A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE

Interagency Task Force on Antimicrobial Resistance

Co-Chairs:

Centers for Disease Control and Prevention

Food and Drug Administration

National Institutes of Health

Participating Agencies:

Agency for Healthcare Research and Quality

Centers for Medicare and Medicaid Services

Department of Agriculture

Department of Defense

Department of Veterans Affairs

Environmental Protection Agency

Health Resources and Services Administration

Health and Human Services/ Office of the Assistant Secretary for Preparedness and Response

Preface

This 2011 revision of the A Public Health Action Plan to Combat Antimicrobial Resistance, provides a listing of projects that the Federal Agencies which are part of the Interagency Task Force on Antimicrobial Resistance are pursuing or planning to pursue in an effort to respond to the complex and pressing topic of antimicrobial resistance. The past decade has seen extraordinary change in the microbiology and epidemiology of antimicrobial resistant microbes and subsequent changes in treatment and patient outcomes. The Interagency Task Force on Antimicrobial Resistance is making further strides to ensure the currency and relevance of the Action Plan as the Task Force continues to look towards the future by taking the following steps:

- Actions, the numbered items which follow each goal, will be reviewed biannually by the Task Force. New actions will be added as needed and existing actions may be modified or deleted in response to progress or changes that occur in the future with regard to antimicrobial resistance. This will allow the Action Plan to be updated over time and to help all Task Force agencies to continue to collaborate most effectively in achieving Action Plan goals.
- The listing of projects meant to help combat the issue of antimicrobial resistance (the lettered items which follow below each action) will be revised annually. New projects may be added, and existing projects may be modified in response to intervening events. Completed projects will be moved to an Action Plan annex and their outcomes will be cross-referenced to the yearly progress report for the year during which the project was completed.
- A few projects were completed during the review and comment period for this latest version of the Action Plan. Rather than deleting these activities, readers are referred to the recently published document 2009-2010 Progress Towards Implementation of: A Public Health Action Plan To Combat Antimicrobial Resistance (available at: http://www.cdc.gov/drugresistance/annualReports.html#ar09) for updates about these projects. The Task Force will report on the outcomes of activities planned for completion in 2011 in the 2011 Annual Update which will be available during the first half of 2012.

The Task Force and all participating Federal agencies are continuing to stress the importance of good communication with the many stakeholders who share the Task Force's goals of preventing and controlling antimicrobial resistant infections. The Task Force remains committed to continuing communication with the public and health professionals, since antimicrobial resistance so profoundly affects public health and clinical medicine. Given the public health consequences of AR and its ever changing nature, the Task Force will continue to address the issue of antimicrobial resistance in this and future versions of the Action Plan.

A Public Health Action Plan to Combat Antimicrobial Resistance

Table of Contents

A Public Health Action Plan to Combat Antimicrobial Resistance

Executive Summary

The Interagency Task Force on Antimicrobial Resistance (hereafter referred to as the Task Force) was created in 1999 to coordinate the activities of federal agencies in addressing antimicrobial[a] resistance (AR) in recognition of the increasing importance of AR as a public health threat. 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 Centers for Medicare and Medicaid Services (CMS), the Department of Agriculture (USDA), the Department of Defense (DoD), the Department of Veterans Affairs (VA), the Environmental Protection Agency (EPA), the Health Resources and Services Administration (HRSA), and the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response (HHS/ASPR).

In 2001, the Task Force developed an initial Action Plan, outlining specific issues, goals, and actions important for addressing the problem of AR. This document, entitled *A Public Health Action Plan to Combat Antimicrobial Resistance, Part I: Domestic Issues*, reflected a broad-based consensus of participating federal agencies, which was reached with individual input from state and local health agencies, universities, professional societies, pharmaceutical companies, healthcare delivery organizations, agricultural producers, consumer groups, and other members of the public. Continued collaboration with these partners has been vital to achieving successful implementation of the Action Plan.

This revised Action Plan is based in part on individual input obtained at a consultants' meeting held in Atlanta, Georgia, in December 2007. Present at the public meeting were consultants with wide-ranging expertise in areas such as human and veterinary medicine, pharmaceutical and diagnostics manufacturing, animal husbandry, clinical microbiology, epidemiology, infectious diseases and infection control, and state and local public health officials.

The Action Plan includes action items organized into four focus areas: Surveillance, Prevention and Control, Research, and Product Development. Within each of these four areas, specific goals are listed. The focus areas and goals are as follows:

I. Surveillance

- Goal 1: Improve the detection, monitoring, and characterization of drug-resistant infections in humans and animals.
- Goal 2: Better define, characterize, and measure the impact of antimicrobial drug use in humans and animals in the United States.

[a] In this document, the term "antimicrobial" is used inclusively to refer to any agent (including an antibiotic) used to kill or inhibit the growth of microorganisms (bacteria, viruses, fungi, or parasites). This term generally applies to agents intended for healthcare, veterinary, and agricultural applications.

II. Prevention and Control

- Goal 3: Develop, implement, and evaluate strategies to prevent the emergence, transmission, and persistence of drug-resistant microorganisms.
- Goal 4: Develop, implement, and evaluate strategies to improve appropriate antimicrobial use.

III. Research

- Goal 5: Facilitate basic research on antimicrobial resistance.
- Goal 6: Facilitate the translation of basic research findings into practical applications for the prevention, diagnosis and treatment of resistant infections.
- Goal 7: Facilitate clinical research to improve the treatment and prevention of antimicrobial drug resistant infections.
- Goal 8: Conduct and support epidemiological studies to identify key drivers of the emergence and spread of AR in various populations.

IV. Product Development

- Goal 9: Provide information on the status of antibacterial drug product development and clarify recommended clinical trial designs for antibacterial products.
- Goal 10: Consider opportunities for international harmonization and means to update susceptibility testing information for human and animal use.
- Goal 11: Encourage development of rapid diagnostic tests and vaccines.

The Task Force will continue to facilitate coordination among agencies and monitor implementation of the plan. As with the 2001 Action Plan, the Task Force will continue to publish annual reports detailing how the plan is being implemented, solicit comments from the public, and if necessary, update the plan.

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 resistance 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 that are resistant to the drug's action. The extensive use of antimicrobial drugs has resulted in drug resistance that threatens to reverse the medical advances 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*), skin, bone, lung, and bloodstream infections (e.g., *Staphylococcus aureus*), urinary tract infections (e.g., *Escherichia coli*), foodborne infections (e.g., *Salmonella* or *E. coli* acquired from meat, eggs, nuts, fresh produce etc), and infections transmitted in healthcare settings (e.g., enterococci, *Acinetobacter baumanii, Pseudomonas aeruginosa*, and *Klebsiella* spp.).

Antimicrobial resistance (AR) is not a new phenomenon; however, the current magnitude of the problem and the speed with which new resistance phenotypes have emerged elevates the public health significance of this issue. In addition, the scarcity of new antimicrobial agents limits treatment options, particularly for patients with infections caused by multidrug-resistant organisms. For example, surveillance data for *S. pneumoniae*, a common cause of bacterial respiratory tract infections, showed that 24 percent of isolates were not susceptible to penicillin. In addition, resistance to several other antibacterial drugs is common; 1.5 percent of isolates were resistant to cefotaxime (a "third generation" cephalosporin antibiotic), and resistance to the newer fluoroquinolone antimicrobials has already been reported.[b] Nearly all strains of *Staphylococcus aureus* in the United States are resistant to penicillin, and many are resistant to newer methicillin-related drugs. Vancomycin for many years has been the only uniformly effective treatment against these methicillin resistant strains, but over the last decade there have been reported strains of *S. aureus* with decreased susceptibility and isolates resistant to vancomycin. The public health burden of methicillin-resistant *Staphylococcus aureus* (MRSA) is staggering with over 90,000 invasive MRSA infections per year estimated in the U.S. population.[c]

---

[b] Active Bacterial Core Surveillance (ABCs) Report Emerging Infections Program Network *Streptococcus pneumoniae*, 2008 available at: http://www.cdc.gov/abcs/reports-findings/survreports/spneu08.pdf

[c] Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, Harrison LH, Lynfield R, Dumyati G, Townes JM, Craig AS, Zell ER, Fosheim GE, McDougal LK, Carey RB, Fridkin SK; Active Bacterial Core surveillance (ABCs) MRSA Investigators. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA. 2007 Oct 17;298(15):1763-71.

