2011 PROGRESS TOWARDS IMPLEMENTATION OF:

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 Health

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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

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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), the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response (HHS/ASPR), and the Department of Health and Human Services Office of the Assistant Secretary for Health (HHS/OASH).

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.

The 2011 revision of the Action Plan was 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.

[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.

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

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]

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[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.

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[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.

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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).

Progress: The study has been implemented with continued patient enrollment through May 2012. A published final report is expected by the end of 2013.

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).

[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.

Progress: NARMS representatives participated in regular interagency calls and ad hoc calls with Booz Allen Hamilton contractors and FDA business process improvement experts to help refine goals and requirements for the integrated database.

CDC, ARS, and FDA continued to contribute summary data for interagency executive summary reports which will continue until true integration of specimen-level data can be achieved.

ARS and FDA have been using Crystal Dashboard to post interactive graphs of NARMS data on the web since 2004. ARS provided the templates to CDC and FDA to incorporate data for interactive graphs exhibiting data simultaneously from all three arms of NARMS. Interactive graphs were first added as a supplement to the online publication of the 2005 NARMS Executive Report. ARS also linked the NARMS data with USDA VetNet data for concurrent analysis of susceptibility and PFGE of isolates. Data is routinely submitted to USDA FSIS for use in their regulatory program.

In 2011, CDC obtained security approvals for Crystal Dashboard software that will allow them to post interactive graphs of NARMS data on the NARMS webpage. OCISO approval was obtained in 2011, and the software was purchased. CDC also made major headway on construction of the CDC NARMS database and web tool that will allow CDC to acquire specimen-level data from state participants and ultimately communicate specimen level and summary susceptibility data back to the participants in ways that will allow them to query, report, and share the information they need when they need it.

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

Progress: NARMS representatives participated in regular interagency calls and ad hoc calls with Booz Allen Hamilton contractors and FDA business process improvement experts to refine requirements for the integrated database. CDC continued to contribute summary data for interagency executive summary reports which will continue until true integration of specimen-level data can be achieved. In 2011, CDC obtained security approvals for Crystal Dashboard software that will allow us to post interactive graphs of NARMS data on the NARMS webpage. CDC also made major headway on construction of the CDC NARMS database and web tool that will allow CDC to acquire specimen-level data from state participants and ultimately communicate specimen level and summary susceptibility data back to the participants in ways that will allow them to query, report, and share the information they need when they need it.

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).

Progress: In 2011, NARMS partners published 2009 data in the NARMS Executive Report (FDA), the human isolate annual report (CDC), the food animal annual report (USDA) and the retail meat report (FDA). on the respective NARMS websites. In 2011,

NARMS scientists published 22 peer-reviewed scientific manuscripts describing clinically- and epidemiologically-relevant trends and mechanisms of resistance among *Salmonella*, *Shigella*, *Campylobacter*, *E. coli* nd other pathogens. In addition to contributions to peer-reviewed scientific journals, CDC-NARMS scientists continued to work with CLSI to share data relevant to breakpoint decisions, and conducted and presented value-added studies with isolates from the NARMS collection relevant to breakpoint setting for fluoroquinolones and macrolides. These studies included results from drugs and/or methods not routinely tested by NARMS. In the case of azithromycin, results of preliminary testing and changes in clinical use of this drug led to the decision to add azithromycin to the routine NARMS test panel for Enterobacteriaceae. CDC also analyzed susceptibility data for outbreak isolates tested from 2004-2008 and enhanced testing of isolates from enteric disease outbreaks.

ARS and FDA routinely uploaded provided AR and PFGE information to CDC's PulseNet database for outbreak investigations and supported FSIS during the outbreak and recall investigations by providing AR and PFGE data. ARS-NARMS also began on-farm pilot studies of resistance in swine, beef, dairy, broiler and turkey production to evaluate the prospects for a new preharvest component for NARMS. ARS-NARMS provided 160 NARMS isolates to FDA for use in the FDA SAFE project to develop new diagnostic tests.

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).

Progress: The laboratory successfully passed the external quality-assessment testing and began testing GISP isolates during 2011.

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

Progress: The activity has started and is ongoing.

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).

Progress: The Antimicrobial Resistance Option of the NHSN Antimicrobial Use and Resistance (AUR) Module is being revised to allow submission of electronically captured data only; the protocol is undergoing revisions in an attempt to make the data model similar to EARS-Net; informatics standardization of data submission via clinical document architecture (CDA) is planned for 2013. Begin piloting of facility submission of aggregate antimicrobial resistance data via CDA in 2012, begin receiving data by 2014, provide ongoing periodic reports of the collected resistance data by 2014.

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

Progress: The first published report of NHSN AR data covered 2006 and first half 2007 HAI data. The next report will cover 2009 and 2010 compared to 2007 and 2008 HAI data. All data analyses and creation of data tables are complete. Writing is in progress. The second report is expected to be published by summer 2012.

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).

