CDC

Timeline: Begin within three to five years

(58) Assess the risk of AR emergence and spread due to environmental contamination by antimicrobial drugs or by resistant bacteria in animal and human waste. Collect information on whether environmental contamination by antimicrobial drugs can lead to the development of resistance in bacteria that live in the soil or in water. (Related Action Item: Surveillance #21)

Coordinators: USDA, CDC, EPA, FDA

Timeline: Initiated

(59) Assess the impact of antimicrobial use in companion animals (pets) on colonization and infection with drug-resistant organisms in the animals and their human household contacts.

Coordinator: CDC

Timeline: Begin within three to five years

2. Goal.—Promote judicious antimicrobial use in agricultural settings

a. Action Items

(60) Work with veterinary and agricultural communities to help educate users of veterinary and agricultural antimicrobial about AR issues, and promote the implementation and evaluation of guidelines that address:

—Judicious antimicrobial use in agricultural settings

—Performance and interpretation of antimicrobial susceptibility tests performed on specimens from different species of animals

—Point-of-care tests for infection, including AR infections

Coordinators: USDA, CDC, FDA; Collaborator: EPA

Timeline: Initiated

(61) TOP PRIORITY ACTION ITEM.—In consultation with stakeholders, refine and implement the proposed FDA framework[26] for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for re-evaluating currently approved veterinary antimicrobial drugs.

Coordinator: FDA

Timeline: Initiated

(62) Strongly encourage involvement of veterinarians in decisions regarding the use of systemic antimicrobial drugs in animals, regardless of the distribution system

through which the drug is obtained (e.g., regardless of whether a prescription is required to obtain the drug).

Coordinators: FDA, USDA

Timeline: Initiated

(63) Evaluate the potential impact of making all systemic veterinary antimicrobial drugs available by prescription only.

Coordinators: FDA, USDA

Timeline: Begin within three to five years

(64) Convene an expert group to consider how to incorporate AR issues into regulations governing the use of pesticides. Invite external experts, stakeholders, and the public to provide input.

Coordinator: EPA

Timeline: Begin within one or two years

E. Issue.—Efforts to prevent and control AR emergence and spread must be comprehensive and multi-faceted, and involve a wide variety of non federal partners and the public, and become a part of routine practice nationwide.

1. Goal.—Ensure input from non-federal experts on federal efforts to combat antimicrobial resistance

a. Action Items

(65) Establish an ongoing mechanism to obtain periodic input from external experts on AR issues. This will include ensuring input from stakeholders (e.g., state and local health agencies, the private sector, and the public) in developing and reviewing federal efforts to address antimicrobial resistance.

Coordinators: CDC, FDA, NIH; Collaborators: USDA, EPA, DOD, DVA, AHRQ, HRSA, HCFA

Timeline: Begin within three to five years

2. Goal.—Develop and evaluate comprehensive demonstration programs to prevent and control AR

a. Action Items

(66) TOP PRIORITY ACTION ITEM.—Support demonstration projects to evaluate comprehensive programs that use multiple interventions to promote judicious drug use and reduce infection rates. These projects will:

—Assess how interventions found effective in research studies can be applied effectively on a routine basis and on a large scale and how this application can be done most cost-effectively

—Evaluate the use of these programs in health care systems (federal and non-federal), in the community, and in agricultural settings

—Involve partnerships with local and state agencies, health care systems, professional societies, community organizations, schools, private industry, and the public

Coordinator: CDC; Collaborators: FDA, DVA, DOD, HRSA, HCFA, USDA

Timeline: Initiated

3. Goal.—Incorporate effective AR prevention strategies and programs into routine clinical practice

a. Action Items

(67) Utilize federal health care systems (e.g., DOD, VAH, etc.) as model systems for AR surveillance and prevention and control activities involving judicious drug use, optimized diagnostic testing, infection control, and vaccination practice.

Coordinator: CDC; Collaborators: DVA, DOD, HCFA, HRSA

Timeline: Begin within three to five years

(68) For all health care systems for which federal funds are provided, identify and promote strategies to establish AR prevention and control activities as part of quality monitoring programs.

Coordinator: CDC; Collaborators: DVA, DOD, HCFA, HRSA

Timeline: Initiated

(69) Encourage nationally recognized accrediting agencies such as the National Committee for Quality Assurance (NCQA) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), to include accreditation standards that promote efforts to prevent and control AR, including judicious antimicrobial use, infection control, vaccine use, and diagnostic testing. These standards may draw on the findings of existing data and demonstration programs and AHRQ Evidence-Based Practice Centers.

Coordinator: CDC; Collaborators: HCFA, AHRQ

Timeline: Begin within one to two years

III. RESEARCH

INTRODUCTION

Antimicrobial resistance is among the most challenging problems in microbiology, clinical medicine, and public health. Antimicrobial resistance is not one problem, but an overarching term for a whole array of problems. Microbiology, the study of microorganisms, tells us that the processes by which drug resistance occur, are essentially those of evolution. To evolve is to change, and this change is inevitable. Basic and clinical research provides the fundamental knowledge necessary to develop appropriate responses to antimicrobial resistance emerging and spreading in hospitals, communities, farms, and the food supply. Major scientific accomplishments throughout the years have contributed much to the understanding of the fundamental biological processes of AR within microbes and the resulting impact on human, animals, and the environment and provides us the opportunity to influence these very processes and outcomes.

The broad scope of the U.S. research community has a major contribution to make in meeting the challenge of AR in order to reach the goals the AR Task Force has set forth. The research and development of diagnostic tests, new antimicrobial agents, novel therapeutic products, and vaccines and other preventive approaches in response to AR is a multi-step process that begins with basic research discoveries and ends with the availability and use of a new product or implementation of a process. Along this pathway three areas need to be addressed: the identification of gaps and needs in the molecular and cellular understanding of resistance, the infrastructure to support a robust research community, and finally a pathway for movement of research findings into the development of new products.

Through efforts of the Interagency Task Force, important research questions about microbial physiology, ecology, genetics and mechanisms of resistance have been identified. Existing gaps in knowledge and understanding should be addressed to augment the federal and private sector response to the overall problem. Efforts are underway to build and enhance the field of AR research, through increased focus, recognition, and collaboration. The aim is to develop a research infrastructure to support a critical mass of AR researchers who will interact, exchange information, and stimulate new discoveries. In order to move novel ideas arising at the research bench to useful products or approaches, support of the underlying infrastructure to study and test products and a mechanism to transition to industrial partners is necessary.

This effort will involve federal agencies that conduct, support and promote basic and clinical research in academia and industry and will involve prioritizing needs, identifying key opportunities, recruiting new investigators to the field, and making responsible use of resources to address AR problems.

A. Issue.—Specific scientific gaps remain in the understanding of microbial physiology, ecology, genetics and mechanisms or resistance.

1. Goal.—Address existing research needs and identify new ones

a. Action Items

(70) Additional research is needed to enhance the understanding and assess the impact of:

—Mechanisms of AR emergence, acquisition, spread, persistence, and decline, with special regard to multi-drug resistant organisms
—Emergence and transfer of resistance genes among microorganisms in vivo, including epidemiologic factors
—Effects of preventive, therapeutic, and growth promoting agents on the micro biota of animals, plants, soil, and aquatic environments
—Host factors and immune modulators (e.g., cytosine) in clinical resistance to treatments for opportunistic infections
—Variations in antimicrobial use patterns that may affect the emergence and spread of resistance and the outcome of treatment, including:
  —Differences in duration and dosage in the administration of antimicrobial agents
  —Prophylactic use of antimicrobial (including antibacterial and antifungal) agents
  —Drug combinations used to treat resistant organisms
  —The rotation (cycling) of antimicrobial drugs to prevent the emergence of resistance
  —The determinants of colonization and infection with drug-resistant pathogens

Coordinator: NIH; Collaborators: CDC, FDA, DVA, USDA, EPA, DOD

Timeline: Initiated

(71) Conduct further government-wide, in-depth, assessment of the scope and composition of AR research to identify research opportunities.

Coordinators: NIH, CDC, FDA, USDA; Collaborators: DOD, DVA, AHRQ, EPA, HCF

Timeline: Initiated

B. Issue.—The existing research infrastructure needs to ensure a critical mass of researchers in AR and related fields.

1. Goal.—Augment the scientific research infrastructure

a. Action Items

(72) Work with the appropriate peer review structures to ensure that the requisite expertise is applied to the review process to facilitate funding of quality AR research.

Coordinators: NIH, DVA, FDA

Timeline: Begin in one to two years

(73) TOP PRIORITY ACTION ITEM.—Provide 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. Examples include tools such as microbial genome sequences, information on comparative genomics, DNA chip technology, and informatics.

Coordinator: NIH; Collaborators: DOD, USDA, FDA

Timeline: Initiated

(74) Encourage sharing of AR data between industry and the research community.

Coordinator: NIH; Collaborators: DOD, USDA, FDA

Timeline: Begin in three to five years

2. Goal.—Develop a critical mass of researchers in AR

a. Action Items

(75) Bring new researchers into the field, by utilizing appropriate strategies such as training and research opportunities.

Coordinator: NIH; Collaborators: CDC, FDA, USDA, DOD, DVA

Timeline: Initiated

(76) Organize conferences that address research issues relating to AR.

Coordinator: NIH; Collaborators: CDC, USDA, FDA, DVA, DOD, AHRQ

Timeline: Initiated

C. Issue.—Special efforts are needed to translate research findings into medically useful products for human and veterinary use, such as novel antimicrobial therapeutics, diagnostic tests, vaccines and other tools for preventing AR emergence and spread.

1. Goal.—Address the governmental role in translating novel ideas into new clinically relevant products, focusing on gaps not filled by pharmaceutical industry and other non-government groups

a. Action Items

(77) Explore the need to encourage preclinical studies on the toxicology, pharmacokinetics, and pharmacodynamics of novel therapeutic agents for the treatment of multi-drug-resistant pathogens and facilitate the transition of potential products from preclinical to clinical studies leading to development by industry of novel therapeutic agents.

Coordinator: NIH; Collaborators: DOD, DVA, FDA, USDA

Timeline: Begin within one to two years

(78) TOP PRIORITY ACTION ITEM.—Develop a human clinical trials network, involving medical research centers and health-care institutions, to coordinate and conduct clinical trials addressing AR issues that are difficult to resolve in industry-sponsored studies, including:

—Novel therapies

—Existing antimicrobials administered in treatment regimens and combinations that may not be included in approved indications and dosing schedules

—Other products and practices relevant to the control and treatment of antimicrobial-resistant pathogens including devices, diagnostics, disinfectants, etc.

Coordinator: NIH; Collaborators: CDC, DVA, DOD, FDA

Timeline: Begin within one to two years

2. Goal.—Develop rapid, inexpensive, point-of-care diagnostic methods to facilitate judicious use of antimicrobials

a. Action Items

(79) TOP PRIORITY ACTION ITEM.—Identify, develop, test, and evaluate the impact of new rapid diagnostic methods. Such methods should include:

—Tests for resistance genes that are associated with drug resistance including non-culture specimens

—Rapid point-of-contact diagnostics for patients with viral respiratory infections and clinical syndromes such as otitis media, sinusitis, and pneumonia

—Rapid methods for detecting drug resistance among fungi, parasites, and mycobacteria

Coordinators: NIH, FDA; Collaborators: DOD, USDA, CDC, AHRQ, DVA
Timeline: Initiated

3. Goal.—Develop new products and strategies to prevent and treat colonization and infection with resistant organisms in patients, prevent transmission of resistant infections in the community, and prevent AR emergence

a. Action Items

(80) Encourage basic research in support of the development and appropriate use of vaccines. Vaccines are needed to:

—Prevent prevalent viral infections that predispose to bacterial infection or are mistaken for bacterial infections and are inappropriately treated with antibacterial agents (e.g., influenza virus)

—Prevent colonization, infection, and transmission of resistant organisms such as enterococci and staphylococci

—Prevent common bacterial infections (*S. pneumoniae*, nontypable *Haemophilus influenzae*) to reduce antibacterial use

Coordinators: NIH, FDA; Collaborators: CDC, DOD, DVA, USDA
Timeline: Initiated

(81) Encourage basic research in support of novel approaches to preventing or treating infections with resistant organisms. Novel approaches may include:

—Bacteriophage therapy

—Active (vaccine) and passive (antibody, hyperimmune globulin) immunization

—Host-derived antimicrobial agents

—Non-antibiotic antimicrobials with broad or nonspecific anti-infective activities (e.g., defending and non-specific immunostimulants)

—Microbial ecology

Coordinator: NIH; Collaborators: DOD, DVA, FDA, USDA, CDC
Timeline: Initiated

IV. Product Development

INTRODUCTION

New products are not being developed rapidly enough to address increasing microbial resistance. Needed products include not only new classes of antimicrobials able to kill otherwise resistant organisms, but also vaccines and anti-infective devices with the potential to prevent infections as well as improved diagnostic tools to aid in appropriate use of therapeutics. With respect to antimicrobial drugs, each new agent represents a major investment by a pharmaceutical company, which must shepherd the product through pre-clinical studies and clinical testing, followed by large and expensive clinical trials. Pharmaceutical companies may be reluctant to invest extensive resources in the development of drugs, such as those antimicrobials targeted to resistant organisms, which are often given for short time periods to small numbers of patients. Manufacturers are similarly concerned that judicious use policies may limit sales and profits. On the other hand, when a drug is used widely, allowing recovery of costs and profitability, resistance may develop more rapidly and shorten the useful life of the drug.