Many other pathogens – including the bacteria that cause tuberculosis and gonorrhea, human immunodeficiency virus, the fungi that cause yeast infections, and the parasites that cause malaria – are also becoming resistant to standard therapies. For instance, CDC modified its treatment recommendations for gonorrhea in 2007 due to increasing and widespread fluoroquinolone resistance in *Neisseria gonorrhoeae*.[d] Even as we act to address the problem of AR, we lose quick and reliable treatment options for infections that have been a manageable problem in the United States since the 1940s. Drug choices for the treatment of common infections are becoming increasingly limited and expensive – and, in some cases, nonexistent.

The unpredictable and fluid nature of AR is illustrated by the prevalence of resistant *Acinetobacter baumannii* among military personnel in and returning from conflict areas and the hospital outbreaks of *Clostridium difficile* and *Acinetobacter baumannii*.[e]

Additionally, antimicrobials have been used extensively in livestock and poultry since their discovery for the treatment, control, and/or prevention of animal diseases, as well as for production purposes (e.g., to enhance growth, improve feed efficiency). In contrast to human medicine where treatment is customarily directed at the patient, entire groups of animals may be treated by the use of medicated feed and/or water. As a result of continued exposure to antimicrobials, the prevalence of resistant bacteria in the fecal flora of food animals may be relatively high. Determining the impact of these resistant bacteria on the management of human infections is an ongoing challenge as many classes of antimicrobials used in food-producing animals have analogues to human therapeutics and are therefore capable of selecting for similar resistance phenotypes.

Risk

Drug-resistant infections may be acquired in healthcare 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

[d] Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2006: Fluoroquinolones No Longer Recommended for Treatment of Gonococcal Infections. MMWR 56(14);332-336. April 13, 2007.

[e] Scott P, Deye G, Srinivasan A, Murray C, Moran K, Hulten E, Fishbain J, Craft D, Riddell S, Lindler L, Mancuso J, Milstrey E, Bautista CT, Patel J, Ewell A, Hamilton T, Gaddy C, Tenney M, Christopher G, Petersen K, Endy T, Petruccelli B.An outbreak of multidrug-resistant *Acinetobacter baumannii-calcoaceticus* complex infection in the US military health care system associated with military operations in Iraq. Clin Infect Dis. 2007 Jun 15;44(12):1577-84. Epub 2007 May 8.

Jones A, Morgan D, Walsh A, Turton J, Livermore D, Pitt T, Green A, Gill M, Mortiboy D. Importation of multidrug-resistant *Acinetobacter* spp infections with casualties from Iraq. Lancet Infect Dis. 2006 Jun;6(6):317-8.

Moran KA, McAllister CK, Gray PJ Multidrug-resistant *Acinetobacter* extremity infections in soldiers. Davis KA,. Emerg Infect Dis. 2005 Aug;11(8):1218-24.

Tan ET, Robertson CA, Brynildsen S, Bresnitz E, Tan C, McDonald C. *Clostridium difficile*-associated disease in New Jersey hospitals, 2000-2004. Emerg Infect Dis. 2007 Mar;13(3):498-500.

Munoz-Price LS, Weinstein RA. *Acinetobacter* infection. N Engl J Med. 2008 Mar 20;358(12):1271-81.

overseas. While anyone may acquire a drug-resistant infection, certain people are at increased risk, e.g., patients in hospitals and children in daycare centers. However, resistant microbes are increasingly appearing in new settings. MRSA, which for 30 years was almost exclusively a problem in hospitals, is now occurring in the community.[f]

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 increases. Individuals infected with drug-resistant organisms are more likely to remain in the hospital for a longer time, and to have a poor prognosis.[g] In a 2008 study of antimicrobial resistant infections acquired in the hospital, the medical costs attributable to the infection ranged from $18,588 to $29,069 per patient, hospital stays were extended between 6.4 to 12.7 days, and the attributable mortality of the infection was 6.5%. Using the most conservative estimates, the total cost of resistant infections in the 188 patients from this study was $13.35 million dollars. These findings suggest that significant health and economic benefits are possible through efforts to reduce antimicrobial resistance and healthcare-associated infections.

Solutions

AR will always be with us. The challenge before us is to transform this increasingly urgent threat into a manageable problem. In the past, the Institute of Medicine, the American Society for Microbiology, the World Health Organization (WHO), the Congressional Office of Technology Assessment, the Government Accountability Office, the Infectious Disease Society of America, and other panels of distinguished experts have provided recommendations and options for government action to address the dangers posed by AR. In addition, a 2009 U.S.-EU Summit Declaration included a statement to establish a transatlantic task force on AR.[h] 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.

---

[f] Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, Harrison LH, Lynfield R, Dumyati G, Townes JM, Craig AS, Zell ER, Fosheim GE, McDougal LK, Carey RB, Fridkin SK; Active Bacterial Core surveillance (ABCs) MRSA Investigators. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA. 2007 Oct 17;298(15):1763-71.

[g] Roberts, RR, Hota B, Ahmad I, Scott RD II, Foster SD, Abbasi F, Schabowski S, Kampe LM, Ciavarella GG, Supino M, Naples J, Cordell R, Levy SB, Weinstein, RA. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clin. Infect. Dis. 2009; 49:1175-84.

[h] http://www.whitehouse.gov/the-press-office/us-eu-joint-declaration-and-annexes

Focus Areas

The Action Plan includes action items organized into four focus areas: Surveillance, Prevention and Control, Research, and Product Development. The Action Plan contains specific action items, projects and implementation steps. In addition to these, a selection of AR activities, in which the Task Force will actively engage within the next two years, are highlighted below.[i]

I. 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 that have again become untreatable, as in the pre-antibiotic era. Identification of antimicrobial use information sources and integration of data with existing monitoring and surveillance systems will allow experts to quickly interpret trends and identify strategies to prevent or mitigate the development and/or spread of AR.

The Action Plan incorporates several action items aimed at strengthening, expanding and coordinating existing national and international surveillance systems for antimicrobial-resistant microorganisms. Additional action items in this area focus on reviewing barriers to timely dissemination and updating of surveillance data and providing recommendations and best antimicrobial use practices.

Over the next few years, CDC will address several action items in this focus area by continuing to expand and improve its surveillance systems that collect data on AR. For instance, the National Healthcare Safety Network (NHSN) is a surveillance system that provides healthcare facilities a way to track, analyze, and interpret data on healthcare-associated infections (HAIs), including those caused by antimicrobial-resistant pathogens. NHSN will be expanded to improve its capacity for collection and analysis of data on multidrug-resistant organisms (MDROs) and antimicrobial drug use. In addition to monitoring resistance in healthcare settings, CDC will maintain surveillance activities for pathogens affecting the general population through efforts such as the Emerging Infections Program (EIP), a population-based network of CDC and state health departments, the Gonococcal Isolate Surveillance Project, and the National Tuberculosis Surveillance System. Through the EIP program, CDC closely monitors invasive bacterial pathogens through Active Bacterial Core surveillance and tracks resistance among enteric pathogens through the National Antimicrobial Resistance Monitoring System. In addition to monitoring resistance among bacterial pathogens, CDC will continue to monitor resistance among non-bacterial pathogens such as influenza, malaria and human immunodeficiency virus, both domestically and internationally.