Progress: Algorithm-detected central line-associated bloodstream infection reporting measures complete (15 facilities): final results in draft form to be published; details of approach being discussed with two hospital groups for trial implementation (in proprietary system) summer 2012. Any reporting to the National Healthcare Safety Network postponed until successful experience with external partner. VAP measure for adults complete, changed to VAE (Ventilator associated event and infectious ventilator associated complication- iVAC) and plan to implement in 2013. Study to correlate iVAC and VAP prevention bundles in progress through CDC Epicenter program. SSI algorithmic detection work on hold currently.

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.

Progress: MRSA, *C. difficile* and carbapenem resistant Enterobacetriaceae are received regularly as part of several population-based surveillance systems. Other organisms with unusual resistance profiles are received for reference confirmation of unusual antimicrobial susceptibility profiles. Proposals for routine isolate collection in conjunction with EIP surveillance activities have not advanced due to lack of funding.

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).

Progress: Population-based surveillance for invasive MRSA infections and *Clostridium difficile* infections (CDI) are ongoing in multiple EIP sites since 2005 and 2009, respectively. As part of this surveillance, MRSA (starting 2005, but reduced isolate submission in 2012 from 9 sites to 5 sites (1000/year to 600 per year) and C.difficile isolates (starting 2011) are collected and submitted to CDC for molecular characterization and antimicrobial susceptibility testing. Annual reports from the invasive MRSA surveillance program are posted online. CDI surveillance data are expected to be presented and published in 2012. Surveillance for infections due to selected multidrug-resistant Gram-negative bacteria is underway in 3 EIP sites, with an additional 2 sites to begin surveillance in 2012. Convenience samples of MRSA and *C. difficile* have been collected since 2005 and 2009, respectively. Isolates of carbapenem resistant *E. coli* and *Klebsiella* species are now being submitted (September 2011) as part of the Multi-drug resistant Gram negative Surveillance Initiative (MuGSI) project. Operational consideration for routine isolates submission from NHSN hospital through EIP sites were made in 2011 funding cycle, but considered to be cost prohibitive at this point.

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).

Progress: The full-scale, healthcare-associated infections and antimicrobial use point prevalence survey was conducted between May and September 2011 in 183 hospitals in 10 states. More than 11,000 patients were surveyed. Data cleaning is underway, and results are expected to be presented by fall 2012.

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).

Progress: Culture analysis failed to recover any isolates of VRE or *C. difficile*. For MRSA, 3,480 meat samples of chicken breast, ground beef, ground turkey and pork chops were tested, from which 80 MRSA were recovered for an overall prevalence of

2.3%. Most (43%) were SCCmec Type IV, and spa type t008 (30%), and 70% were PVL+. PFGE showed 16% were USA 100, 30% USA 300, and 31% USA 500. Work is ongoing to complete susceptibility testing and genetic analysis.

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

Progress: During 2010-2011, more than 1600 ground beef, ground turkey, pork chop, and chicken breast samples were collected at 9 sites participating in the NARMS retail meat program and tested for *Clostridium difficile*. No *C. difficile* was isolated. A manuscript has been drafted and is currently under review.

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).

Progress: See 2009-2010 Annual Progress Report.

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

Progress: USDA collaborative study with Texas A&M complete. Three publications involving *C. difficile*. *Clostridium difficile* in Poultry and Poultry Meat. 2011. Harvey, R, Norman, K, Andrews, K, Hume, M, Scanlan, C, Callaway, T, Anderson, R, and Nisbet, D. Foodborne Pathogens and Disease. 8(12), 1321-1323..
Clostridium difficile in retail meat and processing plants in Texas. 2011. Harvey, R, Norman, K, Andrews, K, Norby, B, Hume, M, Scanlan C, Hardin, M, and Scott M. J of Veterinary Diagnostic Investigation. 23(4) 807-11. Prevalence and genotypic characteristics of *Clostridium difficile* in a closed and integrated human and swine population. 2011. Norman, K, Scott, M, Harvey, R, Norby, B, Hume, M, and Andrews, K. Applied and Environmental Microbiology. Aug. 5755-5760. Emerging pathogens related to resistance and the NARMS project will be initiated according to FDA needs.

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).

Progress: In 2010, the CDC's Emerging Infections Program began population-based surveillance for *Clostridium difficile* infection (CDI) in select counties across 8 states. The first year of surveillance data is analyzed to be presented in summer/fall 2012: focus

is determining methods for adjustment of laboratory testing variations and population differences for national estimates. National Estimates should be available in mid-2013. Population-based surveillance for MRSA began in 2005 in 9 US metropolitan areas, and data from this surveillance has continued to be analyzed annually; 2010 estimates demonstrate 82,000 invasive infections, compared to 111,000 estimated in 2005. Special studies in 2012 being conducted to identify incidence by specific patient population to aid in vaccine study design.

