Testimony
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CDC's Role in Monitoring and Preventing Antimicrobial Resistance

Statement of
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Introduction

Good morning Chairman Brown, Ranking Member Enzi, and other distinguished Members of the Committee. I am Dr. Fred Tenover, and it is my pleasure to be here today in my capacity as Director of the Office of Antimicrobial Resistance at the Centers for Disease Control and Prevention (CDC). While I have certain managerial responsibilities at CDC, I continue to work as an active microbiologist and have authored or co-authored over 290 journal articles and 31 book chapters in the field of clinical medicine and microbiology. I also serve as Director of the World Health Organization's Collaborating Centre for Global Monitoring of Antimicrobial Resistance and am an Adjunct Professor in the Division of Epidemiology at Emory University's Rollins School of Public Health. CDC appreciates the opportunity to address this timely issue and I look forward to discussing with you our growing concerns about the problem of Antimicrobial Resistance

Antimicrobial resistance will always be with us, it is not a new issue; but we need to continue to find manageable solutions. Resistant microorganisms have been reported for over 60 years; however, it is the increasing magnitude of the problem and the fact that so many different types of microorganisms are becoming resistant to antimicrobials, a general term for drugs, chemicals, or other substances that either kill or slow the growth of microbes, that is of major concern to us. Although most bacterial, fungal, viral, and parasitic pathogens remain susceptible to a least some antimicrobial agents, the increasing rates of resistance are requiring more complex options for treating individual patients and are causing the medical community to change long-established treatment regimens for many infectious illnesses to different antibiotics that may be more expensive,

or combinations of antibiotics instead of a single drug. When a patient with a resistant organism is treated with an ineffective antibiotic, the organism will continue to infect the patient and could potentially spread to other patients, further extending the resistance problem. However, with surveillance, reduced antibiotic usage, vaccination of persons at high risk, and product development antimicrobial resistance is manageable.

To provide a sense of the problem, unpublished data from CDC's National Nosocomial Infection Surveillance System indicate that >90% of strains of *Staphylococcus aureus,* a bacterial species that causes a spectrum of illnesses from minor skin infections to serious life-threatening diseases, are no longer treatable with penicillin, while one third of *Streptococcus pneumoniae* isolates, a common cause of ear infections, pneumonia, and meningitis, are also no longer treatable with penicillin. Many such penicillin resistant strains are, in fact, multiply resistant to other commonly used drugs like ceftriaxone, erythromycin, and trimethoprim-sulfamethoxazole. In addition, strains of Salmonella Newport, which cause infections in food animals, such as dairy cows, have been shown to be resistant to as many as seven antibiotics. CDC data further show that a small but growing subset of the gram-negative bacterial strains that cause healthcare-associated infections, like *Acinetobacter baumannii* and *Pseudomonas aeruginosa,* have become resistant to all available antimicrobial agents. And worldwide, tuberculosis due to strains resistant to the two most commonly used anti-tuberculosis agents, isoniazid and rifampin, was recently estimated to affect approximately half a million persons annually.

Antimicrobial Use and Resistance

Simply put, antibiotics are the most important tool we have to control many life threatening infectious diseases, yet increasing levels of antibiotic resistance are compromising the effectiveness of these drugs. Bacteria, in particular, have developed multiple ways of becoming resistant to antibiotics. The more often bacteria are exposed to antibiotics, the more chances they have to 'learn' to survive through one of these mechanisms. Many people may not know the extent to which antimicrobial agents are used. Antimicrobial agents also are widely used in animals (as prevention measures and for growth promotion), fish, vegetables and fruit (to prevent outbreaks of bacterial disease in orchards), decorative plants, and even in marine paint (to inhibit growth of sea life on ships). It is imperative that we assess the use of all antimicrobial agents carefully and use them only when necessary, to avoid promoting the development of resistance among bacteria and other microorganisms. Unnecessary use of antibiotics reduces the effectiveness of the drugs we have at a time when there are relatively few new antimicrobial agents in development.

CDC's Antimicrobial Resistance Program

CDC's key responsibilities regarding antimicrobial resistance are:

- to define the scope and magnitude of the problem,
- to define the risk factors that lead to the development and spread of resistant microorganisms,
- to develop evidence-based guidelines and design and implement programs that minimize the development and spread of resistant infections in humans and animals,

- to respond to outbreaks of resistant microorganisms, and
- to conduct research on the prevention and control of resistant organisms in a variety of settings.