Due to these economic realities—as well as to scientific limitations and a lag in the perception of a need for new agents—very few novel antimicrobial drugs have reached the market for several years. A major aim of this interagency effort is to work with the private sector to explore and test innovative ways to address these issues. Approaches to be considered include providing incentives (and overcoming disincentives) to promote and assist the development of important products to address AR.

Product development is also a very important issue for veterinary medicine and agriculture. U.S. agencies and private sector partners must intensify efforts to en-

courage 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. Again, increased attention also needs to be turned to strategies to prevent infections of animals (e.g., vaccines, changes in husbandry) and to the improved use of existing and new products.

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

1. Goal.—Provide a systematic assessment of the current status and projected future needs for AR products

a. Action Items

(82) TOP PRIORITY ACTION ITEM.—Create an Interagency AR Product Development Working Group to identify and publicize priority public health needs for new AR products (e.g., innovative drugs, targeted spectrum antibiotics, point-of-care diagnostics, vaccines, anti-infective medical devices, and biologics). The Working Group will:

—Obtain input from stakeholders, including pharmaceutical companies, physicians, epidemiologists, and microbiologists, on which products are needed

—Include experts in the non-medical disciplines (e.g., engineering and remote sensing, etc.)

—Model future resistance trends, product needs, and potential markets, taking into account AR surveillance data and numbers of patients at high risk of developing drug resistant infections (e.g., increases in immunocompromised patients)

—Evaluate current market incentives for the development of priority AR products (Related Action Item: Product Development #83)

—Reassess AR product priorities on a regular basis

Coordinators: FDA, USDA, CDC; Collaborators: NIH, AHRQ

Timeline: Begin within one to two years

B. Issue.—Existing market incentives and regulatory processes may be insufficient to stimulate the development of certain priority AR products while fostering their appropriate use.

1. Goal.—Investigate and act upon potential approaches for stimulating and speeding the entire AR product development process, from drug discovery through licensing

a. Action Items

(83) TOP PRIORITY ACTION ITEM.—In consultation with stakeholders, economic consultants, and the AR Product Development Working Group (Related Action Item: Product Development #82), identify ways (e.g. financial and/or other incentives or investments) to promote the development and/or judicious use of priority AR products for which market incentives are inadequate.

—All such proposals will require careful economic modeling and analysis. New approaches should be used on a trial basis, for limited time periods, and the costs and benefits of incentives used in these pilot programs should be monitored to assess the return on the public investment.

Coordinators: FDA, CDC; Collaborators: USDA, AHRQ

Timeline: Begin within three to five years

(84) In consultation with academia and industry, consider whether government has a constructive role to play in discovery of drugs and other products targeted to address areas where market incentives are limited and unmet needs exist (e.g., novel antimicrobial drugs targeted to specific resistant organisms). (Related Action Items: Research Issue B)

—Such a role could utilize intramural, extramural or partnership type mechanisms. Products developed under such mechanisms could be licensed commercially either with or without specific stipulations regarding use.

Coordinator: NIH; Collaborators: USDA, FDA, CDC

Timeline: Begin within three to five years

(85) Continue ongoing approaches that streamline the regulatory process, including clinical trials, to help bring AR products (including drugs, vaccines, diagnostics and devices) to market as efficiently and rapidly as possible, while still assuring their safety and efficacy.

—This might involve use of an expedited process in which certain drugs are considered for approval after the completion of Phase 2 clinical trials, in accordance with Subpart E of the Investigational New Drug (IND) regulations. It might also involve defining new surrogate endpoints that indicate a meaningful response benefit over existing treatments for particular infections (e.g., CD4

counts as surrogate markers in the treatment of HIV/AIDS), in accordance with Subpart H of New Drug Application (NDA) regulations.

—In the case of approvals for anti-infective medical devices, AR concerns will be addressed during the pre-and post-licensing review, to ensure that these products reduce infection without engendering significant resistance.

Coordinator: FDA; Collaborator: USDA

Timeline: Initiated

C. Issue.—The development and use of antimicrobial drugs and related products in agriculture should be optimized to reduce the transfer of resistance to pathogens that can infect humans.

1. Goal.—Promote the development and use of new and existing AR products that reduce the risk of the development and transfer of antimicrobial resistance to humans, as well as new approaches to reducing agricultural use of antimicrobial drugs

a. Action Items

(86) In consultation with stakeholders and expert consultants, identify ways to promote the development of new and alternative veterinary treatments and the improved use of existing therapies that are unlikely to stimulate resistance to drugs in clinical medicine. This action will include consideration of the incentives and approaches listed in Action Item #31 (Prevention and Control), and the implementation of pilot programs to stimulate the development of priority products that meet critical animal health needs.

—Approaches for evaluation should include ways to improve and/or reduce the use of specific antimicrobial drugs, as well as ways to prevent infection, such as vaccines, changes in animal husbandry, and the use of competitive exclusion products (e.g., treatments that affect the intestinal flora of food animals).

Coordinators: FDA, USDA, NIH, CDC, EPA

Timeline: Begin within three to five years

(87) Streamline the regulatory and approval process for veterinary and agricultural antimicrobial drugs and related products that are unlikely to result in transfer of antimicrobial resistance to humans.

Coordinators: FDA, EPA, USDA

Timeline: Begin within three to five years

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Senator COCHRAN. Dr. Koplan, sometimes health scares are sensationalized. Some people may tend to overstate concerns to get the attention of the public and—for no real private or selfish reason. I think in the use of some words for example, we tend to have our attention riveted to a health problem like the word "outbreak."

I remember when I first heard about an outbreak when I got to Congress, I thought, "My goodness, that has to be millions of people involved in this outbreak." But I found out there were only a few.

An outbreak is a word of art and does not really describe the total numbers of people who are involved in a disease problem or threat to human health.

But is this a problem that you would consider to be overstated or exaggerated or is this the real thing? The words that are being used today seem to have an alarmist tone to them, but is that justified? Do we have a serious situation here that requires the immediate and urgent action of these Federal agencies, and State governments, and other health professionals and researchers?

Dr. KOPLAN. It is the real thing. And I think your words are well chosen. It requires immediate and urgent action.

It is—these are diseases that we are all prey to at some time or other, our children, our parents, our neighbors—infectious diseases that—organisms that cause infectious diseases are all around us and they are not going away.

And this pattern of resistance has been both a repeated one and one that is getting worse for a number of organisms. And these are the organisms that if we are hospitalized or we get sick, a wide range of illnesses can befall us.

And we want antibiotics that work when we or our friends or relatives get sick. And we are in a situation where the armamentarium that we can bring to bear on it is severely compromised and will continue to be unless we take aggressive, intensive and immediate steps to address it.

Senator COCHRAN. I know you have mentioned that penicillin was discovered—what, 50 years ago, more or less——

Dr. KOPLAN. Yes.

Senator COCHRAN [continuing]. And we are just now hearing more and more about the resistance problem. Is this a problem that has been growing in seriousness for a good while now or is it—why has it just seemed to have come on us all of a sudden and affects a lot more than just penicillin?

Dr. KOPLAN. Well, I think to some extent, we probably have been complacent at certain times, thinking we had a pretty good set of antibiotics to use and that the infectious disease era was behind us.

And our complacency has caught up with us, that we always need new agents, antimicrobial agents, but we also need to prolong the use, as Dr. Henney said, of the ones we have got. And the life span of some of these antimicrobials has decreased over ones that we have used for longer period of time.

The organisms are in competition with us and they may not be able to do some of the things we do, but they can do other things much better, and one of them is adapt to the environment they are in and produce resistance to the antibiotics that we provide.

So it is not a—it has been a problem since the day Sir Alexander Florey discovered penicillin. The next day the bugs were getting together to figure out how they could combat it. But it has become an increasing problem with more complicated organisms, complicated medical procedures and an environment in which these antimicrobials have not been used as responsibly as they might.

Senator COCHRAN. Now, Dr. Henney, you mentioned the action you took just yesterday to require physicians to give information to patients and to include the warnings in effect about taking antibiotics as directed and only when necessary.

Why has this been so late in coming since the problem has been emerging over time now? And it seems that the medical community ought to have been notified by Federal agencies of this kind of thing long before now.

Dr. HENNEY. Well, Mr. Chairman, I think that there has always been information on the label that clearly articulates what a product's indications or contra-indications might be. I think what we are trying to do with this proposed rule is to underscore those kind of messages, particularly in the antibiotic area, where judicious use is so important, and reminding physicians every time they use one of these antibiotics how important these products are and that resistance could occur.

So in nearly every section, now, in the label, we will underscore information to the physician. Right at the start of the product label, there will be statements to this effect in the clinical pharmacology section. Again, the underscoring is to identify and determine susceptibility to the different antibiotics prior to treating or as soon as possible.

Underscoring in the indications and usage sections; in the precaution sections, all throughout the label, this message is that these products must be used quite judiciously if they are going to be effective for the patient that is in front of you, but also for all of the other patients that you might treat into the future for whom you have a responsibility to use these products wisely.

Senator COCHRAN. There has been a tremendous increase in product advertising by pharmaceutical companies, drugs by name, trade names, battling for the attention of the consuming public—what impact, if any, has that had?

I will ask Dr. Henney and Dr. Koplan both this question. Can it have a positive influence, or has it had a negative influence? Is it part of the problem in this area?

Dr. HENNEY. Well, we have really seen an increase of direct consumer advertising in the past 3 years. And I think there was actually even an article in the New York Times on this matter this morning about how direct consumer advertising may be influencing what patients might know about products and what the practices of industry are in terms of using this vehicle to market their products.

I think that we see two things when the advertising is full and complete, when there is a balanced approach to providing both benefits and risk. It makes consumers more aware of products, but it also sometimes serves as a reminder that they are supposed to be taking a drug that they may have put to the side. There are some real positives to this.

On the other hand, we hear a lot of expression both from the medical community and somewhat from the lay public that they feel bombarded with these advertisements in terms of sorting out what it all means.

We have actually taken several actions against companies where we have found the advertising to be out of bounds in terms of expressing more of the benefits and a limited amount of the risks that might be involved with products that are advertised.

It is our intention to look specifically at the direct to consumer advertising issue as it relates to antimicrobials because of our commitment to this whole issue of resistance. And that will be undertaken in our center on drugs.

Senator COCHRAN. Dr. Koplan, what is your reaction to that question and that problem?

Dr. KOPLAN. This is an area of Dr. Henney's expertise in particular. But I would say that the message we are trying to get out, and sometimes it may be in conflict with this direct marketing, is to consumers that antibiotics are not always in their best interest and that there are a large number of infectious diseases they may have and which antibiotics are either of no benefit or potentially harmful to them and that they need to consider that when they are meeting with their doctor.

And we have programs in partnership with the American Academy of Pediatrics and American Academy of Family Physicians to encourage placement of information in doctors' waiting rooms and in other settings for consumers to begin to get a better appreciation that antibiotics are great when needed, but they are not always needed.

If I could correct a previous statement I made?

Senator COCHRAN. Yes.

Dr. KOPLAN. I do not want to leave an inaccuracy in the record, but it was Professor Fleming that invented penicillin. I do not want to be historically incorrect here. Thanks.

Senator COCHRAN. You mentioned—both of you mentioned the action plan that involves your agencies and also the NIH, is there a request pending or will—would it be submitted to the appropriations committee for additional funding to carry out that plan? What in your judgment would be the proper level of funding for Federal agency action in this area?

Dr. HENNEY. Mr. Chairman, with respect to the public health service plan that has been developed, I think that what the agencies went through was really outlining these specific actions that we need to take.