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

Progress: NP swabs were collected from children aged 6-59 months in an emergency department from July 2010-July 2011. After broth enrichment, samples were cultured for SP; isolates were serotyped and antimicrobial susceptibility performed. Clinical and immunization records were reviewed. Findings during time periods 1 (July-Dec 2010) and 2 (Jan-July 2011) were compared. A total of 673 children were enrolled; 196 (29%) were colonized with SP. Mean age of carriers was 27 months. SP carriage was higher among black children, children with asthma, and daycare attendees ($p< 0.05$). Commonly carried serotypes included 19A (20.4%), 15B/C (15.3%), 35B (11.2%), 6C (9.2%), and 11A (8.2%); 23.5% were PCV13 serotypes. Infants aged 6-23 months receiving ≥2 doses of PCV13 increased from 25.2% to 45.4% from period 1 to 2 ($p< 0.001$). Overall SP carriage rates were unchanged from period 1 to 2, but serotype 19A declined from 26.6% to 9.7% (P=0.0047) and PCV13 serotypes declined from 29.8% to 12.5% (P=0.0058). Nonsusceptibility (I+R) to ceftriaxone and penicillin declined from 23.4% to 7% (P=0.0034), and 25% to 12.5% (P=0.0363), respectively.

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 (PHL) 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).

Progress: 20 PHL have been trained to do pyrosequencing. Three PHL have been trained to do neuraminidase inhibition assays and two more will be trained later this year. Web-based reporting system is currently being piloted in several states**.**

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).

Progress: A PCR assay was completed and published that identifies pneumococcus as well as whether the organism is susceptible or not to beta-lactam and macrolide/lincosamide agents.

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).

Progress: Trends in the incidence of infections caused by antimicrobial resistant *Streptococcus pneumoniae* showed that the introduction of the 7-valent pneumococcal conjugate vaccine in 2000 continued to have substantial benefits in terms of preventing resistant infections through 2010 when PCV13 was introduced. Increases of resistant infections due to specific clones of the PCV13 serotype 19A continued to markedly increase through 2010. Serotyping and susceptibility testing of the majority of year 2010 - 2011 pneumococcal isolates has been completed. To continue tracking of resistant pneumococcal clones, comparative genotypic analysis of all pediatric ABCs isolates from pre PCV13 introduction (2008-2009) has been completed and characterization of post PCV13 introduction (2011-2012) isolates is underway. Invasive GAS isolates are collected in all ABCs sites and GBS isolates in 7 of 10 ABCs site, with 2 of these considering expansion of age groups or catchment areas. All isolates are tested by broth microdilution against a standard panel including beta-lactam antibiotics and vancomycin, and unusual resistance patterns are flagged for further evaluation. Fortunately, no unusual GAS isolates have been found, although the proportion of macrolide-resistant isolates that also have constitutive lincosamide-resistance has increased; we remain vigilant for the rarely occurring GBS with increasing MICs to beta lactams. No vancomycin-resistant streptococcal isolates have been identified. Infrastructure for isolate collection is in place and improved logistics planning are ongoing to sustain ongoing evaluation in 2012 and future years.

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).

Progress: 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).

Progress: 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).

Progress: NARMS held a public meeting in St. Louis, MO in July, 2011 with stakeholders from public health (including several participants from CDC), industry, and consumer advocacy groups. The meeting included domestic and international partners, and discussions focused on sampling strategies for food animals. As a result, FDA modified funding to USDA to accommodate more on-farm sampling projects, and the isolates from sample sources other than swine are being submitted directly to FDA for susceptibility testing.

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).

Progress: To date, at least 8 state health departments have administered a survey to acute care facilities within their jurisdiction to estimate regional CRE prevalence and to assess for facility implementation of recommended surveillance prevention measures. At least 6 states had provided feedback of the survey results to acute care facilities via electronic newsletters and/or regional presentations. A summary of the CRE survey results (aggregate data) was presented at the 2011 Annual CSTE meeting. Following the survey activity, as part of formative research to better understand the health department experience with the CRE survey and their perceived roles and responsibilities in responding to an emerging pathogen, key informant interviews were conducted with select states. Manuscript in preparation. A toolkit entitled "Guidance for Control of Carbapenem-Resistant Enterobacteriaceae" designed to assist healthcare facilities and health departments in responding to outbreaks of CRE has been completed and cleared, and is currently being formatted for publishing on CDC website.

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

Progress: Expert recommendations for surveillance have been shared/published.

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

Progress: As of December 31, 2011, 332 isolates have been collected; of these susceptibility phenotype analysis suggests that 35, 16, and 5 isolates expressed AmpC β-lactamases, ESBLs and carbapenemases, respectively. Importantly, an outbreak of *Enterobacter aerogenes* was identified at the Nebraska Medical Center that produced KPC-4, which hydrolyzes all B-lactam antibiotics. Subsequent infection control and molecular analysis confirmed the tranfer of a 66kb plasmid, pNE1280 from *E. aerogenes* to *Serratia marcescens* within a hospital unit. pNE1280 is very similar to a previously characterized plasmid, pCTXM360, conferring resestance to cefotaxime, but not carbapenems due to the absence of blaKPC-4. This plasmid has been sequenced and a TN4001-like transposon that encodes blaKPC-4 has been identified. A manuscript is being prepared for submission to the Journal of Emerging Infectious Diseases. These results have been presented in poster format at the Missouri Valley Branch ASM meeting in Lincoln, NE, the 2011 APHL National Meeting in Omaha, NE, and the 2011 ASM General Meeting in New Orleans. The surveillance data show that carbapenem resistance has only been detected in Omaha and in a tertiary care center. The identification of these plasmids resulted from characterizing isolates identified during the surveillance. ESBL and AmpC beta-lactamases have been detected in other geographic locations, but prevalence is very low (<5%). The collection of isolates will continue through the 2012 funding period and beyond until 800 isolates have been collected.