II. Prevention and Control

The prevention and control of antimicrobial-resistant infections requires measures to promote the appropriate use[j] of antimicrobial agents and prevent the transmission of infections (whether drug-

[i] These highlighted activities are provided as illustrative examples and do not represent a comprehensive list.

[j] In this Action Plan, appropriate antimicrobial drug use is defined as use that maximizes therapeutic impact while minimizing toxicity and the development of resistance. In practice, this means prescribing antimicrobial therapy

resistant or not). While development of new antimicrobial agents and effective stewardship of existing agents are cornerstones of activities to protect the health of the nation in the face of expanding AR, successful prevention or elimination of resistance occurs with successful prevention or elimination of resistant microbes. Public health initiatives can be successful. For example, drug-resistant malaria is rampant in parts of the world, but malaria was effectively eliminated from the United States through mosquito control efforts. Antibiotic resistance in *Haemophilus influenzae* was the critical issue that determined antibiotic choice for virtually all invasive bacterial infections in young children in the United States as recently as 15 years ago, but following the introduction of *Haemophilus infuenzae* serotype b (HIB) vaccines this problem has nearly been eliminated.

Other action items in this area focus on extending the useful life of antimicrobial drugs by encouraging appropriate use through educational efforts such as the **Get Smart: Know When Antibiotics Work** campaigns, preventing infection transmission through improved infection control methods and use of vaccines, and preventing and controlling emerging AR problems in agriculture, human and veterinary medicine.

AR prevention and control activities that will be key over the next few years include several interagency collaborations focused on controlling and preventing MRSA infections within healthcare settings. Based upon the successful collaboration between the VA Pittsburgh Healthcare System and CDC that demonstrated a reduction of MRSA infections, the initiative was expanded into an additional 17 sites within the Veterans Health Administration (VHA). The successful prevention of MRSA at the local and regional levels led the VA to expand its MRSA Prevention Initiative, which is now a nationwide effort to reduce occurrence of healthcare-associated MRSA infection from developing while patients are in hospital. VA is also evaluating lessons learned from the MRSA Prevention Initiative to explore expanding this beyond just MRSA to other MDROs, including *Clostridium difficile*.

Also continuing over the next few years is an interagency initiative to identify and help suppress the spread of MRSA and other related infections through an ongoing partnership between CDC and AHRQ. The two agencies are working together closely to identify gaps in the prevention, diagnosis, and treatment of MRSA and related infections across the healthcare system and to fund research, implementation, measurement, and evaluation practices that mitigate healthcare related infections.

Several Task Force member agencies, including AHRQ, CDC, FDA, NIH, CMS and VA, are working to implement the 2008 HHS *Action Plan to Prevent Health Care-Associated Infections* (HAI)[k], which includes both *Clostridium difficile* and MRSA. By working to implement the HHS HAI Action Plan these agencies and partners will impact several areas and action items covered in this 2010 AR Action Plan.

---

when and only when beneficial to a patient; targeting therapy to the desired pathogens; and using the appropriate agent, dose, and duration.

[k] The HHS Action Plan to Prevent Healthcare-Associated Infections is available on the HHS website at: http://www.hhs.gov/ophs/initiatives/hai/infection.html

III. Research

Understanding the fundamental processes involved in AR within microbes and the resulting impact on humans, animals, and the environment forms an important basis for influencing and changing these processes and outcomes. Basic and clinical research provides the fundamental knowledge necessary to develop appropriate responses to the emergence and spread of AR in hospitals, communities, farms, and the food supply. Critical activities in this focus area include support of basic research to uncover new targets and new antimicrobials, investigations into the development of resistance and host-pathogen interactions, optimization of treatment for resistant pathogens, and translation of research findings into clinically useful products, such as novel approaches to detect, prevent, and treat antimicrobial-resistant infections.

Over the next few years, NIH will engage in AR research activities that address several action items in this focus area. For example, NIH currently supports and continues to solicit clinical trials aimed at identifying ways to reduce the use of licensed antibacterials in both community and healthcare settings These trials focus on areas of greatest antimicrobial drug exposure, including pulmonary tuberculosis, pneumonia, otitis media, sinusitis, skin and soft tissue infection, bacteremia, intraperitoneal infection, and surgical prophylaxis. Eligible strategies include, but are not limited to: shorter courses of antimicrobial treatment; using antimicrobials only where indicated; different dosages/frequencies to achieve desirable in vivo efficacy; validation of the key components of multi-drug therapy; prudent antimicrobial use; optimal use of off-patent antimicrobials to prevent the emergence of resistance; and new indications for licensed products.

Recently renewed NIH activities in support of basic research include the Genomic Sequencing Centers for Infectious Diseases and the Bioinformatics Resource Centers for Infectious Diseases. The objective of the sequencing centers is to provide rapid and cost-efficient production of high-quality genome sequences of microorganisms and invertebrate vectors of infectious diseases and to make the resulting genomic data rapidly and readily accessible to the broader scientific community through publicly accessible international databases. In addition, the sequencing centers will provide comparative genomics and genotyping services to examine genetic variation in populations and communities of human pathogens and also across the human genome to identify genetic associations with observable phenotypes in the pathogen and in the human host.

The scope of the bioinformatics resource centers is to provide facilities, equipment, qualified personnel, and all necessary resources and services to collect, archive, update, integrate, and maintain genomics and other types of research data from human pathogens. In addition they provide the scientific community free access to resources for the query, analysis and display of such information through user friendly interfaces.

IV. Product Development

There is a critical need for new drugs, vaccines, and diagnostic tests to treat, prevent, and diagnose infections, including serious and life-threatening infections caused by drug-resistant bacteria. FDA is working on a study to better understand the trends over time in the development

of new antibacterial drugs, the number of drugs approved, and reasons why development programs may not have achieved approval.
The Action Plan incorporates action items that will facilitate the development of vaccines and diagnostic tests for pathogens for which AR poses a significant problem for treatment or public health.

FDA is working on a number of guidances on approaches to evaluating new antimicrobial products. Providing guidance can help by identifying recommended scientific approaches and also to identify areas where additional developmental work would be beneficial for the design and conduct of studies. Over the last few years, FDA has held several public workshops and/or Advisory Committee meetings to discuss clinical trial designs for evaluating antibacterial drugs. FDA has also published several guidance documents that describe recommended approaches regarding clinical trial designs.[l]

One particular example of the efforts to date is the work to refine clinical trial designs for studying antibacterial drugs for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). As part of these efforts, in 2009, FDA co-sponsored a public workshop with the Infectious Diseases Society of America, the American College of Chest Physicians, the Society of Critical Care Medicine, and the American Thoracic Society regarding scientific issues in clinical trial design for HABP and VABP. This public workshop provided information about, and gained perspective from, health care providers, academics, and industry on various aspects of antimicrobial drug development for HABP and VABP, including diagnosis, treatment, trial endpoints, and statistical issues in analysis of results of trials in HABP and VABP.