In addition to the responsibilities listed above, CDC laboratories are responsible for:

- tracking the spread of resistant microorganisms both nationally and globally,
- providing national reference laboratory services to confirm unusual antimicrobial resistance patterns, and
- working with professional societies to standardize methods for testing antimicrobial resistance among a variety of microorganisms including fungi, viruses, and parasites.

Defining the Scope and Magnitude of Antimicrobial Resistance

CDC uses several types of surveillance systems (including data from laboratories, hospital information systems, and microbiologic examination of retail meats), to monitor the development and spread of resistant microorganisms and the infections that they cause. The organism groups under surveillance include many bacterial species (including *Mycobacterium tuberculosis*), fungi, viruses, and several parasites, such as malaria. Examples of surveillance systems at CDC include the Active Bacterial Core Surveillance (ABCs) system conducted through CDC's Emerging Infections Program (a network of sites that work together to conduct population-based surveillance and research projects), the Gonococcal Isolate Surveillance Program (GISP), and the National Healthcare Safety Network (NHSN). To conduct surveillance for resistant microorganisms and infections, CDC collaborates with many partners, including healthcare facilities; state public health

departments; other federal agencies, including the Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA); and international organizations, such as the World Health Organization. Recently CDC also developed a training tool for laboratorians to enhance their understanding and improve their proficiency in performing antimicrobial susceptibility testing (M.A.S.T.E.R.). Accurate antimicrobial susceptibility test results not only help physicians choose the best therapy for their patients, but guide infection control efforts to the most serious infections.

Surveillance data are used not only to monitor resistance rates among microorganisms, but to indicate the effectiveness of prevention programs, to set national benchmarks for infection control efforts, to monitor the effectiveness of treatment guidelines, and to inform timely changes regarding treatment recommendations. In addition, surveillance data collected through the ABCs system provide a source of national, population-based estimates of the antimicrobial resistance disease burden of multiple bacterial species, while NHSN serves both as a system for tracking healthcare-associated infections and as a sentinel warning system for unusual resistant organisms, such as vancomycin-resistant strains of *Staphylococcus aureus*.

Data from CDC's surveillance systems have often identified the emergence of new resistant microorganisms, such as the recent recognition by the ABCs system of the first ciprofloxacin-resistant strains of *Neisseria meningitidis* in the upper Midwestern United States reported this year, or the recognition of first strains of vancomycin-resistant enterococci in U.S. hospitals, reported by the National Nosocomial Infection Surveillance

system, the predecessor to NHSN, a decade ago. Such reports have prompted outbreak investigations from which CDC has garnered a wealth of information on the development and spread of resistant organisms.

Promoting Appropriate and Optimal Antimicrobial Use

Multiple efforts are underway at CDC to promote appropriate antimicrobial use to preserve the effectiveness of the antibiotics we have for the longest period of time. CDC's "Get Smart: Use Antibiotics Wisely" campaign has been very successful in delivering educational messages on appropriate antibiotic use to physicians and the general public. Since its inception in 2003, this program has delivered its message of the importance of prudent antibiotic use through state health department initiatives, physician's offices, on television, over the radio, and in print media. Since the late 1990s, there has been a 25% reduction in antibiotic prescriptions generated during outpatient visits for presumed viral infections, for which antibiotics are ineffective, which was a key target of the campaign. Additional educational efforts include developing curricula on prudent antibiotic use for medical schools and primary care residency programs. These programs are designed to raise the awareness of key healthcare providers to the downsides of unnecessary antibiotic use. The "Get Smart" program has expanded to include "Get Smart on the Farm" to focus on use of antimicrobial agents in animals, and has partnered with another CDC program, the "Campaign to Prevent Antimicrobial Resistance", which focuses on educating healthcare-based physicians about antimicrobial resistance issues, in an attempt to further decrease unnecessary antibiotic use.

CDC has long worked to promote the appropriate treatment of tuberculosis, both here and abroad, in order to minimize the development and spread of resistant TB. CDC provides financial and technical assistance to all 50 states and 10 large cities to reduce the spread of TB and ensure curative treatment for those with TB. Important to this effort is ensuring that patients are treated drugs that will work against the strain that they have contracted. In 2006, over 92 percent of all patients with an initial positive TB culture in the U.S. were tested for TB drug susceptibility. CDC also supports TB laboratories and funds regional training and medical consultation centers for healthcare workers to ensure appropriate treatment and diagnosis.