We will now go back and look at those plans and develop a budget and make sure that that is reflected in future budget requests. But it was really the intention, in terms of the first effort of this plan, to look at the domestic side of this issue and what should be done.

I think the next step would also be to look internationally at what we would need to do, but I am sure that we will all be coming forward, the many agencies that are involved here, to tell you what it will take to accomplish this on the part of the Federal agencies involved.

Senator COCHRAN. Among the specific actions in the plan, are there any areas that have greater priority than any others, or is that something that you are going to come up with later in—in your request for funding?

Dr. HENNEY. Well, there was great intention as the different agencies crafted this plan to make sure that they gave emphasis to those things where they thought that they could make the greatest impact and difference. So of the 87 action items that are listed in that plan, I believe 11 are listed as the top priority.

Senator COCHRAN. OK. Dr. Koplan, what is, in your view, a program, an example of a program that you have already implemented that has worked in this area? So are there any lessons that have been learned from previous initiatives that have been implemented by the Centers for Disease Control?

Dr. KOPLAN. Thank you. There are some model programs that show great promise. One specific example is in the State of Iowa where officials along with colleagues in Nebraska and South Dakota, the Indian Health Service and CDC recognized a marked increase in vancomycin-resistant enterococci, a bacteria that can wreak havoc in a number of bodily systems and can be quite fatal, particularly amongst hospitalized patients and residents of long-term care facilities. Through this educational program and careful surveillance they sought to reduce the amount of this infection.

Over the course of a couple of years, they were able to see a fairly rapid improvement and a decrease in the rates of resistance within an area right around Sioux City, Iowa, but covering three States.

This gives us optimism that even with tools we have in hand now, we can turn around some of these patterns and trends of resistance.

Senator COCHRAN. We also have what is called an Emerging Infections Plan. How does the action plan relate to CDC's Emerging Infections Plan?

Dr. KOPLAN. I think they dovetail very nicely. The plan for antibiotic resistance provides more specific steps that need to be taken in this area and is really the next step for us of how we then move ahead.

The Emerging Infections Plan is a 5-year plan of which about 40 percent of the action items in that are underway. And we hope to add another 40 percent in the next year.

Senator COCHRAN. Dr. Henney, what is the most immediate area where the Food and Drug Administration and the pharmaceutical industry can work together to address the problem of resistance?

Dr. HENNEY. Well, I would say in two or three areas, Mr. Chairman.

Clearly, in the whole area of product development and whether that is an antimicrobial, whether that is a vaccine or whether it is a diagnostic tool. I think the early consultation with the agency about plans underway so that we can facilitate and make efficient our review of a new application certainly is one area where we need to work effectively with industry and are doing so.

I think second is clearly the implementation of this in terms of labeling. And I think, third, we need to sit down both with industry and others and look at the balance that we need in terms of recognizing how much of an industrial investment it takes to develop a new product that we might then limit in terms of our recommendation for use.

So we do need to have discussions as to incentive programs that might be developed to recognize that. That may require legislation and, if so, we will be back to you to discuss that.

I think we clearly have incentive programs in other areas, orphan drugs, pediatrics and the like, and what we will be discussing internally and certainly with industry and others is, "Do we have an appropriate tool now that could be applied that could be effective in this area in this balancing act, or do we need another?" And if so, I think we need to come back to you if we need that kind of different or a more unusual kind of approach.

Senator COCHRAN. Let me thank you both again for being here today to discuss this important issue. We appreciate the time you have spent in preparing for the hearing and the quality of the statements you have made this morning.

It gives us a big challenge, I think, to work with you in a supportive way to try to make sure that the funds are there as you need them to deal with this very serious problem, not just a United States problem, but as you both pointed out a worldwide problem that needs our immediate and best efforts.

Thank you very much.

Dr. KOPLAN. Thank you.

Dr. HENNEY. Thank you.

STATEMENT OF F.E. "ED" THOMPSON, M.D., STATE HEALTH OFFICER, STATE OF MISSISSIPPI

Senator COCHRAN. Our next panel of witnesses I have already identified. I hope you will all come forward and take places at the witness table.

Dr. Ed Thompson, who is the State Health Officer at the Mississippi Department of Health; Dr. Martin Rosenberg, who is Senior Vice President and Director of Anti-Infectives with SmithKline Beecham Pharmaceuticals; Dr. Merle Sande, Professor and Chairman of the Department of Medicine at the University of Utah School of Medicine; Dr. Alice M. Clark, who is Director of the National Center for the Development of Natural Products at the University of Mississippi; and Dr. Mark L. Nelson, who is Senior Director of Chemistry at Paratek Pharmaceuticals in Boston, Massachusetts.

Thank you very much for being here and for helping us with this hearing. We have copies of your statements, which will be printed in the record in their entirety and we invite you to proceed to discuss your thoughts about this subject in a summary fashion and in whatever way you think would be helpful to our committee.

Let us start with Dr. Thompson. Welcome. You may proceed.

Dr. THOMPSON. Thank you, Senator. Mr. Chairman, members of the staff, I am Dr. Ed Thompson, State Health Officer of Mississippi. I am representing ASTHO, the Association of State and Territorial Health Officials.

From your statement, Senator, earlier and from those of the previous witnesses and from seeing who is in this room, I realize today that I am doing what we in Mississippi call preaching to the choir. But I will try to bring the perspective of State health departments on this important issue of antimicrobial resistance.

We are greatly concerned about the specter of increasing antimicrobial resistance. Our parents were the last generation to grow up in the pre-antibiotic era.

Now, largely due to our own profligate misuse of these wonder drugs, we face the real probability that our children may live in a post-antibiotic era, in which infectious diseases once again cannot be cured.

This is a textbook of pediatric medicine. It belonged to my grandfather. He, like me, was a physician, but he practiced before antibiotics were available.

If you read the treatments in this 1914 medical book, you realize how helpless doctors once were against infectious diseases. There was little they had to offer their patients but to—to wait, to hope and too often to watch them die.

As a physician, I never want to go back to the helplessness that underlies so much of this and other medical books of that era.

Even rural States are well aware of the threat of antimicrobial resistance. In 1976, multi-drug resistant tuberculosis was diagnosed in an 18-year-old high school student in Alcorn County, in rural north Mississippi.

Testing of his immediate contacts revealed an infection rate of 50 to 80 percent. Subsequent testing of his entire school found an infection rate of 21 percent.

Within a year, two of his classmates had developed multi-drug resistant active tuberculosis. In all, between 1965 and 1977, 23 cases of drug-resistant TB were identified in the county.

The outbreak demonstrated for the first time that multi-drug-resistant tuberculosis could be transmitted from one person to another. The outbreak was identified and investigated by the State Department of Health with assistance from the Centers for Disease Control.

It illustrates clearly the integral role that State public health agencies play in addressing any emerging public health threat.

Despite the important contributions of Federal agencies, the initial detection, response and much of the control effort will depend on State and local public health departments.

Recently, a survey of Mississippi clinical laboratories found 40 percent or more of Staphylococcus aureus isolates to have some level of penicillin resistance.

We also found that many labs in the State were not performing resistance testing adequate to detect such pathogens. As noted in the 1999 GAO report on Emerging Infectious Diseases, this is the case in many States.

State health departments have a crucial role in two major components of a national response to the threat of emerging antimicrobial resistance. The detection of resistant organisms and the prevention of their emergence.

State health departments will play a pivotal role in detecting the development of resistant organisms. State laws and regulations requiring the reporting of disease are the basis of all disease surveillance. These laws and regulations can be modified by States to require reporting of resistant organisms.

Nebraska is one good example of States in which this is already taking place. And at least 26 States have requirements for the reporting of one or more forms of antimicrobial resistance.

State public health laboratories are indispensable in detecting antimicrobial resistance. Our public health laboratories must maintain and expand their capacity to test for drug resistance in organisms of public health importance, especially those not addressed by routine hospital and commercial laboratory work.

Preventing the emergence of new resistant organisms will require changing patterns of antibiotic use by health-care providers and the public. And the center of this effort will be education of both providers and patients.

Most State and local health departments have relationships and communication channels with their medical communities that afford an excellent venue for ongoing provider education. While national level action, as described previously, will be necessary, State-based efforts will be the key to success.

Maryland's "Use Antibiotics Wisely" campaign in the Baltimore area is an excellent example of this kind of effort.

To fulfill our responsibility in detecting and preventing the emergence of drug-resistant microorganisms, States will need help. Extending surveillance to include antimicrobial resistance will require increased epidemiology staffing and laboratory capacity in the States.

States cannot bear the cost of this alone. Funding from the Federal level is needed as well. ASTHO commends this committee for beginning to consider that need.

ASTHO particularly supports two significant national efforts to address antimicrobial resistance. The first of these is the Public Health Service's draft, "Public Health Action Plan to Combat Antimicrobial Resistance."

This plan is a sound approach, providing a framework for addressing all aspects of the issue, its implementation—and funding—should be a national public health priority.

The second is legislation introduced by Senators Frist and Kennedy. Their bill, S. 2731, includes Federal actions to address antimicrobial resistance, as well as other urgent public health threats.

Importantly, it also authorizes funding to respond to these threats. Its provisions can contribute to restoring some of the public health infrastructure described by the Institute of Medicine as in disarray over a decade ago and still not repaired.

PREPARED STATEMENT

Again, ASTHO commends this committee for moving to address this important public health issue. And for myself, speaking as a doctor and for other doctors like me, I ask you, Senator, please do not send us back to the bed sides of our patients with nothing more to offer than our grandfathers had.

Senator COCHRAN. Thank you, Dr. Thompson, for your excellent statement. The illustration that you provide us is very impressive. We do not want to go back to that earlier generation.

[The statement follows:]

PREPARED STATEMENT OF ED THOMPSON

Mr. Chairman, and members of the committee, I am Dr. Ed Thompson, State Health Officer of Mississippi, and past president and current member of the Executive Committee of ASTHO, the Association of State and Territorial Health Officials. I will speak today to the role of states in addressing the challenge of antimicrobial resistance.

ASTHO, and the state health officials who make it up, are gravely concerned about the specter of increasing antimicrobial resistance. While advances in basic sanitation and the advent and use of effective vaccines against a number disease agents are the backbone of most of our progress in combating infectious disease, the development of effective antibiotic agents made possible the control of such diseases as TB and Syphilis, and rendered such former scourges as pneumonia and wound infection treatable instead of fatal. Our parents were the last generation to grow up in the pre-antibiotic era. Now, largely due to our own profligate use of these "wonder drugs," we face the real possibility that our children may live in a " post-antibiotic" era, in which infectious diseases can no longer be cured.

The book on the table in front of me is a textbook of pediatric medicine. It belonged to my grandfather. Like me, he was a physician, but he practiced before antibiotics were available. As you read the "treatments" described in this 1904 medical book, you realize how nearly helpless doctors were when their patients became ill with infectious diseases. The only thing they could really do was wait, hope, and too often, watch them die. As a physician, I never want to go back to the helplessness that underlies so much of this and other medical books of that era.

STATE PERSPECTIVES

Even rural states are well aware of the threat of antimicrobial resistance.

In 1976, Tuberculosis was diagnosed in an 18 year-old high school student in rural north Mississippi. TB bacilli isolated from the student were resistant to multiple antimicrobial agents. The student's father had been diagnosed with multi-drug resistant TB 12 years earlier, and had stabilized after erratic treatment. His mother

had died of TB 10 years previously; her organisms were not tested for antimicrobial sensitivity. The father's drugresistant TB was found to have re-activated.

Testing of the student's close contacts on the football and baseball teams and in his classes found an infection rate of 50–80 percent. Subsequent testing of the entire school revealed a 21 percent infection rate. Within a year, two of his fellow students developed multidrug resistant TB. In all, from 1965 to 1977, 23 cases of drug-resistant TB were identified in the county. Prior to this occurrence, many experts believed that drug-resistant TB could not be transmitted. This outbreak demonstrated for the first time that multidrug-resistant TB could be spread from one person to another. The outbreak was identified and investigated by the Mississippi State Department of Health, with assistance from the Centers for Disease Control. It clearly illustrates the integral and vital role of state and local public health departments in dealing with any emerging public health threat. Despite the critical and valuable activities of Federal agencies, detection and first response, as well as much of the control effort, will necessarily depend on state and local health departments.