In the next few years, FDA will engage in activities to address a number of the action items in the Product Development focus area. FDA will be working to provide clarity on recommended approaches for evaluating new medical products for bacterial disease through publishing guidance documents. FDA plans to publish guidance documents on recommended clinical trial designs for evaluating antibacterial drugs for conditions such as acute bacterial skin and skin structure infections and hospital-acquired and ventilator-associated bacterial pneumonia. In addition, FDA also plans to publish guidance for establishing performance for in vitro diagnostics assays for MRSA and vancomycin-resistant enterococci (VRE). These guidances will describe recommended approaches for developing new antimicrobial products for specific uses.

The Biomedical Advanced Research Development Authority (BARDA), in the HHS Office of the Assistant Secretary for Preparedness and Response[m] is designing and implementing programs

[l] Examples of recent guidance documents: Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval (draft, October 2007), Acute Bacterial Sinusitis: Developing Antimicrobial Drugs for Treatment (draft, October 2007), Acute Bacterial Otitis Media: Developing Drugs for Treatment (draft, January 2008), Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment (draft, August 2008), Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment (draft, March 2009), Non-Inferiority Clinical Trials (draft, March 2010)

[m] See http://www.phe.gov/about/barda/Pages/default.aspx for more information on BARDA

that create partnerships between government and industry based on support and incentives that induce the commercial enterprises to address public health and biodefense priorities.

BARDA is currently supporting the development of intravenous formulation of a next generation aminoglycoside antibiotic for the treatment of plague and tularemia, as well as ventilator-associated pneumonia. BARDA is projecting an expansion of this program in the near-term by supporting the development of more novel antimicrobial candidates for the treatment and prevention of diseases caused by bacterial threat agents as well as diseases caused by clinically prevalent infectious diseases, including those that are AR.

The Focus Areas

Within each of the goals listed for each focus area are several action items that define topic areas for specific projects or implementation steps (numbered items). Wherever possible, action items are populated with specific projects or implementation steps (lettered items) to provide greater specificity for planned federal activities. The action items, projects, and implementation steps do not represent an exhaustive list of activities.[n] The expected completion dates for specific projects and implementation steps are indicated with a date. For example, (2011) means that the work is expected to be completed by the end of the 2011 calendar year. Some activities are ongoing and are indicated as such. Since project planning is itself an ongoing activity, these will be updated at least every 2 years.

Focus Area I: Surveillance

Overarching goals

In order to develop and implement effective control strategies there must be 1) continuous or periodic monitoring of infections caused by AR microorganisms and 2) comprehensive knowledge of the use of antimicrobial agents across all sectors.

Goal 1: Improve the detection, monitoring, and characterization of drug-resistant infections in humans and animals.

1.1 Develop strategies to more accurately assess the burden of antimicrobial drug resistance in the community through the enhancement of existing systems including the EIP, and the Epidemiology and Laboratory Capacity (ELC) sites.

a) Implement a multi-site community-onset pneumonia etiology study among persons admitted with pneumonia and evaluate the specific role of antibacterial and antiviral resistance in determining outcomes associated with pneumonia (2011) (see 2009 – 2010 Annual Progress Report).

b) Facilitate surveillance for resistant enteric bacteria by construction of a web interface for data entry and reporting results between state and federal participants in the National Antimicrobial Resistance Monitoring System (NARMS) (2012).

c) Implement electronic tools to query resistance prevalence among enteric pathogens collected in NARMS (2015).

[n] Because of the rapidly evolving nature of AR, there will likely be new or emerging challenges in antimicrobial resistance subsequent to the publication of this Action Plan. The Task Force is committed to identifying and responding to these issues as they arise.

d) Report regular summaries of antimicrobial resistance trends and mechanisms among foodborne bacterial pathogens on the NARMS website and in the literature (2011 and ongoing).

e) Expand the Gonococcal Isolate Surveillance Project (GISP) to include a State public health laboratory for sentinel site reference susceptibility testing (2011) and initiate a CDC administered external quality assessment testing to ensure accurate testing at all 5 sentinel sites (2012).

f) Expand GISP to include surveillance to identify the emergence of cephalosporin-resistant *Neisseria gonorrheae* by monitoring for gonorrhea cephalosporin treatment failures (2011).

Coordinator: CDC; Collaborators: FDA, USDA, VA

1.2 Develop strategies to more accurately assess the burden of antimicrobial resistance in healthcare settings through the enhancement of existing systems including NHSN, the EIP, and ELC sites.

a) Expand NHSN to use electronically captured antimicrobial susceptibility data from participating facilities for reporting of resistance rates and trends; pilot expansion plan in 2011-2012, provide results of pilot in 2012, develop a web-based query for users in 2014 and provide ongoing periodic reports of the collected resistance data (see 2009 – 2010 Annual Progress Report).

b) Report regular summaries to provide national estimates of the resistance burden using data reported on HAIs to NHSN (2011 and ongoing).

c) Evaluate the utility of electronic rules for identifying and reporting central line-associated bloodstream infections, surgical site infections (2011), catheter-related urinary tract infections (2012), and ventilator-associated pneumonia (2012), including associated pathogens; and compare electronic algorithms with traditional manual surveillance by infection control professionals (CLABSIs 2011) (see 2009 – 2010 Annual Progress Report).

d) Develop a system to collect representative sets of bacterial isolates to assess changes in resistance mechanisms or strains nationally and work with the Clinical and Laboratory Standards Institute (CLSI) to determine the impact of changes on antimicrobial susceptibility testing and reporting practices in the United States.

e) Collect convenience samples of bacterial and fungal isolates through the EIP to assess changes in antimicrobial-resistant pathogens such as MRSA (2011), *Clostridium difficile* (2011), and selected gram-negative bacteria (2012), as well as community-associated pathogens such as *S. pneumoniae*, *N. meningitidis*, and *Salmonella* spp.; determine the feasibility of routine isolate submission for validation of antimicrobial susceptibility data submitted to NHSN (2012).

f) Implement (2011) a periodic national prevalence survey for healthcare-associated infections, including those caused by antimicrobial-resistant pathogens (see 2009 – 2010 Annual Progress Report).

Coordinator: CDC; Collaborator: VA

1.3 Assess the presence of antimicrobial-resistant microorganisms, such as MRSA, *Clostridium difficile*, and vancomycin-resistant enterococci (VRE), among food animals, retail meats, and household environment in the United States. Assessment should include comparison of isolates from humans, environment, retail meats, and food animals.

a) Design and implement a 1 year prevalence study of MRSA, VRE, and *Clostridium difficile* from retail meat (2011).

b) Evaluate the quantity of *Clostridium difficile* recovered from retail meats in FoodNet sites (see 2009 – 2010 Annual Progress Report).

c) Conduct a pilot study to evaluate *Clostridium difficile* environmental contamination in households of infected and non-infected patients (see 2009 – 2010 Annual Progress Report).

d) Characterize and compare recovered food bacterial isolates with those associated with environmental assessments and human illness (2012).

Coordinator: CDC; Collaborators: FDA, USDA

1.4 Identify patient populations colonized or infected with antimicrobial-resistant pathogens which may be important both for transmission of pathogens themselves and the transfer of resistance genes (e.g. vancomycin-resistant *Staphylococcus aureus*). Use this information to develop prevention strategies.

a) Identify populations at risk for *Clostridium difficile* and MRSA infections based on data from population-based surveillance systems (see 2009 – 2010 Annual Progress Report).

b) Conduct studies of colonization with antimicrobial-resistant *S. pneumoniae* to determine the effects of antimicrobial use and pneumococcal vaccination on colonization (2012).