In addition to these programmatic educational efforts, CDC sponsors the TB Trials Consortium (TBTC), which conducts clinical trials of TB medications on four different continents to optimize the effectiveness of current tuberculosis treatment regimens and identify new TB drugs that could be used to treat drug-resistant strains. The TBTC includes members from TB control programs, academic medical institutions, and CDC, as well as international partners from the commercial sector, the not-for-profit private sector, and the public sector, all of whom are essential for this work. The Global Alliance for TB Drug Development is a public/private partnership with whom CDC works to stimulate new drug development for treating tuberculosis. Over 30 organizations, including the Bill & Melinda Gates Foundation, National Institute of Allergy and Infectious Diseases at the National Institutes of Health, the Rockefeller Foundation, the U.S. Agency for International Development, the World Bank, and WHO, are stakeholders along with CDC in this

innovative partnership. The major goals are to shorten the treatment of TB, minimize the impact of drug-resistant TB, and facilitate TB control in the poorest countries in the world.

Successes and Setbacks in Prevention and Control Activities

Multiply Resistant Pneumococcal Infections

The fight against antimicrobial resistance can best be viewed as a continual series of successes and setbacks. For example, pneumococcal infections resistant to penicillin and multiple other antibiotics became common during the 1990's. But in 2000, a new vaccine called Prevnar® became available for children in the United States and CDC began tracking the vaccine's impact on resistant pneumococcal infections. Since the vaccine was introduced into the routine childhood immunization program in the United States, penicillin-resistant pneumococcal infections declined by 35 percent. Not only has the vaccine been shown to prevent antibiotic-resistant infections, it has been shown to reduce the need for prescribing antibiotics for children with pneumococcal infection in the first place. CDC data also show that adults are getting fewer resistant pneumococcal infections because the vaccine is preventing spread of pneumococci from infected children to adult populations. Since 2001, it is estimated from CDC data that 170,000 severe pneumococcal infections and 10,000 deaths have been prevented by vaccine use. According to data published in the *Archives of Pediatric Adolescent Medicine*, the vaccine is highly cost-effective, saving an estimated $310 million in direct medical costs each year.

Yet, even as infections caused by the most common multidrug resistant strains of pneumococci were declining in frequency, the CDC began noting through its Active

Bacterial Core Surveillance System a gradual increase in infections caused by a new multidrug resistant strain of pneumococcus called serotype 19A. This strain is not covered by the current vaccine. While the amount of serotype 19A invasive pneumococcal disease is small compared with the very large amount of disease averted by introduction of the vaccine, it still emphasizes the continuing struggle public health faces against microorganisms that are uniquely capable of adapting and surviving even our newest prevention measures. Fortunately, CDC's ongoing surveillance through the ABCs system detected this trend and indicated the need to develop a new vaccine that will confer protection against serotype 19A strains. A new vaccine containing 19A strain is already in clinical trials.

MRSA Infections

In a similar fashion, *Staphylococcus aureus* is a bacterial species that is commonly carried on the skin or in the nasal passages of 25% to 30% of healthy people in the United States. This organism, however, can and does cause a lot of skin infections, although most of these infections are minor. More importantly, *S. aureus* can cause life-threatening disease including bloodstream infections, endocarditis (infection of the heart valves), toxic shock syndrome, and pneumonia, particularly among hospitalized patients. Methicillin-resistant strains of *S. aureus* (also called MRSA) first emerged in Europe in 1961 but by the 1980s were causing infections in patients in many U.S. hospitals. The continued increase in the rates of MRSA infections in U.S. hospitals has been a topic of considerable concern for over a decade and has resulted in a series of local, regional, and national interventions to halt its spread. For example, CDC in collaboration with the Veterans Affairs Pittsburgh

Healthcare System achieved a 60% reduction in the rate of MRSA infections after it implemented a series of infection control procedures based on CDC guidelines designed to decrease the transmission of MRSA in hospitals. The measures included strict attention to hand hygiene, enhanced surveillance for infections, effective use of isolation rooms, and behavior modification techniques to emphasize the importance of the new procedures. These interventions are being implemented in VA medical centers nationwide and in multiple other healthcare systems. In addition, CDC is working with the Agency for Healthcare Research and Quality (AHRQ) to improve MRSA prevention in the healthcare facilities.