The threat is not only real, it is imminent. A 1995–1996 survey of Mississippi clinical laboratories found 40 percent or more of *Staphylococcus aureus* isolates from six major hospitals covering all parts of the state to have intermediate to high level of penicillin resistance. We also found small but disturbing numbers of isolates of vancomycin-resistant enterococci throughout the state. We also found that many labs in the state were not performing antibiotic sensitivity testing adequate to detect such pathogens. As noted in the 1999 GAO report on Emerging Infectious Disease, this is the case in many states.

States have direct experience with another aspect of emerging antimicrobial resistance: its cost. In 1990, Mississippi's public health clinics treated roughly 14,000 cases of Gonorrhea. The drugs used were oral ampicillin and probenicid. The cost of treatment was $1 per patient, resulting in a total expenditure of $14,000 annually. By 1991, due to the emergence of increasing penicillin resistance in our gonococcal isolates, we began using ciprofloxacin as our standard therapy. At a cost of $2 per patient, it cost us a total of $24,000 to treat that year's 12,000 gonorrhea cases.

Even more dramatic is the effect of drug resistance on the cost of TB therapy. In 1983 a Mississippi patient with multidrug resistant TB had to be transported to National Jewish Hospital in Denver, at that time the only institution in the country able to treat his disease. The total cost of his treatment, at state expense, was $286,000, over a quarter of our total inpatient TB budget for that year.

STATE FUNCTIONS AND CAPACITIES

Two major components of a national response to the threat of emerging antimicrobial resistance in which states have a crucial role are the detection of resistant organisms and the prevention of their emergence.

In detecting the development of resistant organism, the traditional role of state health departments in disease surveillance positions us perfectly to play a pivotal role. State laws and regulations requiring the reporting of disease are the basis of all such surveillance. These laws can be modified as necessary to require reporting of resistant organisms. Nebraska is but one example of states in which this is already taking place. At least 26 states have requirements for the reporting of one or more forms of antimicrobial resistance to the state health department. The relationships developed by state health departments with physicians, infection control practitioners, laboratories, and hospitals in their states around general disease surveillance will facilitate expansion of surveillance for resistant organisms.

A key element in state-based national surveillance for antimicrobial resistance is coordination and standardization of reporting requirements. This responsibility falls to CDC and ASTHO's affiliate organization, The Council of State and Territorial Epidemiologists (CSTE).

State public health laboratories are an indispensable component of a national approach to detecting antimicrobial resistance. Already a source of reference laboratory services in our states, our public health laboratories must maintain and expand their capacity to test for drug resistance in organisms of public health importance. This is particularly important for organism or drugs not routinely addressed by hospital and commercial laboratories. Here, a key participant in all planning is another ASTHO affiliate organization, the Association of Public Health Laboratories (APHL).

Preventing the emergence of new resistant organisms will depend heavily on changing patterns of antibiotic use by health care providers and the public. The center of this effort will be education, of both providers and patients.

Changes in antibiotic prescribing patterns can never be expected to occur unless public expectations about antibiotics are changed. Efforts must focus on educating

the public about what antibiotics cannot treat, to reduce demand for antibiotic prescriptions for viral or other non-bacterial illnesses. Equally important, they must stress the proper use of antibiotics by patients when they are properly prescribed: take the whole bottle, don't "share" with family and friends, and don't self treat.

State and local health departments can help in these educational efforts, and can initiate many of their own. A coordinated national educational campaign, however, is even more critical.

It is in the area of provider education that state health departments can be the most important contributors. Most state and local health departments have relationships and communication channels with their medical communities that can afford the best venue for ongoing provider education. In Mississippi, although most physicians subscribe to a number of different publications, the only one that uniformly goes to every physician licensed to practice in the state is the monthly "Mississippi Morbidity Report," a newsletter published by the State Department of Health and well suited to disseminating information about antimicrobial resistance and its prevention. Most state health agencies have similar publications. Other key state-level players are state medical associations, medical specialty societies, and pharmacists' associations. While national level efforts will also be necessary, these state-based efforts will be the key to success. Maryland's "Use Antibiotics Wisely" program in the Baltimore area is an excellent example of this kind of effort.

FUTURE NEEDS—THE NEXT STEPS

Despite the vital role states play in detecting and preventing the emergence of drug resistant microorganisms, and our willingness to fulfill that responsibility, we will need help. Extending surveillance to include antimicrobial resistance is clearly within the power and ability of states to accomplish, but it will require both increased epidemiology staffing and laboratory capacity in the states. States cannot bear the cost of this alone. Funding from the federal level is needed as well. ASTHO commends this committee for beginning to consider that need.

ASTHO particularly supports two significant national efforts to address antimicrobial resistance as a public health threat. The first of these is the CDC's draft "Public Health Action Plan to Combat Antimicrobial Resistance." This plan is a sound approach, providing a framework for addressing of the issue. It incorporates the role of State Health Departments as I have described them above. Its implementation—and funding should be a national public health priority.

The second is the legislation placed before the Senate by Senators Frist and Kennedy. Their bill, S. 2731, includes federal actions to address antimicrobial resistance as well as other urgent public health threats. Importantly, it also authorizes funding to respond to those threats. Its provisions contribute to restoring some of the public health infrastructure described by the Institute of Medicine as "in disarray" over a decade ago and still not repaired.

Again, ASTHO commends this committee for moving to address this critical issue. And for myself, speaking as a doctor, and for other doctors like me, I ask you, please: don't send us back to the bedsides of our patients with no more to offer than our grandfathers had.

STATEMENT OF MARTIN ROSENBERG, Ph.D., SENIOR VICE PRESIDENT AND DIRECTOR OF ANTI-INFECTIVES, SMITHKLINE BEECHAM PHARMACEUTICALS

Senator COCHRAN. Dr. Martin Rosenberg is the senior vice president and director of SmithKline Beecham Pharmaceuticals. Dr. Rosenberg.

Dr. ROSENBERG. Yes.

Senator COCHRAN. You may proceed.

Dr. ROSENBERG. Thank you very much for the invitation to come and present some information on this very important subject.

What I would like to concentrate on, in fact, is the industry response to this issue and, again, perhaps to go back a little bit in time to be able to understand today's response in relationship to what the industry has done previously.

As you indicated before, antibiotic resistance and the discovery of antibiotics have almost come hand in hand from the time when penicillin was first discovered 50 years ago. In that first 25 years,

the industry, of course, continued to identify new compounds and a limited spectrum of compounds that were in fact, the compounds that have been used for the last 50 years to defend us against these micro-organisms.

In the second 25 years of that 50-year period, the industry has been focused on derivatizing these same compounds, making derivatives of these compounds, chemical derivatives such that we now have these semi-synthetic antibiotics, which, in fact, still work against the same targets in the micro-organisms but, of course, what has been achieved is incremental increases in potency and effectiveness, and therefore the industry as it developed these limited set of materials that have basically satisfied the unmet medical needs that we had during the Seventies and Eighties of being able to defend us against micro-organisms, basically felt that the job had been done.

And what had happened during the Eighties is that industry began to turn much of its science to other unmet medical needs. And what we saw certainly in the period of the Eighties was industry start to move its research efforts to some of the—the other diseases that were, of course, important as antibiotic—as antibiotics were solving the unmet medical needs at that time.

I think the awakening really came in the early Nineties. And it really happened—you asked the question before as to kind of how these—how these microbes all of a sudden appeared or was it there all the time, well the resistance was there at low levels all the time.

But it was really in the Nineties that we really began to see maybe because of our surveillance methods became better, but also because the bugs themselves had found solutions over time, which they had cemented into themselves in such a way that it was beginning to be very difficult to go back to non-resistant types of pathogens.

Once these bugs can adapt, these incredible abilities to avoid the limited set of compounds we had—and remember our compounds were always derivatives of derivatives of the same materials, and therefore the mechanisms that they achieved were simply constantly catching up with our ability to destroy these by the advancements we made.

And in that awakening in the early Nineties, I think the industry all of a sudden began to realize that the products that had been developed over the last 30 or 40 years were not sufficient to deal with what could be the problem as it continued to fester.

What happened at that time was very interesting. There was quite a different spectrum of activities in the different industrial components. Some industries continued to downplay antimicrobials and kept their efforts in other areas of unmet medical need, not thinking that the commercial success of these compounds would allow them good return on investment.

Other companies, many of them still retain a watching brief in this area. And a few companies have, in fact, seen that the problem may be getting out of hand enough to start to reinvest in this area.

Now, the problem with the reinvestment is that we had basically run out of ways to discover antibiotics. The way we discovered antibiotics originally was, of course, we grew bacteria on plates, on

petri dishes, and we screened for things that killed them. And that gave us the limited number of compounds that we have today to use against these bugs.

What happened in the Nineties, though, was, in fact, a breakthrough in science, and as usual along with new scientific technology comes this idea, often in industry and academia to spur new avenues of discovery in this area.

And, of course, what we have all heard, we probably have heard this term "genomics" in the—and the information content that one can now obtain from any living organism.

We have heard just recently, of course, about the first mapping of the human genome, but, of course, the same technology has been applied over the last few years to many of the pathogen genomes.

And from this information, from this new genomic information coupled with new chemical technologies, what we now have for the first time probably in decades are new discovery strategies to identify new and novel antibiotic materials that work through novel mechanisms of action, in other words work on systems in the bacteria that were unknown prior to, in fact, the advent of this information.

And it is now that information, which will form the basis of some of the new strategies to develop new antimicrobial agents for the 21st Century.

However there is a problem here. And that problem really extends from the fact that the investments for industry to do this are tremendous, huge investments. The lead time—you asked again about that concern of is this problem now or is it soon to be in the future?

You have to remember that the lead times to do discovery and to commercialize are often a decade of time goes by before you actually get these products to market. And the risks are incredibly high.

And because of that and because of the competition, because of genomic information also leading to new breakthroughs in cancer, and Alzheimer's disease, and all of the other diseases that the pharmaceutical industry can invest in, this area of antimicrobials has to compete with those areas and therefore it has to compete on the commercial basis as to what the industry is willing to invest.

And therefore one of the key requirements will be, of course, that there is a commercially supportive environment that has to be created to be able to take this new information and allow the industry to continue that investment to produce a new wave of antibiotics in the future.

PREPARED STATEMENT

And, of course, as I think Dr. Henney said, that will require very interesting collaborations with government and it will probably require appropriate incentives for people to be able to make these investments at a time when the commercial interests in this is a difficult sale within the pharmaceutical industry.

Senator COCHRAN. Very interesting statement. We appreciate so much your being a part of this panel and giving us this perspective.

[The statement follows:]

PREPARED STATEMENT OF MARTIN ROSENBERG

The occurrence of microbial resistance is predictable, inevitable and can only worsen in the absence of the discovery of new mechanism of action antibiotics.

Bacteria are relentless and highly efficient at evolving and adapting. For each human generation, bacteria undergo 100,000 generations—more than all mankind has undergone. Bacteria can pass resistance to their progeny, as well as to their neighbors, even other species of bacteria. Bacteria utilize a variety of ingenious mechanisms to defeat antibiotics including: modifying the antibiotic to inactivity, pumping them out of the bug, becoming inpenetrable to the drug and by altering or adding gene information such that the target of the antibiotic is ignored.

Antibiotics were first discovered only 50 years ago; however, there has only been one new class of antibiotic developed in the past 25 years. Why has this happened?

The current arsenal of drugs satisfied the medical need until recently. Industry shifted resources to other areas of higher unmet medical need. Basic research funding also shifted to human biology due to new advances in molecular approaches. Moreover, there were no new strategies for discovering antibiotics—efforts remained focused on derivative improvements of current medicines. The shift in scientific emphasis have led to a shortage of scientific expertise in certain areas of microbial research.

But all the news isn't bad. The technical advances of the 1990s, in particular genomics, are revolutionizing our ability to study the very genes that define a living organism. Genomics provides access to the entire genetic dictionary of any biological species—both man and microbe.

For the first time, genomics is unveiling many new potential targets for antibiotic discovery. Our current antibiotics work against only a handful of bacterial targets; fewer than 15. Genomics gives us access to scores of potential new targets for drug discovery. This information also enables us to create tests for rapid diagnosis and improve our surveillance methods for resistant organisms. Thus, our current technology advances will help us achieve the rationalization of antibiotic prescribing practices—that is prescribing the appropriate antibiotic at the right dose and duration for the infection and thereby reduce empirical prescribing. Most importantly, these new technologies provide for the first time in decades, new strategies for discovering novel antibiotics.