Coordinator: CDC; Collaborator: NIH, VA

1.5 Strengthen and expand multi-state, national and international surveillance systems for antimicrobial-resistant microorganisms and ensure adequate sentinel surveillance for the emergence and spread of critical resistance phenotypes (e.g., penicillin-resistance in Group A *Streptococcus*, multidrug resistant and extensively drug-resistant tuberculosis (XDR TB), oseltamivir-resistant influenza viruses), and strive for more timely dissemination of surveillance data.

a) Increase the number and capacity of public health laboratories that routinely monitor for influenza antiviral resistance by developing new assays for rapid testing for antiviral resistance (2011) and developing web-based reporting systems (2012).

b) Increase the capacity of state public health laboratories to identify antimicrobial-resistant organisms among cases of culture-negative clinical syndromes (e.g., meninigitis, empyema) using real-time polymerase chain reaction (PCR) for species-specific genes and markers of antimicrobial resistance (2013).

c) Routinely evaluate isolates captured through ABCs with unusual resistance profiles (e.g., penicillin-resistant Group A or Group B *Streptococcus*, or vancomycin resistance among any of the *Streptococcus* pathogens) to identify resistance and characterize the molecular mechanisms (annually) (see 2009 – 2010 Annual Progress Report).

d) Assess the impact of including data on susceptibility to multiple fluoroquinolones and injectable agents (aminoglycosides and capreomycin) to the national TB reporting system for enhanced detection of XDR TB (see 2009 – 2010 Annual Progress Report).

e) Complete a pilot exercise to expand routine nationwide surveillance for MDR TB to include additional drugs and determine whether this additional surveillance provides useful information that warrants broader implementation (see 2009 – 2010 Annual Progress Report).

f) Organize, plan and conduct a NARMS public scientific meeting to highlight results and related AR research and solicit input from stakeholders and international partners on future enhancements and improvements (see 2009 – 2010 Annual Progress Report).

Coordinator: CDC; Collaborators: DoD, FDA, USDA, VA

1.6 Work with public health associations, including Association of Public Health Laboratories (APHL) and Council of State and Territorial Epidemiologists (CSTE), to define minimal surveillance activities for AR for local, state, and regional health departments. Enhance the accurate detection and identification of AR by clinical and public health laboratories.

a) Develop consensus definitions for outbreaks of antimicrobial-resistant pathogens that are reportable to health departments to optimize the detection, investigation and resolution of outbreaks (2011).

b) Disseminate expert recommendations for effective state-based surveillance for multidrug-resistant organisms related to healthcare-associated infections (see 2009 – 2010 Annual Progress Report).

c) Implement standard protocols for antimicrobial susceptibility testing through CDC's ELC Program (ongoing) (see 2009 – 2010 Annual Progress Report).

d) Develop and implement an antimicrobial susceptibility testing training program for public health laboratories (2012).

e) Establish a web-based training program, updated annually, on laboratory detection of AR (pilot in 2013 and implement in 2014).

Coordinator: CDC

1.7 Promote participation of microbiologists and local, state, and national public health workers in the design of systems to collect and disseminate AR data to appropriate end-users. Identify methods to assist laboratories in summarizing and disseminating AR data to appropriate end-users and provide methods for individual laboratories to compare their data with data in surrounding regions.

a) Establish state-based surveillance networks utilizing NHSN to aggregate local-level data on healthcare-associated infections, multidrug-resistant organisms, and/or *Clostridium difficile* infections for targeted prevention interventions (2011) (see 2009 – 2010 Annual Progress Report).

b) Coordinate the collection of AR data for select veterinary bacterial pathogens by partnering with State veterinary diagnostic laboratories (2011).

Coordinator: CDC; Collaborators: FDA, USDA, VA

1.8 Collaborate with surveillance systems in other parts of the world to build global surveillance of AR microorganisms.

a) Establish liaisons with reference laboratories in countries without well-developed surveillance systems, both to improve the accuracy of global surveillance for resistance and to improve local use of the data (ongoing) (see 2009 – 2010 Annual Progress Report).

b) Support and assist WHO on matters related to integrated surveillance of AR and containment of food-related AR through participation in the newly establish WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR) (ongoing). (see 2009 – 2010 Annual Progress Report)

- NARMS scientists from FDA, CDC and USDA will provide expert advice to the WHO-AGISAR steering committee through participation and information sharing (2012) (see 2009 – 2010 Annual Progress Report).
- Support laboratory capacity building activities in WHO member countries for AR monitoring by developing AR modules for Global Foodborne Infections Network training courses (2011-2012).

c) Develop collaborations with International Emerging Infections Program (IEIP) sites to improve surveillance systems for AR, facilitate prevention programs, and ensure appropriate responses to outbreaks of resistant organisms (ongoing) (see 2009 – 2010 Annual Progress Report).

d) Collaborate with IEIP sites to expand surveillance systems to measure the burden of AR and the impact of infection control interventions in healthcare settings (2011).

Coordinator: CDC; Collaborators: DoD, FDA, USDA

1.9 Develop national and international surveillance systems to monitor understudied areas, such as resistance in protozoan parasites (e.g. *Plasmodium* spp.) helminthes or understudied sexually transmitted diseases (e.g., *T. pallidum, T. vaginalis*, *Herpes simplex*), neglected tropical diseases, and resistance to disinfectants, sanitizers, and insecticides.

a) Identify resistance mechanisms in *Trichomonas* and use this information to develop laboratory tests for detection of resistance (2012).

b) Identify and characterize markers of artemisinin-based combination therapies (ACT) resistance in malaria for the purpose of developing new laboratory tests for surveillance (2012).

c) Work with international partners to conduct in vivo/ in vitro studies to monitor the efficacy of anti-parasitic drugs (2013).

d) Collect a repository of specimens with characterized antimalarial drug sensitivity patterns for the development of laboratory test development and quality control (2012). Laboratory tests will be used to expand surveillance.

e) Work with international partners to improve laboratory capacity in endemic countries for the detection and surveillance of malaria drug- resistant parasites (2012).

f) Evaluate current strategies for deploying insecticides for public health that reduce or minimize resistance and as necessary develop new strategies. (2012).

Coordinator: CDC; Collaborator: DoD

1.10 Assess the risk of AR emergence and spread in food borne pathogens due to environmental contamination by antimicrobial drug residues and pesticides in collaboration with the existing Pharmaceuticals in the Environment Subcommittee of the Office of Science and Technology Policy.

Coordinator: FDA; Collaborator: EPA

Goal 2: Better define, characterize, and measure the impact of antimicrobial use in humans and animals in the United States.

2.1 Identify sources of antimicrobial use information in the United States for humans, animals, agriculture, aquaculture, and other sectors to establish baseline data on antimicrobial use. Develop a standard for collecting and reporting schemes for antimicrobial use data that allow aggregation, reporting, and comparisons of trends across sectors.

a) Gain access to and summarize de-identified data on antimicrobial use from market research companies, health maintenance organizations, federal healthcare systems, and other medical care systems in the United States to aid in quantifying antimicrobial use in humans and understanding geographical heterogeneity in antimicrobial use (2011).

b) Perform a national antibiotic use point-prevalence survey - pilot survey to be completed by 2010 and full survey by 2012 (see 2009 – 2010 Annual Progress Report).

c) Revise the Antibiotic Use and Resistance module of NHSN to accept electronic data on antibiotic use from healthcare facilities by 2011 and begin receiving data by 2012.

d) Collect and publish annual reports on animal antimicrobial drug distribution data through implementation of Section 105 of the Animal Drug User Fee Amendments of 2008 (2010 and ongoing) (see 2009 – 2010 Annual Progress Report).

e) Collect data through the National Animal Health Monitoring System to produce 3 reports on antimicrobial use practices on livestock and poultry operations in the United States. These reports (shown below) will be produced by July 2011 (see 2009 – 2010 Annual Progress Report):

- Food Safety Pathogens Isolated from U.S. Dairy Operations, 1996-2007
- Antimicrobial Use and Resistance on Beef Cow-calf Operations in the U.S. 2007-08
- Antimicrobial Use and Resistance Across Livestock and Poultry Operations - A compilation of data from the National Animal Health Monitoring System studies

Coordinator: FDA, CDC; Collaborators: USDA, VA

2.2 Develop mathematical models to guide studies of use and resistance in both humans and animals by collating existing data on correlations between antimicrobial use and antimicrobial resistance from studies in veterinary and human healthcare settings (e.g., cephalosporin use and prevalence of vancomycin-resistant enterococci in intensive care units) and community settings (e.g., fluoroquinolone use for respiratory tract infections and macrolide resistance in pneumococci).

a) Compare retail pharmacy sales of outpatient oral antimicrobials to geographic differences in bacterial resistance (2011).