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

Progress: See 2009-2010 Annual Progress Report.

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

Progress: In 2011, a cross-cutting and connective effort between DHQP, DLSS, and DLPP was initiated with the planning of the update of the Multi-Level Antimicrobial Susceptibility Testing Resources (MASTER) training activity. A kickoff meeting was held in summer 2011 and the instructional design team was identified in fall 2011. Internal and external subject matter experts were identified in 1st quarter of 2012. The AST project is on track to be completed by January 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).

Progress: Forty-nine states and 2 territories received funding in 2009-2010 through the American Recovery and Reinvestment Act (ARRA). Funding used to create state-based HAI programs, bring relevant stakeholders together. At least 10 state-based mandates use NHSN for tracking CDI or MDROs, and several ARRA funded state-healthcare facility collaboratives are underway using NHSN. The surveillance data are guiding the targeting of prevention efforts. Published a CDC Vital Signs summarizing the reporting experience and sharing prevention success from three states' efforts. Plan to expand use of module nationally as hospitals comply with pay for reporting requirement of CMS Hospital Quality Reporting Program.

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

Progress: None.

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).

Progress: In 2011, NARMS scientists hosted visits from and provided consultation to more than 20 scientists from China, Japan, Haiti, Korea, and Thailand to help them understand our surveillance programs and to help them design their own such programs. Many of these consultation opportunities were facilitated by the Global Foodborne Infections Network (GFN) and international EIP programs as well as support by the ministries of health in the countries. DFWED scientists continued to participate in formal GFN training courses that include an antimicrobial susceptibility testing component.

Continued collaboration with the Republic of Georgia National Centers for Disease Control and Public Health (NCDC) on a laboratory-based *Salmonella* surveillance project, which includes antimicrobial susceptibility testing of *Salmonella* isolates identified in sentinel sites.

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).

Progress: Representatives from NARMS participated in the 3rd meetings of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). For more information on WHO-AGISAR activities see (http://www.who.int/foodborne_disease/resistance/agisar/en/index.html).

From 2009 to present, NARMS partnered with WHO Global Foodborne Infections Network (GFN) to provide partial support to training activities included on antimicrobial resistance in 14 Asian and Latin American countries. Sixteen projects on antimicrobial resistant, which includes onsite problem solving through NARMS participation, have been initiated.

The US NARMS assisted in establishing, and continues to collaborate, with the Canadian CIPARS [Canadian integrated program on antimicrobial resistance surveillance] program to ensure harmonized surveillance in North America (FDA-CVM); CDC, FDA and ARS NARMS scientists serve as members of the WHO-Advisory Group on Integrated Surveillance of Antimicrobial Resistance and participated in the WHO-AGISAR meeting in Oslo, Norway in June of 2011.

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).

Progress: Antibiotic use studies in Guatemala and Egypt have been completed. The Egypt IEIP is currently developing a communication campaign to reduce antibiotic use with support from CDC's Get Smart program.

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).

Progress: Antimicrobial susceptibility testing for pneumococcal isolates collected during a carriage study in children and HIV-infected adults in Kenya has been completed. Laboratory data is currently being merged with the associated epidemiologic information prior to completion of analysis. Repeat testing of carriage isolates collected after pneumococcal vaccine introduction is being considered.

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).

Progress: Genotyping of a collection of *T. vaginalis* isolates using microsatellites has revealed existence of two major phylotypes with resistant isolates aggregating within one of the phylotypes. This suggests a single or limited number of genetic differences are associated with resistance and that a molecular tool could be developed to detect resistance more rapidly than what is possible with standard methods [Conrad, M., A. Gorman, J. A. Schillinger, P. L. Fiori, R. Arroyo, N. Malla, M. L. Dubey, J. Gonzalez, S. Blank, W. E. Secor, and J. M. Carlton. 2012. Population genetics of the sexually transmitted pathogen *Trichomonas vaginalis* and evidence for sexual recombination. PLoS Negl. Trop. Dis. (In Press)]. The STD Surveillence Network (SSuN) assessment of prevalence of resistance in *T. vaginalis* isolates in 6 cities (100 isolates per city) is comple [Kirkcaldy, R.D., P. Augostini, L. E. Asbel LE, K. T. Bernstein, R. P. Kerani, C. J. Mettenbrink, P. Pathela, J. R. Schwebke, W. E. Secor, K. A. Workowski, D. Davis, J. Braxton, and H. S. Weinstock. 2012. *Trichomonas vaginalis* antimicrobial resistance in 6 US cities, STD Surveillance Network, 2009-2010. Emerg. Infect. Dis. (In Press)]. There is a range of 1.3 to 7.5% resistance prevlaence among the clinics in the cities tested, with an overall resistance prevalence of 4.3%.

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).