However, it must be recognized that application of this research to antibiotic drug discovery and development requires a large investment of resources, long lead times and carries high risks. It is imperative that these research efforts progress in a commercially supportive environment. Investments required to commercialize new antibiotics will only be sustained if regulatory and market forces allow sufficient returns to be achieved relative to other areas of medical need. It is imperative that government and industry work together to identify ways to promote the development and appropriate use of priority anti-infective products for which market incentives are inadequate.

To accomplish this requires effort and resources on the part of governments, academia and industry alike. Significantly reducing the severe medical consequences resulting from the growth of microbial resistance can only be accomplished effectively through collaboration.

STATEMENT OF MERLE A. SANDE, M.D., PROFESSOR AND CHAIRMAN, DEPARTMENT OF MEDICINE, CLARENCE M. AND RUTH N. BIRRER PRESIDENTIAL ENDOWED CHAIR IN INTERNAL MEDICINE, UNIVERSITY OF UTAH SCHOOL OF MEDICINE

Senator COCHRAN. Dr. Merle Sande is Professor and Chairman of the Department of Medicine at the University of Utah School of Medicine.

We will hear from you next, Dr. Sande.

Dr. SANDE. Thank you, Senator. My name is Merle Sande and I guess I am the token clinician on the council.

I have been a primary physician in infectious diseases for the last 35 years. And I will try to give you my perspective on this problem.

In thinking about what happened, I really do not know how we got into this mess. You know, 50 years ago, we were told by astute microbiologists and infectious disease clinicians that this would

happen. They knew then that if we misused and abused antibiotics, their life expectancy would be limited.

And in those days when a physician treated an infection, he made a diagnosis. He isolated the organism and he treated very specifically and very effectively.

These antibiotics were treated like gold and something happened over the last 30 or 40 years that I really do not understand. Somehow, it has become standard of care to treat runny noses and fevers and coughs with antibiotics.

Now, I will bet you if I took a survey in this room today and asked you all if you developed acute bronchitis with a chronic or acute productive cough and green sputum and you went to your physician, what would you expect? And I will bet you that two-thirds of you would say, "I want an antibiotic."

And the facts are they do not work for bronchitis. They have no effect for bronchitis. They do not work at all. But, yet, we have that expectation.

And that today is our dilemma. And what they do do when you treat bronchitis is they create a perfect environment for the development of resistant strains.

So we have seen that—you have all heard this morning that this problem is out of control. Antibiotic use is out of control and the emergence of drug resistance is out of control.

Now, as Marty Rosenberg has said, I think that in the past—and I think your question, Senator, was very astute, why did we not act—we react before?

Well, you know, the drug companies always pulled us out. They always found a new drug—a new drug for a new resistant bug. And I think what—from the discussion that Dr. Rosenberg has given, that I do not think we can expect the drug companies to do that in the future.

I think we have to do it ourselves. Now, I think it is important to remember that every time we use an antibiotic, we create an environment for these resistant drugs to develop.

But there is one other point that has not come out yet this morning and that is if you are on an antibiotic, you present a very fertile home for an already drug-resistant bug that is circulating in our environment.

Now, you asked a question about the pneumococcals. How—why did it take so long? It turns out the pneumococcals took about 30 years to really express high-level penicillin resistance. It took about six to eight mutations, but over this time there now are about 12 clones. We call them the international clones of high-level penicillin resistance.

And they spread in our noses and in our throats on 747's throughout the world. Now, we were very interested in this problem and we felt, well, that must mean that the—that the airport hubs in the big cities would be the place where you would find the antibiotic resistance.

So we actually went to southern Utah to some very small, isolated farming communities to see if those ugly bugs had, in fact, found these isolated farming communities. And sure enough they were there.

Thirty percent of all the pneumococci in those highly isolated communities were now resistant to penicillin and other antibiotics and these were these international clones.

So the environment in those small communities that were predisposed to this colonization was, in fact, as you would expect, high-level antibiotic abuse.

Now, I think as a clinician we have a real problem. And I am scared. There are infections out there that I can no longer treat with antibiotics.

Dr. Henney mentioned the new recent advances in the treatment of what we call VRE, which is vancomycin-resistant enerococci. These drugs are fine but they do not kill the bug.

So if we have infections like on heart valves, with endocarditis by these organisms, we cannot cure them. We have got to cut the valve out in—in order to cure the infection.

We have had to change how we approach acute bacterial meningitis. We now use two drugs rather than one. And we are very concerned that next year we will not have any drugs to use to treat bacterial meningitis.

I personally have seen failures in acute otitis media. I have seen failures in pneumonia with drugs that from the beginning of time—my time, have worked to treat these infections and they no longer work.

So I think your—your comment this morning was very astute. Are we overplaying this problem? I do not think we are overplaying this problem at all.

I think this is an extremely serious problem. And I am scared.

Now, on the good side of this, what is very interesting is that once you take the pressure off, once you reduce the antibiotic arena, these bugs will tend to dry up. They will tend to disappear.

There is no selective advantage for this bacteria to have resistant genes if they do not need them. So if, in fact, we are able to reduce antibiotic use and abuse, change our orientation towards the use of these drugs, I am fairly convinced that we can markedly prolong the life of these drugs.

Now, how do we do this, and how do we approach this? This is a real challenge. There is something about changing physician behavior that has eluded scientists from the beginning of time.

It seems like once we learn something it is very hard for us to unlearn it and change our behavior. But there have been, I think, some really interesting observations. And it seems that it is possible.

There is a wonderful study done in Denver by Ralph Gonzalez who is a professor at the University of Colorado. He used the Kaiser system, 350,000 patients to study ways to influence antibiotic use for the treatment of bronchitis.

So first of all he tried educating the physicians and the healthcare providers. It made no difference at all.

But then he used—CDC devised and designed information packets. And these are very creative. And, in fact, they will say—if I can sort of take some liberty here—that antibiotics can be bad for your health.

And, in fact, if you go to a doctor and insist on an antibiotic for an indication that is not there, in fact, it will do harm because it

will set you up and your children up for colonization of resistant bugs. And then if they get infected with those resistant bugs, they are going to be harder to treat.

Now, approaching the families of this large cluster of patients plus the physicians, they were able to reduce antibiotic use by 40 percent. So it is possible, but I think the key here is to educate the population, educate the patients, educate the families that antibiotic use is, in fact, bad for your health.

And I would like to see a much more aggressive national agenda to achieve this. I would try to use the experience with the anti-tobacco campaigns, because I think this is as serious.

And I would hit the families. And I would hit the schools. And I would let the CDC lead this charge. I think that is a very, very critically important initiative.

Now, I would also encourage the expansion of the current surveillance and intervention methods used by the CDC. Dr. Koplan gave you one example of VRE in Iowa and how effective that has been.

But actually the CDC has been very effective in pilot projects particularly through their hospital infections branch and by using surveillance, giving feedback on the surveillance and then supporting the professionals that are in place with facts that they have been able to change behavior in hospitals and reduce blood-stream infections by 40 percent.

And in some recent studies in ICU's, intensive care units, they have actually, by controlling the use of antibiotics, been able to reduce the drug-resistant bacterial infections by a significant amount.

So I would like to see the CDC projects that have been worked now go national. Let us put them into all the hospitals. And I think this is one to—one way to control in-hospital infections and the emergence of resistance.

Now, let me go back to the drug companies, because I think this is a very complicated interaction, but I think we need the drug companies on our side. I think that the public health message that reducing antibiotic use for indications that are not there is good. And I think that the drug companies in the long term will do better profit-wise if they preserve their drugs for a longer period of time.

Now, maybe we need to give them some relief on patent times, extend the patent times. But to answer your question specifically about patient directed advertising for antibiotics, I think it stinks. I think it is a terrible thing. It is totally going in the wrong direction. So what you are doing with this is you are encouraging antibiotic use, when, in fact, we need to be discouraging antibiotic use.

But I think a partnership between government, academia and the—and the drug industry could work in the right direction if handled in the right way, and I think that is a very important thing to go after.

Now, one of my, I guess, pet peeves in terms of this area is our new medical system of HMO's in which the orientation is rapid fast delivery of medical care, get the patient in, get the patient out, do not spend a lot of money on them, but keep them happy.

Now, when you think about this, what this tends to create is an adversarial relationship with those of us who are trying to control

antibiotic use. It is much easier if you see somebody with a cold—and by the way 53 percent of the time that a patient in this country goes to see a doctor for a cold, they come out with an antibiotic. And it does no good at all.

But it is easier. It is faster. You do not use diagnostic tests, just give them an antibiotic. And that is the most cost-effective way to deliver medical care.

But it is just dead flat wrong. And that is why we got in this trouble. So now I do not know how to do this but I think there needs to be incentives for HMO's to play the game correctly.

I think there need to be incentives whether it is through JCHO or tax breaks or whatever it is for these HMO's to do surveillance in their own organizations and reward the physician for going along with the CDC-approved protocols that use judicious antibiotics.

I think anything else is going to—is going to not work. So I think this is another very important area.

And so finally I think that our future in medical care is going to be focused on the use of computers. There are some wonderful examples where clinical decision support systems have worked to limit antibiotic use, reduce errors, and decrease costs.

And one of the best is actually in Salt Lake City at the LDS Hospital, where they have reduced antibiotic use by 40 percent; and costs and errors by about 50 percent over the last 12 years.

So I think supporting the development of these tools to help young clinicians—now, I am afraid that some of us are too old to respond well to computers, but I think the young physicians will use these computer tools and help guide the use of antibiotics in—in this arena.

So, Senator, I am delighted to be here today. I feel passionately about this, because as a clinician I find myself very concerned that tomorrow I will not have the tools of my trade. I will not be able to treat these severe infections that I have been treating for the last 35 years. And I really worry about my grandkids. So thank you very much.

Senator COCHRAN. Thank you, Dr. Sande, for your very helpful and informative, provocative, interesting presentation to our committee this morning. We appreciate your being here and we think it has been a valuable contribution.

STATEMENT OF ALICE M. CLARK, Ph.D., DIRECTOR, NATIONAL CENTER FOR THE DEVELOPMENT OF NATURAL PRODUCTS, UNIVERSITY OF MISSISSIPPI

Senator COCHRAN. Dr. Alice Clark is Director of the National Center for the Development of Natural Products at the University of Mississippi.

Dr. Clark, we welcome you and encourage you to present your suggestions for dealing with this. You may have to emphasize research coming from where you do.

Dr. CLARK. Thank you. I will. Thank you.

Good morning, Senator Cochran. Thank you for the invitation to be here and to provide input on this important topic.

I am, as the Senator noted, Alice Clark, director of the Natural Products Center at the University of Mississippi. I am also Professor of Pharmacognosy in the School of Pharmacy there.

I will focus my comments today primarily on the role of academic research in addressing the issue of antimicrobial resistance. And I hope to leave you with three major messages: the need for urgent attention to the problem; the need for basic and applied research to discover and develop new drugs to treat resistant pathogens; and the role of natural products in this discovery process.

Antimicrobial resistance is an urgent and massive threat to the health of our citizens. It transcends cultural, economic, ethnic and geographic boundaries. It can and will affect anyone anywhere as we have heard.

We have also heard that we are rapidly approaching a time when infections that were once considered ordinary may become life-threatening because we have no effective therapies for them.

We have heard reference to the development of resistance to vancomycin by enerococcus. This is a potentially deadly combination that raises a fearful question that most people neither want to ask nor hear, "Now, what?"

Many of the pathogens that concern us are presently fortunately familiar primarily to the health-care professionals. We must do whatever is necessary to prevent terms like VRE and MRSA and VISA—when we are not talking about the credit card—from becoming so common in our community that they become household names.

Although we have contributed to the problem, we are not entirely to blame for it. It is important to remember that antimicrobial resistance is also due to evolutionary adaptation by the pathogens, which means that it will likely always exist as it always has existed even in the earliest days of the antibiotic era.

This means that we have to work hard to stay one step ahead of the pathogens. We are now beginning to understand not only the enormous magnitude of the problem, but also importantly what causes resistance at both the molecular and systemic levels, how and where it occurs. This understanding can empower us to do something about the problem.

As a pharmacy educator, teaching antibiotics to senior pharmacy students for 20 years, I have seen the effects of antimicrobial resistance over this time. Unfortunately, I have also known someone whose life was cut short by one of these insidious pathogens that was no longer affected by drugs that we once considered miracle cures.

And this, in spite of the fact, that dozens of new antimicrobial drugs were introduced into the market over the past few decades.

Unfortunately, though, the problem is that less than a handful of these could be considered totally new classes of antimicrobials acting by novel mechanisms. And even more unfortunate and something that should serve as a call to arms for all of us is that resistance is now being reported to many of those few antibiotics that just a few short years ago were considered breakthroughs for their time.