Coordinator: CDC; Collaborators: NIH, USDA, VA

2.3 Implement systems to detect the development and spread of resistance in microorganisms during implementation of new programs that significantly impact antimicrobial drug use (e.g., pay-for-performance mandates on antibiotic timing for community-acquired pneumonia, guidelines for intrapartum prophylaxis to prevent neonatal group B streptococcocal disease, mass population-based treatment campaigns for trachoma or helminthic infections, or large studies of treating partners or contacts).

a) Monitor the use of intrapartum antimicrobial prophylaxis for the prevention of neonatal group B streptococcal infections and the potential impact of prophylaxis on resistant cases of neonatal sepsis (2013).

Coordinator: CDC

Focus Area II: Prevention and Control

Overarching goals

Federal agencies are strong advocates of prevention and control measures that will both decrease the development of new resistant microorganisms and stop the transmission of existing resistant microorganisms in healthcare institutions, communities, and agriculture.

Goal 3. Develop, implement, and evaluate strategies to prevent the emergence, transmission, and persistence of drug-resistant microorganisms.

3.1 Implement and evaluate the impact of community-based interventions, such as vaccination campaigns and the promotion of appropriate antibiotic use to reduce the spread of AR microorganisms, rates of disease, and antimicrobial use, and to improve patient outcomes.

a) Estimate the effectiveness of pneumococcal and influenza vaccines on drug-resistant infections caused by those pathogens (2012).

b) Evaluate factors that influence the prescribing practices of primary care physicians, including academic detailing and benchmark analysis (2011).

Coordinator: CDC; Collaborators, DoD, VA

3.2 Promote use of appropriate interventions, including checklists, to reduce the risk of infection associated with catheters and other devices and procedures in healthcare settings.

a) Facilitate multicenter prevention collaborative focused on device and procedure-related infections in at least 20 states by 2012.

b) Design and implement systems to measure healthcare processes that are linked to outcome data in order to measure the adherence of healthcare personnel to prevention measures.

c) Correlation between adherence to best catheter insertion practices and CLABSI rates (2011).

d) Revise and publish HICPAC guidance for prevention of catheter-associated bloodstream infections (see 2009 – 2010 Annual Progress Report).

e) Revise and publish HICPAC guidance for prevention of surgical site infections (2011).

Coordinator: CDC; Collaborators: AHRQ, VA

3.3 Identify and promote successful AR prevention and control programs in healthcare settings that utilize existing recommendations for preventing transmission of AR organisms.

a) Establish state-based MDRO and *Clostridium difficile* prevention collaborative in at least 10 states by 2011 and evaluate impact by 2013.

b) Evaluate impact of the CMS-Quality Improvement Organization MRSA prevention initiative by 2012.

c) Evaluate impact of the Department of Veterans Affairs National MRSA prevention initiative (2012). Explore the expansion of prevention initiatives to include other MDRO including *Clostridium difficile* and multidrug-resistant gram-negative pathogens (see 2009 – 2010 Annual Progress Report).

d) Facilitate initiation of at least one regional, multi-center prevention collaborative in which acute and long-term care facilities address prevention of multi-drug resistant infections in a coordinated manner (2011).

Coordinator: CDC; Collaborators: AHRQ, VA, CMS

3.4 Evaluate the effectiveness of infection-control practices, products, and devices in healthcare facilities, including long-term healthcare and outpatient settings.

a) Expand CDC's Prevention Epicenter Program to include academic centers, integrated health systems, and healthcare departments to support early translation of technical advances and epidemiologic knowledge into evidence-based recommendations (2011).

b) Initiate studies that will assess the dynamics of contamination of the healthcare environment and the ability of cleaning and disinfection methods to reduce environmental contamination (2011).

c) Evaluate the impact of state-based CDC-funded HAI prevention collaborative by 2013.

d) Quantify the national impact of HAI prevention efforts by publishing annual national summary statistics (standardized infection ratio) of HAI data reported to CDC's NHSN (ongoing) (see 2009 – 2010 Annual Progress Report).

Coordinator: CDC; Collaborators: AHRQ, DoD, VA

3.5 Identify factors that reduce transmission of drug-resistant pathogens, including infection control, in veterinary, agriculture and aquaculture settings (ongoing).

a) Identify critical control points on-farm for dairy production that will decrease antimicrobial resistant salmonellae (2011). Evaluate interventions in dairy production that will decrease antimicrobial resistant salmonellae (2012).

b) Make available grant funds of up to $4 million through USDA's National Integrated Food Safety Initiative to support systematic studies that identify intervention strategies for effective mitigation of AR throughout the food chain. These 4-year grants began in 2010 and will be completed no later than 2015 (see 2009 – 2010 Annual Progress Report).

c) Identify factors important for assuring that antimicrobial drugs are used judiciously in veterinary, agriculture and aquaculture environments (see 2009 – 2010 Annual Progress Report).

Coordinators: FDA, USDA

3.6 Promote research and development of processing technologies to minimize microbial contamination of food.

a) Develop alternatives to current antimicrobial treatments and sanitizers for processing poultry carcasses (e.g. natural Generally Recognized as Safe [GRAS] products) (2011). Evaluate alternative sanitizers for poultry processing and their reduction of food pathogens (2012).

b) Develop alternatives to current processing treatments for the reduction of *Escherichia coli* in beef (2011). Evaluate effectiveness of processing treatments (2012).

c) Identify processing interventions to decrease antimicrobial-resistant microorganisms in eggs (2011). Evaluate alternative interventions in egg processing for reduction of antimicrobial-resistant microorganism (2012).

Coordinator: USDA

3.7 Expand public health education campaigns targeting food producers, food handlers, and the general public about food safety practices that reduce microbial contamination of food.

a) Co-host the 2010 Food Safety Education Conference: USDA and NSF International will co-host a 3-day conference sponsored by HHS, FDA, CDC, and WHO. The conference is designed for attendees to share the most current research, learn best practices, and explore cutting-edge strategies for reducing foodborne illness (see 2009 – 2010 Annual Progress Report).

b) Launch new USDA Food Safety Mobile Program in spring 2010 as part of the Food Safety and Inspection Service's ongoing consumer education campaign to reach consumers where they live. The USDA Food Safety Mobile will travel throughout the United States visiting local community events to educate consumers about food safety. The revamped program will offer consumers in-depth, interactive, hands-on demonstrations on the science of food safety based on the four Be Food Safe Campaign messages: Clean, Separate, Cook and Chill. The Mobile's interactive learning stations are designed to improve consumer's food safety awareness, knowledge, and behavior (see 2009 – 2010 Annual Progress Report).

c) Host USDA Nutrition Month to include Food Safety Day on March 10, 2010 to increase consumer awareness about food safety (see 2009 – 2010 Annual Progress Report).