Progress: We have genotyped single nucleotide polymorphisms (SNPs) in codons 86, 144, 184, 1034, 1042 and 1246 of the Pfmdr-1 gene in about 300 specimen from Kenya and Tanzania and 200 from Ghana (Alam MT. et al. 2011 J. Infect Dis. Jan 15:203(2):220-227). Copy number estimate of Pfmdr1 indicated no duplication of this gene in both Kenya and Tanzania samples. Recently, newer candidate molecular markers associated with potential resistances to artemisinin and other partner drugs such as lumefantrine and halofantrine have been describes (Van Tyne et al. 2011. PLoS Genet. Apr;7(4) and Tim Anderson (personal communication)). Efforts are underway to validate if these new markers can be used for monitoring resistance to ACT.

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

Progress: In western Kenya, 669 children were screened and 274 were enrolled in a 42-day *in vivo* efficacy trial of dihydroartemisinin-piperaquine and artemether-lumefantrine in the treatment of children aged 6–59 months with uncomplicated P. falciparum malaria. The data collection was completed in September 2011 and data analysis and manuscript preparation are in progress. The preliminary results after PCR correction indicate that both drugs are still highly efficacious (>90%) in this region. There is significantly more

recurrent parasitemia due to reinfection in the first 28 days after treatment in those children given artemether-lumefantrine. This is likely because the longer half-life of piperaquine provides a prophylactic effect. Results are consistent with other recent trials with these ACTs in sub-Saharan Africa. There is no evidence of delayed parasite clearance.

In Tanzania, an *in vivo* study was conducted to assess the efficacy of Coartem (Artemether-Lumefantrine, or AL) (the current first line therapy) compared to Dihydroartemisinin-Piperaquine (DP) for the treatment of uncomplicated malaria infection in children aged 6-59 months. Clinical, parasitologic, and hematologic parameters were monitored over a 42-day follow-up period. A total of 323 children were enrolled, 161 into the DP arm and 162 into the AL arm. Data analysis is currently underway.

In Kenya, 129 patients were screened and 83 enrolled for *in vitro* drug sensitivity testing. Six drugs were tested in these *in vitro* assays (chloroquine (CQ), mefloquine (MQ), amadoquine (AQ), dihydroartemisinin (DHA), artesunate (ARS) and lumefantrine (LU). Seventy two samples provided quality drug sensitivity data. No significant changes in the drug response (changes in IC50) have been observed in this study period. All of the samples were sequenced to determine the Pfmdr1 SNP prevalence at codons 86, 144, 184, 1034, 1042 and 1246. Analysis will be performed to determine if the *in vitro* drug sensitivity pattern has any correlation with the molecular marker profile of Pfmdr-1 and other molecular markers. Efforts are also underway to collect *in vitro* drug sensitivity data from Tanzania and Ghana.

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.

Progress: We have collected and saved 83 samples from the *in vitro* drug sensitivity study in Kenya. In addition, about 300 specimens from the *in vivo* study in Tanzania have been collected.

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

Progress: Onsite refresher training was provided in Kenya and Tanzania for the *in vitro* drug sensitivity assays. Provided technical support to Tanzania to improve the molecular surveillance capability there. In addition, two scientists from Ghana visited CDC for a short training to improve drug sensitivity testing in Ghana.

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

Progress: WHO has now incorporated the CDC bottle bioassay protocol developed and introduced by our group into the WHO insecticide resistance surveillance guidelines. This year, we have introduced a variant of this assay into Africa, Asia and the Americas that now allows resistance intensity to be measured in small mosquito samples along with

the resistance frequency determinations that, up to now, were the only means of detecting and assessing the importance of specific instances of resistance. This new technique will make it much easier to assess the significance of resistance problems that are becoming a crisis in our large multi-national malaria control programs.

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.

Progress: None.

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).

Progress: Antibioic prescribing data 2005-2010 have been received. The data are being analyzed, and a manuscript that will characterize outpatient antibiotic use in the U.S. is nearly complete. An additional data request will be made in 2012 to obtain provider data to analyze the provider factors contributing to high antibiotic prescribing (2.1b).

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).

Progress: The full-scale, healthcare-associated infections and antimicrobial use point prevalence survey was conducted between May and September 2011 in 183 hospitals in 10 states. More than 11,000 patients were surveyed. Data cleaning is underway, and results are expected to be presented by fall 2012.

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.

Progress: The Antimicrobial Use Option of the NHSN Antimicrobial Use and Resistance (AUR) Module was revised to allow only submission of electronically captured data; informatics standardization of data submission via clinical document architecture (CDA) is complete (2011), now piloting facility submission of aggregate antimicrobial use data via CDA (2012), begin receiving data during 2012, and provide ongoing periodic reports of the collected use data by 2013.

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).

Progress: The Animal Drug User Fee Amendments of 2008 (ADUFA), Section 105, requires antimicrobial drug sponsors to report the amount of antimicrobial active ingredient in their drug products that have been sold or distributed for use in food-producing animals for each calendar year. ADUFA also requires FDA to summarize the sales and distribution information received from drug sponsors each year and to provide the summaries to the public. FDA published the 2010 summary report of sales and distribution data of antimicrobial drugs approved for food-producing animals on October 28, 2011. On July 27, 2012, FDA published an Advance Notice of Proposed Rulemaking (ANPRM) to solicit comments from the public on possible enhancements to the existing requirements related to the collection of antimicrobial drug sales/distribution data as well as input on alternative methods for monitoring antimicrobial use in food-producing animals. Such information is important for supporting FDA's strategy for promoting the judicious use of medically important antibiotics in food-producing animals. The comment period for this ANPRM is open until September 25, 2012.