New national data from CDC's National Healthcare Safety Network (NHSN), a surveillance tool for hospitals and state health departments that measures healthcare associated infections (HAIs), show that there has been a significant drop in the incidence of both MRSA and methicillin-susceptible *S. aureus* (MSSA) central line-associated bloodstream infections among intensive care unit patients in U.S. hospitals over the last five years. The incidence of MRSA bloodstream infections per 1,000 central line days (i.e., a measurement of infection burden derived from the number of patients who have a central line, or catheter, whether infected or not) decreased by 49.6%, while the incidence of central line-associated MSSA infections decreased even more substantially, by 70.1%. Data on invasive MRSA infections from the Active Bacterial Core Surveillance system for 2005-2006 also show a decrease in hospital-onset and healthcare-associated MRSA infections, confirming this downward trend. Thus, it appears that these practical efforts to

reduce the transmission of MRSA in hospitals are working thereby further reducing the need for antibiotic usage.

Yet, even as we document success in controlling MRSA in hospitals, CDC, through the ABCs system and other public health agencies around the world, have noted the an increase in MRSA infections in community settings. While most of these are skin infections, severe and often fatal cases of necrotizing pneumonia continue to be reported among otherwise healthy people in the community with no links to the healthcare system. Based on national hospital discharge data analyzed by CDC, the number of *S. aureus*-related skin and soft tissue infections resulting in hospitalization doubled from 2000 through 2005; most, if not all, of this increase is likely due to community strains of MRSA. Thus, our MRSA successes in hospitals have to be balanced with the new challenges of controlling MRSA in community settings and CDC will continue to look for practical efforts to reduce these infections in community settings as have been done in hospitals.

Fluoroquinolone-resistant Neisseria gonorrhoeae

While CDC's efforts to control the spread of pneumococci in the community and MRSA in hospitals show success, CDC's efforts to maintain cost effective strategies for preventing the spread of gonorrhea in the United States had a setback in 2007. In 2007, the level of fluoroquinolone (a family of drugs that includes the well-known Ciprofloxacin) resistance among surveillance isolates submitted to CDC's Gonococcal Isolate Surveillance Program (GISP) exceeded the 5% level, which has been used as the threshold for changing nationally recommended treatment. In response, CDC was compelled to announce the

withdrawal of fluoroquinolone antibiotics as a primary treatment of gonorrhea infections, due to the rapid rise of fluoroquinolone resistance among strains of *Neisseria gonorrhoeae*. The loss of fluoroquinolones will likely have a significant impact on the treatment of gonorrhea in the United States as we are now left with only one class of recommended antibiotics, the cephalosporins, to treat gonococcal infections. When cephalosporin resistance emerges, the treatment and control of gonorrhea will become extremely difficult. Currently, there is no recommended treatment available for infected patients who have severe allergies to cephalosporins, and treatment in these patients requires the use of therapies that have greater side effects and for which resistance has already begun to develop.

Although the detection of the increase in gonococcal resistance to fluoroquinolones was timely, it highlights another challenge in CDC's effort to prevent and control this infectious disease, which is the critical need to identify the emergence of cephalosporin resistance in a timely fashion both nationally and locally. When cephalosporin resistant gonococci emerge, preventing their spread will be challenging – but even more so without expansion of existing capacity, since emergence may occur in populations not covered by the current surveillance system, allowing the gonococci to spread before effective control measures can be put in place.

Clostridium difficile Infections

Another example of the fact that taking antibiotics is not without risk is the rapid increase in the United States since 2000 of the number of *Clostridium difficile* infections primarily in

hospitalized patients. *C. difficile* disease can range from mild to debilitating diarrhea, to more severe life-threatening infections. The development of *C. difficile* infections among patients treated with antibiotics has long been considered an unintended consequence of antibiotic use. Recognized in the 1970s as a cause of "antibiotic associated diarrhea", in the 1980s and 1990s this anaerobic bacterial species caused increasing numbers of outbreaks of diarrheal disease in hospitals and long term care facilities.