Coordinator: USDA

3.8 Promote infection control education at all stages of training and practice for healthcare workers in human and veterinary medicine.

a) Complete basic infection control curriculum for posting on the CDC website by 2011.

b) Develop a plan for infection control education of veterinary medicine workers by 2011.

Coordinator: CDC; Collaborator: USDA, VA

3.9 Develop interagency programs in collaboration with regulators, payers, professional societies and other stakeholders to promote effective hand hygiene strategies in communities and healthcare settings and to foster the use of biomedical devices and behaviors that prevent the transmission of infectious organisms in community settings.

a) Develop a plan to collaborate with WHO on their hand hygiene promotion campaign (see 2009 – 2010 Annual Progress Report).

b) In collaboration with academic partners, complete research studies that evaluate the impact of novel technologies for measuring hand hygiene adherence in the healthcare setting (2011).

Coordinator: CDC; Collaborator: AHRQ, VA

Goal 4: Develop, implement, and evaluate strategies to improve appropriate antimicrobial use.

4.1 Identify factors and strategies that promote appropriate antimicrobial use (i.e., best practices) or discourage inappropriate use in all types of healthcare settings, including inpatient and outpatient facilities, clinics and offices. Facilitate the implementation of these strategies.

a) Develop algorithms and reporting tools to facilitate local monitoring of antimicrobial use (pilot 2011 and implement 2012) and resistance rates (pilot 2011) (see 2009 – 2010 Annual Progress Report).

b) Develop a "change package" for improving antimicrobial use in in-patient healthcare settings (see 2009 – 2010 Annual Progress Report).

c) Collaborate with a network of hospitals to identify patient-level indications for and factors associated with antibiotic use to help guide efforts on improving use by 2011.

d) Examine knowledge, attitudes, and behaviors of healthcare providers regarding adverse events and antimicrobial use (see 2009 – 2010 Annual Progress Report).

e) Examine the impact of improved antimicrobial use on adverse events associated with antimicrobials, especially *Clostridium difficile* infections by 2011.

f) Evaluate the benefits and potential unintended consequences of clinical guidelines and policies that bear on antimicrobial use and affect patient care, reimbursement, or other areas of medical practice (e.g., increased use of antimicrobial agents in emergency rooms for unconfirmed community-acquired pneumonia) (2012).

Coordinator: CDC; Collaborators: AHRQ, FDA, VA

4.2 Promote, implement, and evaluate guidelines for appropriate antimicrobial use in agricultural and veterinary settings. Specifically,

a) Seek appropriate expert input to update specific aspects of guidance 152 (particularly the antimicrobial drug ranking in Appendix A of guidance) and publish revised draft guidance for public comment (2011-2012).

b) Publish and seek public comment on draft guidance outlining FDA's current thinking on the judicious use of medically important antimicrobial drugs in food-producing animals (see 2009 – 2010 Annual Progress Report).

c) Publish a revised order to prohibit certain extralabel uses of cephalosporin antimicrobial drugs in food producing animals due to AR concerns (2011).

d) Survey orchards periodically for emerging resistance among agricultural bacterial plant pathogens (e.g., *Erwinia amylovera*, *Pseudomonas syringae*, and *Xanthomonas campestris*) to tetracycline, streptomycin, gentamicin, or other antimicrobial agents that may be used, such as kasugamycin. Monitoring is conducted to comply with pesticide use authorization.

Coordinators: FDA; Collaborators: CDC, USDA

4.3 Promote the development of improved field-based methods to measure the quality of antimalarial drugs, given that poor quality drugs contribute to antimicrobial drug resistance.

Coordinator: CDC

4.4 Develop, implement, and evaluate treatment algorithms for management of common clinical syndromes frequently treated with antibiotics (e.g., ventilator-associated and community-acquired pneumonia, acute bronchitis and sinusitis, and asymptomatic bacteriuria and sexually transmitted diseases.

a) Update the *Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Infections* and develop and disseminate academic detaining sheet with diagnosis and treatment algorithms (2012).

b) Update the *Guidelines for Appropriate Antibiotic Use for Treatment of Acute Respiratory Tract Infections in Adults* and develop and disseminate academic detailing sheet with diagnosis and treatment algorithms (2014).

Coordinator: CDC; Collaborator: NIH, VA

Focus Area III: Research

Overarching goals

Encourage, conduct and support basic and translational research to enhance our understanding of factors leading to the development of AR microorganisms, their transmission in various settings, and optimal modes of prevention, diagnosis and therapy.

Goal 5: Facilitate basic research on AR.

5.1 Conduct and support genetic, biochemical and structural studies of AR factors to enable the identification of novel drug, diagnostic and vaccine targets.

Coordinator: NIH

5.2 Investigate naturally occurring mechanisms of resistance, gene transfer, and host-pathogen interactions.

Coordinators: CDC, NIH; Collaborators: FDA, USDA

5.3 Investigate the role of biofilms in the development of resistant microorganisms and transfer of resistance genes among diverse genera of microorganisms.

Coordinators: CDC, NIH; Collaborators: FDA, USDA

5.4 Develop and make available genomics, metagenomic, bioinformatics, proteomics, structural biology, molecular imaging, and other emerging research technologies. Ensure that genomic, proteomic, and other related data sets are made publicly available rapidly through searchable public online databases and provide data analysis tools to assist researchers in using these resources.

Coordinator: NIH; Collaborators: CDC, DoD, FDA, USDA

5.5 Bring new researchers into the field by utilizing appropriate strategies such as training and research opportunities.

Coordinators: CDC, NIH; Collaborator: FDA

Goal 6: Facilitate the translation of basic research findings into practical applications for the prevention, diagnosis and treatment of resistant infections.

6.1 Facilitate preclinical studies, including toxicology, pharmacokinetics, pharmacodynamics, and *in vitro* and *in vivo* activity of antimicrobial agents to inform the treatment of resistant pathogens.

Coordinator: NIH; Collaborators: CDC, FDA

6.2 Encourage, support and conduct basic and clinical research on the development and use of vaccines and novel or alternative approaches for prevention and treatment of infections in human and veterinary medicine.

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

6.3 Encourage, support and conduct research on the development of novel diagnostic technologies to rapidly distinguish among pathogens and their resistant subtypes at the point of care.

Coordinator: NIH

6.4 Support development of novel broad spectrum antimicrobials with dual indications for community-acquired infections and biodefense threat agents.

Coordinator:HHS/ASPR; Collaborator: NIH, CDC

Goal 7: Facilitate clinical research to improve the treatment and prevention of AR infections.

7.1 Conduct and support clinical research to evaluate the safety and efficacy of novel drugs and vaccines for pathogens where resistance threatens effective treatment.

Coordinator: NIH

7.2 Design and implement studies focused on optimizing the dose and duration of antibacterial agents prescribed for treatment of community-acquired pneumonia, urinary tract infections, skin and soft-tissue infections, and other infectious illnesses.

Coordinator: NIH

Goal 8: Conduct and support epidemiological studies to identify key drivers of the emergence and spread of AR in various populations.

8.1 Investigate the interplay among AR, colonization, and disease in acute, long-term care, and outpatient facilities.

Coordinator: CDC; Collaborator: NIH, VA

8.2 Support research on how prevalence data on antimicrobial resistance can be used to help guide treatment choices. For example, define geographic heterogeneity of resistance rates and determine impact of treatment decisions.

a) Define appropriate methods for collection and distribution of information on prevalence of resistance to community physicians and veterinarians.