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

Progress: Informational reports on antimicrobial use and resistance in livestock operations are available from the USDA National Animal Health Monitoring System (NAHMS) at the website http://nahms.aphis.usda.gov. Recent examples include Dairy 2007: *Salmonella*, *Listeria*, and *Campylobacter* on U.S. Dairy Operations, 1996-2007 (pdf 1.3mb 3/11) (http://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy07/Dairy07_ir_Food_safety.pdf). The report Antimicrobial Use and Resistance on Beef Cow-calf Operations in the U.S. 2007-08 is currently in the clearance process. The report compiling all NAHMS collected data on antimicrobial use and resistance was posted to the website in 2012

(http://www.aphis.usda.gov/animal_health/nahms/beefcowcalf/downloads/beef0708/Beef0708_ir_Antimicrobial.pdf).

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).

Progress: Get Smart Update: A manuscript evaluating the realtionship between antimicrobial prescribing and *S. pneumoniae* antibioic resistance in ABCs sites was published in the October 1, 2011 edition of Clinical Infectious Diseases, titled "Outpatient Antibiotic Prescribing and Nonsusceptible *Streptococcus pneumoniae* in the United States, 1996-2003."

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).

Progress: Intrapartum antimicrobial use in ABCs was last monitored in 2003 and 2004; an evaluation in 2013 or 2014 is being considered to assess the impact of revised newborn group B streptococcal disease prevention guidelines issued in 2010. Additionally, through HAI activities, point prevalence surveys are being conducted that will capture antibiotic use in labor wards. Active Bacterial Core surveillance continues to conduct surveillance for invasive neonatal sepsis in the first 3 days of life in 4 sites and invasive neonatal group B streptococcal disease infections in all 10 ABCs sites. Data from 2007-2009 were analyzed to inform the 2010 GBS prevention guidelines. To date, neonatal sepsis trends remain stable overall. Assessments of the US burden of early-onset invasive neonatal sepsis, including resistant sepsis, and clinical sepsis based on hospital discharge data were completed and published (2011, 2012).

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).

Progress: As of February 2012, 424 cases and 1,602 controls have been enrolled. Preliminary evidence from routine surveillance suggests that the most antibiotic-resistant serotypes are declining. Enrollment in the case-control study is expected to continue at least through 2012 and likely well into 2013.

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

Progress: HCA has completed this intervention.

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.

Progress: CDC is currently assessing the impact of the prevention collaboratives that concluded under ARRA funding. With Prevention and Public Health Funds (PPHF) from the Affordable Care Act, CDC was able to fund new prevention collaborative efforts in 15 states. A significant focus of these new prevention efforts is on preventing the transmission of *C. difficile* and multi-drug resistant organisms in facilities across the continuum of care.

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.

Progress: CDC continues to partner with academic colleagues using innovative and inexpensive wireless technologies to monitor healthcare worker movement and approximate hand hygiene adherence. In 2011 this partnership resulted in the publication of two manuscripts in an effort to further the science and implementation of hand hygiene adherence measurement. One manuscript used data from wireless sensors as a backdrop for simulated human observers of hand hygiene practices; by altering the simulated human observer schedule, authors were able to determine which observer schedules would all viewing of the maximum number of hand hygiene events and the most diversity in healthcare workers observed. Additionally, a qualitative analysis of healthcare worker perceptions of automated hand hygiene technologies found that transparency about the use of the data and accuracy of the technology was key to healthcare worker acceptance and buy-in. DHQP continues to collaborate with colleagues to assess the implications of healthcare worker movement on other infection control practices in non-acute settings (e.g., dialysis).

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

Progress: Rates of adherence to central line insertion practices (CLIP) have increased from 92% in 2009 (n=72,606 insertions) to 95% in 2010 (n=108,118 insertions) to 96% in 2011 (n=122,630 insertions) ($p<0.0001$). Rates of adherence in the Emergency Department, where emergent insertions are most often placed have increased significantly from 83% in 2009 to 93% in 2011 ($p<0.0001$). Adherence to recommended CLIP has improved and is high. In aggregate, these analyses suggest that appropriate CLIP is becoming standard of practice and new prevention efforts should address practices like central line maintenance to progress towards elimination of CLABSI.

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

Progress: Published online 2011 http://www.cdc.gov/hicpac/BSI/BSI-guidelines-2011.html.

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

Progress: In January 2011 participating professional societies and subject matter experts began to submit topics and questions for inclusion in the update. Final selected Core and Arthroplasty section topics and related key questions were presented publically at the June and November 2011 HICPAC meeting. At the February 2012 HICPAC meeting results presented publically included: completed literature search, title and abstract screens, full text reviews, and the final selection of citations for data extraction into evidence tables**.**

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.

Progress: 17 CDI collaboratives have been funded and initiated with ARRA funding.