If we are talking about this in the classroom, then this means it is happening in our communities, in our schools, and in our daycares, in our nursing homes and in our hospitals. We must act now to shift the balance of power back in our favor.

Research is needed to find solutions and keep pace with the microorganisms, who clearly consider this a battle for life and death, and we should as well. We simply must find ways to restock our chemotherapeutic arsenal.

Academic researchers clearly have a role in this effort. The frontiers of knowledge are pushed forward everyday by academic researchers throughout this country.

The information that is generated in academic labs will be a major factor in our overall success in turning the tide of antimicrobial resistance. Information regarding everything from understanding the magnitude of the problem, to understanding how it is that microorganisms evade the action of antimicrobial drugs, to identifying new compounds to serve as leads for drug development.

Presently what is often referred to as the pipeline of new drugs in this category is woefully inadequate. And so the question specifically is how and where will the next new leads be discovered.

The category of antimicrobial drugs is dominated by the antibiotics, which is a term that is unfortunately often misused. Antibiotics are by definition derived from natural products.

In fact, most of our current antibiotics had their original derivation from agents discovered from microorganisms that occur commonly in our environment but principally through a process that could best be described as random screening.

With today's technologies and information that search can take place at a scale and with a focus never dreamed of by our scientific forefathers. Nevertheless drug discovery and development by its very nature remains a lengthy, iterative, and expensive process built largely on two fundamental questions: where do we search and how do we go about it?

In one approach, we learn all we can about the pathogen and then find or design something that interferes with a critical process in that organism. Certainly, the advances in genomics that were referred to earlier have made this approach more feasible and productive than could have been dreamed possible even 5 years ago.

But we can also take what exists in the world, the chemistry of nature and identify those substances that control the pathogen and then study how they work. This approach has yielded important successes, obviously in the antibiotics, but also in other therapeutic categories, such as the anticancer drugs taxol and campthothecin. There is every reason to believe that similar successes will result from a systematic effort to identify new natural products that are effective against drug-resistant microbes.

But we must broaden the search beyond the commonly occurring microorganisms of the environment, to include plants, marine life and microorganisms from unusual environments. We have not begun to tap the full potential of nature, which is a vast and virtually unlimited source of novel chemical structures with interesting biological effects.

What will be required to accomplish this? As in any endeavor that threatens the security and well being of our citizens, substantial resources must be directed to the effort immediately.

We must improve the use of existing agents and we must discover new agents. We must also accept the reality that virtually any antimicrobial drug may have only a limited finite life span of

medical utility. Therefore, research and education in anti-infective drug discovery and development are badly needed.

Different strategies must be employed and all of these will be important. There will be no single answer, no magic bullet.

We would no more rely on a single strategy to achieve a military victory than we should to achieve important victories against public health enemies.

The time is now to invest in people, facilities, equipment and collaborative multi-disciplinary partnerships between academia, government and the private sector. An investment now will pay off in the future.

Who is to say that a substantial investment 20 years ago to mount an aggressive, concerted effort to address this problem might not have changed the balance of power, and we might be today talking instead about the remarkable successes that can be achieved through a concerted effort.

PREPARED STATEMENT

I urge each of us to do what we can so that 20 years from now that is the story that can be told. Thank you.

Senator COCHRAN. Thank you, Dr. Clark. A very interesting challenge that you put before us, and observations from your experiences and knowledge and expertise are deeply appreciated and helpful to the committee.

[The statement follows:]

PREPARED STATEMENT OF ALICE M. CLARK

Good morning Senator Cochran, committee members. Thank you for the invitation to be here and to provide input on this important topic.

I am Alice Clark, Director of the National Center for Natural Products Research and Professor of Pharmacognosy in the School of Pharmacy at The University of Mississippi.

I will focus my comments today primarily on the role of academic research in addressing the problem of antimicrobial resistance, and hope to leave you with three messages: the need for urgent attention to this problem, the need for basic and applied research to discover and develop new drugs that will be effective against resistant pathogens, and the role of natural products as potential leads for drug discovery.

As you have already heard from this distinguished panel, antimicrobial resistance is an urgent, massive threat to the health of our citizens, and transcends cultural, economic, ethnic and geographic boundaries—it can and will affect anyone, anywhere.

You have also heard that we are rapidly approaching a time when infections that were once considered ordinary may become life-threatening because there may be no effective therapies for them.

We have helped to create this problem through our own behavior: a combination of the overuse and misuse of antibiotics by the public and healthcare providers, a diminished emphasis on research aimed at understanding, preventing and controlling resistance and a diminished emphasis on the education and training of researchers and healthcare professionals who will be prepared to address this problem, now and in the future.

The rapid development of resistance to vancomycin by *Enterococcus* is a deadly combination of the most commonly acquired hospital infection with the last resort drug—raising the fearful question no one wants to ask or hear—Now what? Many of the pathogens that concern us are, presently, familiar only to the healthcare professional. We must do whatever is necessary to prevent terms like VRE, VISA, and MRSA from becoming so common in the community that they become household names. But, resistant Pnemococcus jumped from virtually nonexistent in the early 80s to as high as 30 percent or more in some parts of the country today.

Although it has been noted that we have contributed to this problem, we are not entirely to blame. It is important to remember that antimicrobial resistance is also

due to evolutionary adaptation by pathogens, which means that there will likely always be the development of resistance, as there always has been. It was known even in the earliest days of the antibiotic era that some strains of bacteria developed resistance. This, in turn, means that we must work hard to stay one step ahead of the pathogens, and this can only be achieved by concerted efforts to keep track and predict trends in antimicrobial resistance and, through basic and applied research, to develop strategies to preempt or answer these threats.

Now, thanks in large part to the efforts of those conducting surveillance and monitoring work, we are beginning to understand not only the enormous magnitude of the problem, but, importantly, what causes resistance at both the molecular and systemic levels. This understanding is the first step in identifying workable solutions—understanding can empower us to do something about the problem. However, understanding, in and of itself, is not enough. We must apply that understanding to developing ways to prevent and control antimicrobial resistance.

As a pharmacy educator, teaching antibiotics to senior Pharmacy students for 20 years, I have seen the effects of antimicrobial resistance development over this time. Unfortunately, I have also, as some of you may have, known of someone whose life was cut short by one of these insidious pathogens that is no longer affected by the drugs we once considered miracle cures—this, in spite of the fact that dozens of new antimicrobials were introduced for clinical use over the past 20 years. In many cases, the principal distinguishing characteristic of a newly introduced antimicrobial was that it was effective against a specific resistant pathogen or overcame a specific type of resistance.

Yet, unfortunately, less than a handful of these could be considered totally new classes of antimicrobials, acting by novel mechanisms. Even more unfortunate, and something that should serve as a clear and loud call to arms for all of us, is that resistance has been reported to many of those few antimicrobials that were once considered breakthroughs.

If we are talking about this in the classroom, then it is happening in our communities, hospitals, daycares, and schools. We must act now to change the course of this battle and shifting the balance of power once again in our favor.

Research is needed to find solutions and keep pace with the microorganisms, who are clearly in a battle for life or death—as we should be. We simply must find ways to restock our chemotherapeutic arsenal—ideally with multiple weapons that target different molecular sites in the pathogens.

I believe there is a role for academic researchers in this war—the frontiers of knowledge are pushed forward every day by academic researchers throughout this country. The information that is generated in academic laboratories will be a major contribution to our overall success in turning the tide of antimicrobial resistance—everything from understanding the magnitude of the problem to understanding the specific mechanisms by which pathogens evade the action of antimicrobial drugs to identifying new leads for drug development.

Presently, what is often referred to as the pipeline of new drugs is woefully inadequate. Specifically, where and how will new leads that can become the next antimicrobial drugs agents be discovered? The category of antimicrobial drugs is dominated by the antibiotics, a term which, unfortunately is often misused, even by professionals. Antibiotics are, by definition, derived from natural products. Most of the current antibiotics were originally derived from microorganisms that occur commonly in the environment, principally through a process that could best be described as random screening.

With today's technologies and information, the search can take place at a scale and with a focus never dreamed of by our scientific forefathers. Nevertheless, drug discovery and development, by its very nature, remains a lengthy, iterative, and expensive process built largely on two fundamental questions: where do we search and how do we go about it?

In one approach we learn all we can about the pathogen, and then find or design something that interferes with a critical process. Certainly, the advancements in genomics make this approach more feasible and productive than was possible even five years ago. The discovery of new, selective molecular targets in resistant pathogens will no doubt lead to advances in the discovery and design on new, effective antimicrobial drugs.

We can also take what exists in the world, the chemistry of nature, and identify those substances that control the pathogen, and then study how they do this—this approach has yielded important successes in other therapeutic categories, such as the anticancer drugs taxol and camptothecin, and there is every reason to believe that similar successes will result from a systematic effort to identify new natural products effective against drug resistant microbes.

But, we must broaden our search to include other organisms, especially plants, marine life, and microorganisms from unusual environments. We've not begun to tap the full potential of nature, which is a vast and virtually unlimited source of novel chemical structures with a variety of biological effects.

It is estimated that there are more than a quarter million species of terrestrial plants on our planet, yet less than 10 percent of these have been investigated in any way, and certainly not for the presence of novel natural products that may become new antibiotic leads. No doubt, similar statistics could be quoted for other natural sources such as marine life and unusual microbes.

What will be required to accomplish this?

As in any endeavor that threatens the security and well-being of our citizens, substantial resources in the form of coordinated effort, creative energy, synergy of effort, information, and funds must be combined and immediately directed to address this threat.

We must improve the use of existing agents and we must discover new agents. We must also accept the reality that virtually any antibiotic may have only a finite lifespan of medical utility. The "antibiotic gap" in new drugs must be filled through basic and applied multidisciplinary research by creative, well-trained scientists from all sectors. Research and education in anti-infective drug discovery and development are badly needed.

Different strategies must be employed, and all will be important; we would no more rely on a single strategy to achieve a military victory than we should to achieve important victories against public health enemies. There will be no single answer, no single strategy, no single hero, no magic bullet; true success will only be achieved through combined efforts.

The time is now to invest in people, facilities, and equipment, in collaborative multidisciplinary strategies that maximize our information and resources, and in creating and sustaining both physical and intellectual enviromnents that foster partnerships between academia, government, and the private sector to develop innovative solutions.

Investment now will pay off in the future.

Who is to say that a substantial investment 20 years ago to mount an aggressive, concerted multidisciplinary effort would not have changed the balance of power and we might be talking today, instead, of the remarkable successes that can be achieved through a rational, planned, and concerted effort. I encourage each of us to do what we can so that 20 years from now, that is the story that can be told.

STATEMENT OF MARK L. NELSON, Ph.D., SENIOR DIRECTOR OF CHEMISTRY, PARATEK PHARMACEUTICALS, INC.

Senator COCHRAN. Dr. Mark Nelson is Senior Director of Chemistry for Paratek Pharmaceuticals in Boston.

Welcome, Dr. Nelson.

Dr. NELSON. Good morning, Senator Cochran.

Senator COCHRAN. You may proceed.

Dr. NELSON. I am Dr. Mark Nelson, senior director of chemistry for Paratek Pharmaceuticals. And we are a startup company that grew out of research that I conducted with Dr. Stuart Levy while at Tufts University School of Medicine in Boston.

Dr. Levy is a world-recognized authority in the area of antibiotic resistance, and was one of the first scientists in the United States to sound the alarm about the threat of the antibiotic resistance crisis.

Paratek, as a small company, is an emerging company dedicated to the discovery of new antibiotics against these resistant bacteria. I would like to speak to you today about the uncertain future of antibiotics against infections common today in the clinics and hospitals and to also explain to you why antibiotics are a natural resource that must be studied, researched and developed.

The development of new antibiotics is extremely important to our national health while also being strategically important to our national defense.

I would also like to describe some of the difficulties of developing new antibiotics and steps that could be taken to ensure a potent arsenal of antibiotics for the future.

Bacteria have been winning the war against antibiotics for some time now, but the issue really became public in 1994 when Newsweek had as its cover story, "Antibiotics, the End of Miracle Drugs," and they also said, "Warning, no longer effective against killer bugs."

It was sometime later, though, that the scientific community declared the antibiotic resistance problem the New Apocalypse.

Both addressed the issues of antibiotics resistance correctly and told the story of the emergence of these superbugs, antibiotic-resistant bacteria.

In our country, we are seeing infections that are resistant to all known antibiotics and are causing alarm within both the scientific and public domains.