Recently, however, CDC and others have recognized the emergence of *C. difficile* disease, including more life-threatening forms of disease, among otherwise healthy patients in the community. A number of the community patients had not taken antibiotics prior to their illness. Based on data from Ohio, estimates suggest that currently there may be as many as 500,000 cases of *C. difficile* infection occurring annually in the United States, contributing to between 15,000 and 30,000 deaths. Some antibiotic-resistant strains of *C. difficile,* including those resistant to macrolides and fluoroquinolones, are emerging. These strains appear to be more virulent due to increased toxin production and the presence of a novel virulence factor called the binary toxin. Surveillance data from other public health agencies around the world show such strains are spreading globally. While this antimicrobial resistance doesn't directly affect therapy for the *C. difficile* infection, since such infections are treated with other drugs, the resistance may allow *C. difficile* to spread more readily among patients who have received either a macrolide or fluoroquinolone antibiotic. This broadens even further the number of people at risk for acquiring disease. CDC will begin to collect data from healthcare institutions using NHSN to track C. *difficile* infections.

Some challenges to future surveillance activities include limited public health infrastructure for detecting resistance and the heavy reliance on hospital microbiology laboratories around the United States to provide the antibiotic resistance data. While hospital microbiology laboratories recognize the importance of tracking antimicrobial resistance patterns nationwide, many of these laboratories cite increasing pressures from their institutions to discontinue these services due to limited resources and competing priorities.

Working with Federal Partners

CDC's successful collaborations with several federal partners on antimicrobial resistance issues have illustrated the benefits of coordinating activities with other federal agencies. For example, CDC worked closely with the Food and Drug Administration, which works with manufacturers to implement recalls of contaminated products, such as in the recent outbreak of contaminated mouthwashes containing resistant *Burkholderia* species in multiple states. In addition, monitoring the development and spread of antimicrobial resistance among foodborne bacterial pathogens like Salmonella, Shigella, and Campylobacter, such as is done through the National Antimicrobial Resistance Monitoring System, requires the cooperation of three federal agencies (CDC, FDA, and USDA) to screen isolates from humans, animals, and the food supply. Another example is the current AHRQ-CDC partnership to fund a community-wide MRSA initiative to assess the role of and strategies to reduce inter-facility MRSA transmission. The necessity of federal agencies working together highlights the need for the Interagency Task Force on

Antimicrobial Resistance, specifically to facilitate communication among federal partners on the issue of antimicrobial resistance.

The Interagency Task Force on Antimicrobial Resistance

The Interagency Task Force on Antimicrobial Resistance consists of ten federal agencies (Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, Department of Agriculture, Department of Defense, Department of Veterans Affairs, Environmental Protection Agency, Food and Drug Administration, Health Resources and Services Administration, and the National Institutes of Health) and is co-chaired by CDC, FDA, and NIH. Recently, the Task Force held a consultants meeting to obtain input and recommendations for revising and updating "A Public Health Action Plan to Combat Antimicrobial Resistance, which was first released in 2001." In addition to over fifty consultants from the United States, nine international consultants from Canada, Denmark, France, Germany, The Netherlands, and the United Kingdom participated in the meeting. The consultants included experts from human and veterinary medicine, the pharmaceutical and diagnostics industries, animal husbandry industry, clinical microbiology, epidemiology, infectious disease and infection control specialists, and state and local public health departments. Representatives of most of the federal agencies also participated. The open meeting also was attended by members of the public, including representatives of a variety of professional societies, advocacy groups, and concerned citizens. The discussions centered on four topic areas: surveillance; prevention and control; research; and product

development. The consultants focused on issues that they felt were critical to address over the next 3-5 years.

Based on comments from the consultants and the federal agencies, the revised draft Action Plan has been reformatted around five focus areas:

- reducing inappropriate antimicrobial use,
- reducing the spread of antimicrobial resistant microorganisms in institutions, communities, and agriculture,
- enhancing laboratory capacity to detect resistant microorganisms,
- encouraging the development of new anti-infective products, vaccines, and adjunct therapies, and
- supporting basic research on antimicrobial resistance.

The Task Force plans on submitting the revised Action Plan for public comment this fall.

Summary

In summary, given the growing worldwide usage of antimicrobial agents (including antibacterials, antifungals, antivirals, and antiparasitic agents), the pressure for resistant microorganisms to develop and spread remains high. CDC's strengths in surveillance, research, prevention and control, and education have proven to be critical assets in fighting resistance and have been rewarded with some remarkable successes in controlling the spread of resistant infections. Yet, CDC has also seen its share of setbacks, due to the ability of microorganisms to adapt to our prevention measures. We are hopeful that we can retain the vital core needed to continue to monitor the most important resistant

organisms, while we develop and implement new measures to prevent and control resistant infections.

Thank you again for the opportunity to testify today. I am happy to answer any questions you may have.