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

Progress: The 9th SOW with data collection and required facility reporting for the CMS-QIO MRSA prevention initiative ended in July 2011. CDC's original plan to use the data from this initiative to determine the level of correlation between MRSA HAI rates and MRSA Laboratory-Identified (LabID) Event rates is no longer viable, because facilities were not required in the 9th SOW to report both MRSA HAIs and MRSA LabID Events concurrently from the same location within the same month.

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).

Progress: A manuscript describing the impact of the VA MRSA prevention initiative was published in 2011 in the New England Journal of Medicine (N Engl J Med 2011:1419-1430) CDC staff continue to serve as technical advisors to the VA MDRO working group as they implement CDI measurement and prevention strategies on a national scale. The work group has developed a campaign focusing on CDI measurement, reporting, and prevention strategy and tools including a reporting system based on CDC definitions, recommendations for all VA hospitals to migrate to nucleic acid amplification tests (NAATs) or two-step glutamate dehydrogenase and NAAT paradigms, and a soon-to-be published set of key prevention steps for implementation in their acute care hospitals. It is anticipated that the VA CDI prevention initiative will have a national impact on VA CDI rates similar to that seen with MRSA prevention.

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).

Progress: The Vermont Department of Health (VT DOH) has developed a collaborative that includes all the acute care facilities and most of the long-term care facilities in Vermont. Facilities are organized into groups that include acute and long-term care facilities that share patients. Each group has developed and implemented interventions that target MDROs and healthcare-associated infections. As part of this project, they have collaborated with the World Health Organization (WHO) Collaborating Center for Surveillance of Antimicrobial Resistance to facilitate the direct electronic transfer of laboratory data to the MDRO module of the National Healthcare Safety Network. Approximately 14 acute care facilities and 25 long term care facilities are currently collecting data for submission to NHSN. In addition to the limited data provided back to NHSN the system, this project currently collects all laboratory pathogens and has the potential to be a rich source of surveillance information.

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.

Progress: The IOM has recommended research to "compare the effectiveness of various screening, prophylaxis, and treatment interventions in eradicating MRSA in communities, institutions, and hospitals." Particularly with respect to efforts to decolonize hosts, results differ according to geographical location, location of the patients within the hospital, and institutional and practice norms. Using funds from the American Recovery and Reinvestment Act (ARRA), NIH issued a funding opportunity announcement (RFA-OD-10-008) soliciting applications to conduct preliminary comparative effectiveness research (CER) projects on Eradication Methods for Methicillin Resistant *Staphylococcus aureus* (MRSA). One grant was funded; research under this project is ongoing.

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).

Progress: Successfully created the SHEPherD research contract mechanism in fall 2011. The purpose of this indefinite delivery, indefinite quantity contract mechanism is to provide the Centers for Disease Control and Prevention (CDC) and the Division of Healthcare Quality Promotion (DHQP) an "as needed" mechanism to obtain required research services through issuance of individual task orders. The mechanism was designed specifically to attract participants particularly well suited to do patient safety and healthcare epidemiology research, with an emphasis on prevention of healthcare associated infections. This is a five year task order mechanism became active 9/30/2011, and includes 13 vendors with access to over 2,500 US hospitals, information on > 30 million covered lives, the VA healthcare system, and a number of leading academic HAI investigators.
Through the EIP cooperative agreement mechanism, a pilot research project on use of chlorhexidine bathing to reduce MDRO prevalence in long term care facilities has been initiated in collaboration with the Tennessee Dept of Health. A protocol has been developed and approved by IRBs, and the intervention has begun in a single LTC facility.

Through a research contract with Resources for the Future, data collection has been completed for a multi-center study of the epidemiology of antimicrobial use.

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).

Progress: Environmental sampling was initiated in 8 healthcare facilities and has been completed in 3 of these facilities; to date we've collected 320 of 900 samples. We will continue to collect environmental samples through September 30, 2012. Following completion of collection, data will be analyzed and presented at scientific meetings and in written scientific communications.

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

Progress: The Office of Prevention Research and Evaluation has been updating CDC and state-level stakeholders about progress towards ARRA-HAI goals. Currently the evaluation team in OPRE is completing the final analysis of the impact of ARRA funding, including an assessment of quarterly standardized infection ratios (SIRs) in states implementing infection-specific prevention collaboratives. The office is also engaged in a return-on-investment analysis using activity-based costing to assess the costs and returns on HAI prevention collaborative implementation from the facility and state/federal perspectives.

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).

Progress: National summary statistics reflecting the HAI experience in the U.S. were published in June 2010 for central line-associated bloodstream infections (CLABSI), CLABSI and surgical site infections published in March 2011 (on line only). Annual report added CAUTI cleared for publication April 2012. Annual publication of these summary statistics (i.e., standardized infection ratios) is underway for a spring publication.

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 *Salmonella*e (2011). Evaluate interventions in dairy production that will decrease antimicrobial resistant *Salmonella*e (2012).