In the hospitals, "superbugs," such as vancomycin-resistant enerococci, are increasing in frequency and severity, where if the patient develops these infections and vancomycin does not work, the patient may die.

Other infections such as MRSA, which is an acronym for resistant infection of a Staph, increases the costs of a hospital stay dramatically, where the patient is kept in isolation-type condition and expensive precautions must be taken to stop the spread of this infection.

Earlier, I mentioned that antibiotics are a natural resource, and once they become ineffective against an infection, they are functionally useless. Because of this, we must preserve and protect antibiotics as we would any natural resource before these become an extinct species.

I also stated that antibiotics are of strategic importance to our country, not only due to their economic benefit in human health, but because of their use in national defense. Biological weapons that may be antibiotic resistant is a very real threat.

It has even been proposed that these weapons, such as anthrax and other plagues, could be antibiotic resistant, so that efforts to thwart a biological attack will be useless.

Developing an appropriate arsenal of antibiotics against such an attack and preserving their use is of the utmost importance as a counteractive measure.

Now, in the public eye, antibiotic resistance must be addressed quickly with directives and solid objectives that will preserve and increase the number of antibiotics that we have to treat bacterial infections.

There also must be new research initiatives and funding opportunities to study the antibiotic resistance phenomenon and even more importantly to discover new antibiotics. Increasing funding and research initiatives for both academia and pharmaceutical development will help in the fight against bacterial resistance, as the risks and difficulties of developing antibiotics today are many.

The time it takes to discover a new antibiotic is ever increasing, leaving still the time to develop, approve and finally deliver a lifesaving drug to the public.

And there is the role of education. Increasing funding to institutions such as the NIH and the NSF, funding basic research in the areas of the biological and chemical sciences will also help in the fight against drug-resistant bacteria.

Even though the driving force of antibiotic development today rests primarily with the private sector, technological change and the production of new antibiotics will always start with the efforts and dedication of scientists. And education and training of scientists to study antibiotic resistance and to produce new antibiotics will be key.

Legislation may also help in the discovery and production of new antibiotics. Such measures, such as giving older antibiotics extra legal and patent protection could also increase our antibiotic arsenal.

Other mechanisms targeting increased collaboration between pharmaceutical companies may also work to produce antibiotics against superbugs. By fostering collaborations in industry, for example, the Multilateral Initiative on Malaria, companies can create partnerships to speed up the drug discovery and development process and fight this and other microbial diseases.

And the list of possible answers to the antibiotic—antibiotic resistance question goes on.

I would like to conclude by sharing some history with you, illustrating the importance of developing new antibiotics. In 1941, the U.S. Department of Agriculture was approached by researchers from the United Kingdom, anxious for assisting and helping them produce a substance that they found could fight bacterial diseases for the first time. This antibiotic could not easily be mass-produced to fight infections.

Our Government met their challenge and helped them to produce their drug in large enough quantities just in time to help cure the battlefield infections that were rampant in World War II. That drug was penicillin.

PREPARED STATEMENT

It was the proactive role of our Government and its involvement that eventually made antibiotics the life-saving drugs that they are today. And now with the antibiotic-resistance crisis at hand, the role of the government to protect and aid in the development of new antibiotics is even more crucial to the health, prosperity and security of our nation.

Thank you and I welcome any questions you may have.

Senator COCHRAN. Thank you very much, Dr. Nelson, for your contribution to our hearing and the insight that you have provided to us.

[The statement follows:]

PREPARED STATEMENT OF MARK L. NELSON

Good morning Mr. Chairman and Committee members: I am Dr. Mark L. Nelson, Senior Director of Chemistry for Paratek Pharmaceuticals, a start-up biotechnology company that grew out of research that I conducted with Dr. Stuart Levy while at Tufts University School of Medicine in Boston. Dr. Levy is a world-recognized authority in the area of antibiotic resistance, and one of the first scientists in the United States to sound the alarm about the threat of the antibiotic resistance crisis.

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I would like to speak to you today about the uncertain future of antibiotics against infections common today in the clinics and hospitals, and to also explain to you why antibiotics are a natural resource that must be studied and developed. The development of new antibiotics is extremely important to our national health while also being strategically important to our National Defense. I would also like to describe some of the difficulties of developing new antibiotics, and steps that could be taken to insure a potent arsenal of antibiotic agents for the future.

Bacteria have been winning the war against antibiotics for some time now, but the issue really became a public one in 1994, when Newsweek (March 28, 1994) had as its cover story the title "Antibiotics—The End of Miracle Drugs" and "Warning: No longer effective against killer bugs". It was later that the scientific community declared the antibiotic resistance problem "The New Apocalypse". Both addressed the issues of antibiotic resistance correctly and told the story of the emergence of "superbugs"—antibiotic resistant bacteria.

In our country, we are seeing infections that are resistant to all known antibiotics, and are causing alarm within both the scientific and public domains. In the hospitals, "superbugs" such as vancomycin resistant *Enteroccoci,* are increasing in frequency and severity, where if the patient develops these infections and vancomycin does not work as the antibiotic of last resort, the patient may die. Other resistant infections such as MRSA—an acronym for a resistant infection from a common Staph bacterium, increases the costs of a hospital stay dramatically, where the patient is kept in isolation and expensive precautions must be taken to stop the spread of this infection.

Earlier, I mentioned that antibiotics are a natural resource. Once they become ineffective against an infection, they are useless. Because of this, we must preserve and protect antibiotics as we would any natural resource, before antibiotics become an extinct species.

I also stated that antibiotics are of strategic importance to our country, not only due to their economic benefit in human health, but because of their use in National Defense. The use of biological weapons that may use antibiotic resistant bacteria is a very real threat. It is even been proposed that biological weapons such as anthrax and other plagues (*Yersinia pestis*) could be antibiotic resistant, so that efforts to thwart a biological attack will be useless. Developing an appropriate arsenal of antibiotics against such an attack and preserving their use is of the utmost importance as counteractive measures.

Now in the public eye, antibiotic resistance must be addressed quickly with directives and solid objectives that will preserve and increase the number of antibiotics that we have to treat bacterial infections. There also must be new research initiatives and funding opportunities to study the antibiotic resistance phenomenon, and even more important, to discover new antibiotics.

Increasing funding and research initiatives for both academia and pharmaceutical development will help in the fight against bacterial resistance, as the risks and difficulties of developing antibiotics today are many. The time it takes to discover a new antibiotic is ever-increasing, leaving still the time to develop, approve, and finally deliver a life-saving drug to the public.

And there is the role of education. Increasing funding to institutions such as the NIH and NSF, funding basic research in the areas of the molecular and chemical sciences, will also help in the fight against drug resistant bacteria. Even though the driving force of antibiotic development today rests primarily with the private sector, technological change and production of new antibiotics will always start with the efforts and dedication of scientists. And education and training of scientists to study antibiotic resistance and produce new antibiotics will be key.

Legislation may also help in the discovery and production of new antibiotics. Such measures, such as giving older antibiotics extra legal and patent protection, could also increase our antibiotic arsenal.

Other mechanisms targeting increased collaborations between pharmaceutical companies may also work to produce antibiotics against "superbugs". By fostering collaborations in industry, for example, the Multilateral Initiative on Malaria, companies can create partnerships to speed up the drug discovery and development process, and fight this and other microbial diseases.

And the list of possible answers to the antibiotic resistance question and finding new antibiotic goes on.

I'd like to conclude by sharing some history with you, illustrating the importance of developing antibiotics. In 1941, the U.S. Department of Agriculture was approached by researchers from the United Kingdom, anxious for assistance in helping them produce a substance they found could fight bacterial diseases for the first

time. This antibiotic could not easily be mass produced to fight infections. Our government met their challenge and helped them to produce their drug in large enough quantities just in time to help cure the battlefield infections rampant in VMI. That drug was penicillin. It was the proactive role of our government and its involvement that eventually made antibiotics the life-saving drugs they are today.

Now with the antibiotic resistance crisis at hand, the role of the government to protect and aid in the development of new antibiotics is even more crucial to the health, prosperity and security of our nation.

Thank you, and I welcome any questions you may have.

Senator COCHRAN. You mentioned in your written statement the New Apocalypse. If we fail to act on this issue and this challenge, what would you describe as the worst case scenario?

Dr. NELSON. The worst case scenario for the New Apocalypse. Well, the New Apocalypse was described by the scientific community and what could possibly happen if we do not have antibiotics to fight a common drug-resistant infection that could occur, such as a Staphoreus infection that was resistant to such a drug like vancomycin.

Well, I would have to say it would be pandemonium. There would be large loss of life. There would be flooding of hospitals and it would be a crucial time in the health history of the United States.

Senator COCHRAN. Is it your view that companies like yours have a role to play, a special role maybe in the development of new antibiotics?

Dr. NELSON. It is. Our company started out of academia. And what has happened—in the early years it was very difficult to develop and do research in this area.

Now, as the antibiotic resistance movement is growing and people are understanding it, there is more opportunity for smaller research labs to become active and to produce hopefully new antibiotics.

Senator COCHRAN. I want to ask both you and Dr. Rosenberg this question, some—it follows on the questions I have asked earlier witnesses about what the government can do, what the Federal Government particularly can do in terms of funding and legislation? What incentives, in your view, should the Federal Government provide firms in the pharmaceutical business to develop new antibiotic treatments?

Dr. ROSENBERG. I will start.

Senator COCHRAN. OK. Dr. Rosenberg.

Dr. ROSENBERG. Yes. Well, there are a number of certain things that can be done that have already been discussed and that is basic research funding. And that is to be able to make sure that our academic partners, our Government partners are funded to be able to achieve the basic research ideas that eventually find them their ways into the pharmaceutical sector.

The problem in the pharmaceutical sector comes from, in fact, the enormous costs and lead times to develop these as commercial products. And in the end, there has to be seen some kind of return on investment for this industry for us to be able to make that investment, particularly today when the number of other therapeutic modalities that we suffer from and the other diseases and unmet medical conditions attract those investments.

And, of course, no matter how big a company you are, you only have so much money to invest. And therefore you—those invest-

ments are tracked by the level of unmet medical need and the desire to return to our investors some kind of a return on investment for what they have put in.

So then it comes down to: What are the kinds of incentives that you have talked about? Some have been mentioned. There could be effects on patents. One could think about extending patents of antibiotics, new antibiotics, but one could also think of having the industry create antibiotics that may never make money themselves but incentivize them by, for example, extending patents on other drugs they may produce.

And therefore the industry would certainly welcome the ability to get its return on investment through some other unmet medical need mechanism, through some other solution it was providing and still be able to work on products that may never unto themselves produce any revenues for the company. I think those are all kinds of possibilities.

Senator COCHRAN. Yes.

Dr. Nelson.

Dr. NELSON. Patent protection increases would definitely help to foster further development. Other areas would be, as Dr. Rosenberg had mentioned, is education, developing programs that, again, as I mentioned earlier, fostering relationships between companies and even to change how legislature perceives these collaborations.

In some cases, antitrust laws keep drug companies from collaborating because of perceived monopoly of that market. And that is actually one area that people have looked at to help foster these relationships is to change or reexamine some of those issues.

Senator COCHRAN. Let me ask Dr. Rosenberg this as well, what can you do to more completely implement the guidelines for using treatments for ear infections, sinusitis and the like?

Dr. ROSENBERG. Well, I think what you would want to do is address that question to probably Dr. Merle Sande, the physician at the end, given that he is the one who has to actually implement such guidelines.

Senator COCHRAN. Yes. Yes.

Dr. ROSENBERG. I think he would be a better person to ask that question.

Senator COCHRAN. OK. Dr. Sande.

Dr. SANDE. Well, I actually think, Dr. Rosenberg, that you can help.

I think that—well, let me back up. Guidelines are nice, but when it comes down to a—guidelines are based upon public health needs and also trying to take into account the patient/physician relationship. But we have been taught in medical school and throughout our training that our primary responsibility is to our patient, not to the public health. And I think that is a big mistake in our medical education and I think it needs to change.

But when it comes down to sitting down with your patient who says, "Doc, I have got bronchitis, and I really want an antibiotic." And you sit there and talk to that patient, you know the guidelines are not going to support that.

But on the other hand, you have developed a relationship with this patient that is sacred. So you take the easy way out. You write a prescription for an antibiotic.

So I think you need to think of the incentives to the physician to change that behavior. No. 1 I mentioned the study in Colorado where the patient comes in and says, "Doc, I love you dearly. You have been giving me antibiotics for years, but I just found out they were not doing me any good." Now, that would help the physician a lot to go by the guidelines.