Coordinator: CDC; Collaborators: FDA, USDA, VA

8.3 Evaluate the utility 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 to identify reservoirs of resistant organisms.

a) Investigate risk factors for AR development in *Salmonella* and *Campylobacter* in food animals (2014).

Coordinator: CDC; Collaborator: FDA, USDA

8.4 Develop options to capture and record AR research for all federal agencies.

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

Focus Area IV: Product Development

Overarching goals

Encourage the development of new antimicrobial products to improve our capacity to diagnose, prevent and treat infections, including infections caused by resistant microorganisms.

Goal 9: Provide information on the status of antibacterial drug product development and clarify recommended clinical trial designs for antibacterial products.

9.1 Examine trends over time for new drug applications for systemic antibacterial drugs.

a) Perform pilot phase of study to evaluate trends over time for new drug applications for systemic antibacterial drugs; complete assessment of trends over time for new drug applications for systemic antibacterial drugs (2011) and publish findings (2012) (see 2009 – 2010 Annual Progress Report).

Coordinator: FDA

9.2 Publish guidance documents for the following conditions describing recommended approaches on clinical trial designs for evaluating antibacterial drugs.

a) Publish guidance on recommended approaches to clinical trial designs for evaluating antibacterial drugs for acute bacterial skin and skin structure infections (2012) (see 2009 – 2010 Annual Progress Report).

b) Publish guidance on recommended approaches to clinical trial designs for evaluating antibacterial drugs for hospital acquired and ventilator associated bacterial pneumonia (2012) (see 2009 – 2010 Annual Progress Report).

c) Publish updated guidance on recommended approaches to clinical trial designs for evaluating antibacterial drugs for community-acquired bacterial pneumonia. Publish updated draft guidance (2011) and final guidance (2012) (see 2009 – 2010 Annual Progress Report).

Coordinator: FDA

9.3 Publish guidance documents for the following types of devices to provide recommendations regarding product development.

a) Publish final guidance document on premarket notification [510(k)] submissions for medical devices that include antimicrobial agents (2012).

b) Publish draft guidance for establishing performance for *in vitro* diagnostics assays for MRSA and VRE (2011). Publish final guidance (2012).

c) Publish draft guidance document for establishing performance for in vitro diagnostic assays for *Clostridium difficile*. Publish final guidance (2011).

Coordinator: FDA

9.4 Provide regulatory advice on recommended regulatory pathways for evaluating products that target unmet medical or veterinary needs including approaches to evaluating non-traditional products, e.g., cytokine, probiotics, and antimicrobial peptides (ongoing).

Coordinator: FDA; Collaborator: USDA

9.5 Evaluate use of the Orphan Drug Act, or similar incentives, to encourage development and marketing of new antimicrobial agents for human medicine.

a) Part 15 public hearing held April 28, 2008, on issues in AR and the Orphan Drug Act.

Coordinator: FDA

9.6 Sponsor a study to evaluate incentives to promote the development of antibacterial drugs for human use and rapid diagnostic tests (including antimicrobial susceptibility tests), including the impact of such strategies upon appropriate use of such products. Prepare a report for publication describing the study results (2012).

Coordinator: HHS/ASPE

Goal 10: Consider opportunities for international harmonization and means to update susceptibility testing information for human and animal use.

10.1 Pursue interagency collaborations to discuss international harmonization of standards and regulatory requirements for antimicrobial products (e.g., International Conference on Harmonization, International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medical Products) (ongoing).

Coordinator: FDA

10.2 Collaborate with relevant international organizations and use international expert consultations (e.g., the WHO, the World Organization on Animal Health, CLSI standards Institute, the European Committee on Antimicrobial Susceptibility Testing) to enhance product development (ongoing).

Coordinator: FDA; Collaborator: NIH

10.3 Develop a strategy for periodic updating of susceptibility testing information for antimicrobial agents approved for use in humans and animals in the United States (ongoing).

a) Participate in multi-laboratory method trial studies to develop standardized *in vitro* antimicrobial susceptibility testing methods for veterinary pathogens where such tests are lacking (2011) (see 2009 – 2010 Annual Progress Report).

Coordinators: CDC, FDA; Collaborator: USDA

Goal 11: Encourage development of rapid diagnostic tests and vaccines.

11.1 Encourage development, testing, evaluation, and regulatory approval of new rapid diagnostic methods for human and veterinary use to help guide antimicrobial therapy and to facilitate the clinical development of antimicrobial drugs.

a) Promote the development of tests for infections cause by fastidious (e.g. mycobacteria) or difficult to culture organisms (e.g. *Treponema pallidum*, the agent of syphilis) and rapid point-of-care diagnostics to identify patients with viral respiratory infections who do not need antimicrobial agents.

b) Encourage the development and implementation of improved diagnostic tests for drug-resistant TB by conducting a FDA/CDC/NIH co-sponsored meeting to identify gaps in TB diagnostics, streamline regulatory frameworks, and explore models and strategies that may expedite the development of new diagnostics (see 2009 – 2010 Annual Progress Report). Work to develop, evaluate, and implement molecular tests for the detection of MDR-TB directly from pulmonary specimens (2012).

c) Encourage development of rapid point-of-care tests to confirm diagnoses of possible bacterial respiratory infections including otitis media, sinusitis, and pneumonia and rapid point-of-care tests to identify pathogens associated with these infections (ongoing).

d) Collaborate with partners to develop and evaluate rapid methods for identification and characterization of *Clostridium difficile*, MRSA, and other multidrug-resistant organisms for human, animal, and plant sources to support national surveillance efforts (see 2009 – 2010 Annual Progress Report).

Coordinators: CDC, FDA; Collaborators: NIH, USDA, HHS/ASPR, VA

11.2 Encourage development, testing, and evaluation of new vaccines for human pathogens for which AR poses a significant problem for treatment or public health.

a) Working with stakeholders, examine strategies to maximize the quality and the quantity of candidate vaccines for prevention of antimicrobial-resistant infections of public health significance (ongoing).

b) Conduct research to facilitate development of vaccines for resistant pathogens such as *Staphylococcus aureus, Mycobacterium tuberculosis, Clostridium difficile,* enteric pathogens and *Neisseria gonorrhoeae* (ongoing).

c) Conduct research to facilitate development of vaccines for viral respiratory infections that may contribute to increased antibiotic use due to subsequent or co-bacterial infections or inappropriate antibiotic use (ongoing).

Coordinator: FDA; Collaborators: CDC, NIH, VA

11.3 Support advanced development of vaccines for resistant pathogens such as *Staphylococcus aureus*.

Coordinator: HHS/ASPR

Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
APHL	Association of Public Health Laboratories
AR	Antimicrobial resistance
ASPE	Office of the Assistant Secretary for Planning and Evaluation
ASPR	Office of the Assistant Secretary for Preparedness and Response (HHS)
BARDA	Biomedical Advanced Research Development Authority
CDC	Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
CMS	Centers for Medicare and Medicaid Services
CSTE	Council of State and Territorial Epidemiologists
DoD	Department of Defense
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HAI	Healthcare-associated infection
HAP	Hospital-acquired pneumonia
HHS	Department of Health and Human Services
HRSA	Health Resources and Services Administration
IPEC	Inpatient Evaluation Center
MDRO	Multidrug-resistant organism
MRSA	Methicillin-resistant *Staphylococcus aureus*
NHSN	National Healthcare Safety Network
NIH	National Institutes of Health
USDA	United States Department of Agriculture
VA	Department of Veterans Affairs
VAP	Ventilator-associated pneumonia
VHA	Veterans Health Administration
XDR TB	Extensively drug-resistant tuberculosis