But the other way to approach it is to approach it from the incentive way and that is why I mention the HMO's and how they reward the physician. If the physician was rewarded in terms of financial incentives or others, because he went along with the guidelines, then he might question whether he should respond to the patient's desire or not.

It is a complicated issue. But going back to the drug companies, I think they can help sell guidelines by actually utilizing their vast advertising potential to sell the public health aspect of their drugs, how to use them correctly for the benefit of all mankind, not just for the quick buck that may occur this year and disappear next year.

Senator COCHRAN. What about the advertising problem? Is it appropriate in your view? I will ask Dr. Rosenberg and Dr. Nelson—to advertise and promote the use of antibiotics, should we stop that right now, just like we stopped the advertising of smoking, or cigarettes or tobacco products?

Dr. ROSENBERG. I think the advertising issue is a complex one and I think Dr. Henney really described it as the best.

People today want information. Now, whether that information is about how they want to cure a variety of diseases, they will want to get that information. The Internet has proven that, and television advertising certainly has proven that.

And therefore the complexity comes as to how you provide information appropriately so that people are aware of new discoveries and things that they might want to know about versus what harm it does by giving them information that they have to then act on.

Now, the advantage that we have always seen to this was that standing between any information you give them and the ability for them to get access to any of the drugs that are advertised is a physician, supposedly a competent person who is supposed to give them the proper advice. And they cannot get a hold of that material until that physician scripts it on a piece of paper. And therefore——

Senator COCHRAN. So we do not have on the counter, or off-the-shelf purchases of antibiotics. That is not permitted? You have to have a prescription right now to——

Dr. ROSENBERG. You have to have a prescription for almost all oral antibiotics in this country.

Senator COCHRAN. Almost all?

Dr. ROSENBERG. Yes——

Senator COCHRAN. So there are some——

Dr. ROSENBERG [continuing]. Other than the stuff that you put on your cuts and the triple antibiotic creams that you put on your cuts.

Senator COCHRAN. Right.

Dr. ROSENBERG. Every other antibiotic has to be obtained through seeing a physician and getting a script for it.

Senator COCHRAN. All right.

Dr. ROSENBERG. Right.

Senator COCHRAN. OK. I did not give you a chance to answer that.

Dr. NELSON. Well, I think Dr. Rosenberg hit on all the points.

Senator COCHRAN. Gave a good answer, OK.

Dr. NELSON. Correct.

Senator COCHRAN. Well, should there be funding from the Federal Government to help promote the guidelines to combat antibiotic resistance? Is there any need for any special funding programs that embody and endorse the use of guidelines? What do you think?

Dr. ROSENBERG. I think the guidelines are an important start and one of the things that I think we have to recognize, again, is that we are still dealing with empiric treatments; and that is that the physician, particularly the general practitioner, maybe not the infectious disease specialist, but the general practitioner is still dealing with having to make decisions without having all the tools available to them to make that decision.

And therefore the guidelines provide some capability, some context for them to make that correct decision. I think of particular interest in the guidelines and in the thoughts that have gone now into what antibiotics to use has been the fact that the—it seems to be both laboratory data and now clinical data seems to be indicating that the best way to treat these infections so that they do not become resistant is, of course, to use the most potent and best antibiotics.

We used to have a controversy in this area. It used to be save the best to last. And that was use the older ones, save the best to last.

Well, it turns out it is the older ones that often drive resistance. And if there is a wonderful recent publication by the World Health Organization, and if I could just quote you, in fact, coming from their publication—it is called, "Overcoming Antimicrobial Resistance," the WHO states the most effective strategy against antimicrobial resistance is to get the job done right the first time, to unequivocally destroy the microbe," meaning dead microbes do not mutate. And therefore that is how to best defeat resistance is to use your best antibiotic up front—that kills bugs.

Senator COCHRAN. What characteristics of anti-infectives fight antibiotic resistance?

Dr. Rosenberg, yes, sir.

Dr. ROSENBERG. Yes. Well, there are a number of them. Probably the best for antibiotics, of course, would be to have new mechanism of action antibiotics, because they circumvent the—all of the resistant mechanisms that have come forward in using the older antibiotics that we have.

So I think it was mentioned several times that the classes of antibiotics we have are still very few. You can count them on just about two hands.

And because of that, if we can get outside of that scope and be able to create antibiotics that see new targets, that will be one of the greatest ways to circumvent the resistance problems that we are now facing, our older antibiotics.

Senator COCHRAN. Dr. Clark, you noted that we should expand our search for new antibiotic leads to sources that have not been investigated such as plants, natural products. Could you comment on the likelihood that new antibiotics may be found from plants and other sources?

Dr. CLARK. Yes, sir. I think as has been noted, the majority of the antibiotics that we have on the market have been found from a relatively small number and source of microorganisms that occur, for example, in the soil.

We have just plants, as an example, there are over a quarter million species of plants on this planet and less than ten percent of them have been investigated in any way for any of their chemistry and the biology of that—those chemicals.

And so certainly the odds would be in our favor that a systematic evaluation of plants would generate new structures with biological activities against these resistant pathogens.

Senator COCHRAN. Could you explain how you would envision a collaborative, multi-disciplinary partnership between academia, government and the private sector working?

Dr. CLARK. Well, actually we have a very nice model for that in the National Center for Natural Products Research, where we have a partnership with a USDA agricultural research service unit aimed at discovering new agricultural chemicals and new pharmaceuticals from plants. And this is defined through a memorandum of understanding and through partnerships with the private sector to advance those discoveries once they are made.

Senator COCHRAN. Coming from a pharmacy school as you have, as a teacher there, you have been involved in educating pharmacists. Can you comment on the role the pharmacist can have in preventing and controlling the development of antimicrobial resistance?

Dr. CLARK. Gladly. I think this is interesting that in much of the discussion we have had today about educating the consumer and educating the physician, the pharmacist's role has not been highlighted. And the practice of pharmacy today is founded in pharmaceutical care, which is—has as its central tenet, counseling patients regarding the proper use of medication and working with other health-care professions regarding the proper selection and use of medications; and antimicrobials are certainly no—no exception there.

As one of the most accessible health-care professionals to the general public, I think the pharmacists are in a unique position to provide a real input and make a difference in this issue, and it would educate both the consumer, the patient, and the other health-care professionals.

Senator COCHRAN. I think you and Dr. Sande both mentioned that over the past 20 years there have been dozens of new antimicrobials, but that very few were really new or novel. What does this mean in terms of emphasis and the importance of our understanding that at this hearing?

Dr. CLARK. I will take——

Senator COCHRAN. I will ask you, and then Dr. Sande to comment on it, too.

Dr. CLARK. I think that as Dr. Rosenberg pointed out, our search for new antimicrobial agents really has to be broadened and encompass the information available to us now so that we can identify new mechanisms.

Having multiple classes of agents that affect multiple targets, give us multiple weapons in this battle.

Senator COCHRAN. Now, Dr. Sande, you mentioned derivatives. Most of the new drugs were derivatives of older drugs, is that right? And is that——

Dr. SANDE. That is right. And I think what has happened is that the easy targets have been exploited.

Bacteria have just a certain number of ways that you can attack them by. And the ones that are easy to screen, and these multiple screening that the pharmaceutical companies tend to do, have I think exploited the easy targets. So it makes sense then that by slight modification of old drugs, maybe you can develop a drug that will fight a resistant enzyme or will fight a way that the bacteria has mutated around the effect.

But you just manipulate the molecule. I think what Dr. Rosenberg said is absolutely crucial. The future is going to be dependent upon finding new targets. And now with this whole new field of bacterial genomics that should become possible.

But it is going to be slow and it is going to be expensive. And that is what makes me the most concerned is that the pharmaceutical companies are going to look at the bill for this and they are going to say, "Hey, I have got other areas that I can make more money in. That by getting deep into this area, which is a real craps shoot and a fishing expedition."

So I think that is where the government can help. I think by some of the techniques we have talked about they can encourage this long-term investment by the pharmaceutical—if it does not happen, no matter how much we control antibiotics, I think eventually these bugs are going to get resistant to the current groups of drugs that we have.

We are going to need new drugs.

Senator COCHRAN. Dr. Thompson, should there be a national reporting requirement for antimicrobial resistance. You talked about your effort to identify and screen in one county in Mississippi for tuberculosis that was resistant. Should there be a reporting requirement? Should you have had to report that to a national center?

Dr. THOMPSON. Well, the short answer, Senator, is no. But there should be national surveillance of antibiotic resistance.

One part of surveillance is the required reporting of diseases. And this takes place both practically and constitutionally at the State level.

It is to State health departments that there should be required reporting of appropriate level of antibiotic resistance as there is now for a variety of infections without regard to their antibiotic sensitivity.

We have no national reporting requirements for any disease, nor—and speaking now for ASTHO—should we ever have. This should always remain coordinated by the CDC and an affiliate of ASTHO, the Council of State and Territorial Epidemiologists.

We should have a national list of diseases that should be made reportable by the States, but to make the final decision that it is a reportable condition by law, this is a State decision. And we are firmly committed to this being the best way to do it. And it works very, very well for the dozens of diseases that are now reportable.

The same model can work well with antibiotic resistant organisms.

Senator COCHRAN. Do you have any difficulty with hospitals and physicians who refuse to report or just are negligent about reporting these? How do you overcome that challenge?

Dr. THOMPSON. Well, with—one of the biggest problems you have with hospitals and physicians—and I am sure that my clinical colleagues have seen this as well—it is the kind of "I thought it was your uncle" problem.

A man is talking to his wife and he says, "Listen, your uncle has been here for 2 weeks. He is eating us out of house and home. I am tired of it. He has got to go home."

And she says, "My uncle? I thought he was your uncle."

And that is the sort of thing you often see in a large academic institution, a variety of people each thinking the other has reported the condition appropriately, all failed to do so. And coordinating that, making sure that there is someone who is responsible for that; and here the infection control practitioner in the hospital, typically a nurse, is the key to this sort of thing.

That is, again, the sort of thing that State health departments can work very effectively in. By developing relationships with the societies of infection control practitioners in their local jurisdictions, they can develop a communication channel that an infection control practitioner knows that it is to be reported. She takes—or he—takes the responsibility for making sure that it gets reported.

Senator COCHRAN. Can your laboratory process the specimens and handle the additional reporting requirements? And if this is a problem, how do we address it and does the Federal Government have a role in that?

Dr. THOMPSON. Well, yes, Senator, you do. We—we said in, in fact, the GAO report in 1999 commented on the fact that—that most States do not require reporting of very many antimicrobial resistant organisms, and in particular they do not require the submission of specimens from clinical laboratories to the State department of health laboratory for further testing and for testing for specialized patterns of resistance.

The reason we do not is two-fold. One, we have only come to realize in relatively recent years that there is a need to do that. But even more importantly, even once we know it must be done, we cannot process the specimens without additional staff, without some additional laboratory space, without some expansion, some additional technology, some increase in the amount of existing technology we have got.

And until we are able to actually carry out the laboratory work that would be required in processing those specimens, we cannot require the submission of those specimens to us. So we need more resources, some of which must come from the States themselves.

We cannot look to the Federal Government for the entire cost of this. But at the same time, we do need Federal support for this in

much the same way that you have provided fairly recently support for increased State capacity in the area of bio-terrorism response, most recently in the area of arboviral surveillance, with regard to West Nile surveillance.

The Federal funds that you have provided to the States have been—have enabled us to expand what we were already doing to cover new pathogens without supplanting what we were already doing. We simply supplement that and make our efforts greater.

A similar effort in terms of Federal funding is going to be needed for antimicrobial resistance at the State health department level.

Senator COCHRAN. Thank you very much. This has been an—an excellent panel in a cross-disciplinary approach to informing and educating the—the Senate on how we can better respond to this very important challenge that we face.

And I think the description of it by the first panel, our CDC director and the commissioner of the Food and Drug Administration set the tone for the importance of it and the seriousness of it, the comprehensive plan that has been put forward by those two agencies and NIH.

And now with the pharmacy, educators, the companies, the clinicians represented and the State health organizations from around the country represented, I think we have a much better understanding of things that we can do and that we should try to do quickly to help deal with this problem.

And so your participation has been very helpful and very important to us. And we thank you all very much.

CONCLUSION OF HEARING

Thank you all very much for being here. That concludes our hearing. The subcommittee will stand in recess subject to the call of the Chair.

[Whereupon, at 11:28 a.m., Wednesday, September 20, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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