Progress: ARS researchers in collaboration with the Regional Dairy Quality Management Alliance have been sampling participating dairy farms and the surrounding environments for the presence of *Salmonella, E. coli,* and *Listeria*. Milk filters have been collected from numerous farms in the area around a farm with a known persistent *Salmonella* outbreak and analyzed for the presence of *Salmonella*. Preliminary results support the hypothesis that milk filters are an effective way to screen for the presence of *Salmonella* (including resistant *Salmonella*) on dairy farms. Evaluate ways to better characterize/control *Salmonella,* in particular multi-drug-resistant *Salmonella,* for use on commercial dairy farms to enhance food safety. a) Develop *Salmonella* serotype-specific real-time PCR method; b) Determine if *Salmonella* serotype changes due to changing environment or acquisition of antimicrobial resistance; c) Determine if feeding sodium chlorate, with/without nitroethane, is effective in reducing populations of *Salmonella* as well as *E. coli* O157:H7 & generic *E. coli* in milk-replacer fed calves and cull dairy cattle. USDA will hold a workshop in spring 2012 for stakeholders to input on animal health activites the USDA should address for management practices to reduce antimicrobial use, alternatives to antimicrobial use, and antibiotic use monitoring. ARS held an interagency session on alternatives to antibiotics in food safety which will reported at the USDA workshop in the spring.

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).

Progress: Work is continuing on the Washington State and Kansas State NIFSI grants. The grants will be completed in 2014 Check NIFA website for CRIS project and updates. In 2011, a new grant was awarded. At the Ohio State University, researchers hope to reduce the transmission of antibiotic resistant organisms by wildlife within the food supply using a research, control, and outreach strategy. The researchers believe that wildlife are important reservoirs and vectors for the transmission of antibiotic resistant organisms to food-producing animals. Their research will determine the extent, diversity, and carriage of antimicrobial resistant elements at the wildlife-livestock interface and evaluate the impact of wildlife control on antibiotic resistance in livestock. A comprehensive plan for knowledge synthesis and transfer will include the development of risk and economic assessment models, a scoping review of the literature, development of target-audience specific educational materials, and the development of a collection of tools and resources that can be used to enhance the value of the data collected. This 4-year grant will conclude in 2015.

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

Progress: In June 2010, FDA released Draft Guidance 209, Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals, which informs the public of FDA's current thinking on the use of medically-important antimicrobial drugs in food-producing animals and outlines several broad principles for assuring judicious use. On April 11, 2012, FDA announced the publication of three documents intended to support its strategy for implementing the principles outlined in Guidance 209 for assuring the judicious use of medically important antimicrobial drugs in food-producing animals. The three documents include 1) a final guidance for industry (#209), *The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*, that recommends phasing out the agricultural production use of medically important drugs and phasing in veterinary oversight of therapeutic uses of these drugs; 2) a draft guidance (#213), which will assist drug companies in voluntarily removing production uses of antibiotics from their FDA-approved product labels; adding, where appropriate, scientifically-supported disease prevention, control, and treatment uses; and changing the marketing status to include veterinary oversight; and 3) a draft proposed Veterinary Feed Directive regulation, that outlines ways that veterinarians can authorize the use of certain animal drugs in feed, which is important to make the needed veterinary oversight feasible and efficient.

The public comment period for the two draft documents closed on July 12, 2012. FDA is currently analyzing the submitted comments.

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).

Progress: Research was completed on formulations for novel sanitizers that can be used to reduce microbial contamination of processed poultry. Solutions of alkaline salts of fatty acids that possess antimicrobial activity were examined for use in formulations of an effective poultry processing sanitizer. Experiments were conducted to determine the effect of pH on the antibacterial activity of mixtures prepared by dissolving caproic, caprylic, capric, lauric, or myristic acids in solutions of potassium hydroxide (KOH). The high pH of these solutions was produced by KOH, and citric acid was used to reduce the pH of the solutions. Results of experiments indicated that there was little difference in the antibacterial activity of fatty acid mixtures between pH 9.5 to 12.5; however, antibacterial activity of the solutions increased at pH 13.5 or higher. Findings from these experiments demonstrated that the final pH of sanitizers made from fatty acids may influence the ability of the sanitizer to reduce microbial contamination of processed poultry. (new)- Formulations for novel sanitizers will be developed, and improved

techniques utilizing sanitizers already approved for commercial use in processing will be designed. Surfactant based sanitizers used alone or in combination with non-chlorine based sanitizers will be examined as alternatives to chlorine and chlorine dioxide for decreasing microbial contamination of poultry. Additionally, poultry processing conditions associated with broiler carcasses heavily contaminated by *Salmonella* will be evaluated and characterized. Cross contamination during processing will be examined by studying the role of these heavily contaminated carcasses in the spread of *Salmonella* during processing. Furthermore, factors that influence survival and attachment of pathogenic, spoilage, and indicator microorganisms on poultry skin will be examined. Microorganisms on poultry skin will be examined utilizing Benchtop scanning electron microscopy (SEM) with SEM software and with standard microbiological methods.

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

Progress: ARS scientists in Clay Center, NE, investigated whether antimicrobial compounds currently used by the meat industry to control *E. coli* O157:H7 are effective against these non-O157 Shiga toxin-producing groups (O26, O103, O111, and O145). They determined that six antimicrobial compounds were equally effective against *E. coli* O157:H7 and non-O157 on fresh beef. These results will assist the meat industry in developing effective antimicrobial intervention programs against these newly recognized and regulated pathogens. They also determined the efficacy against *Salmonella*. Also, ARS evaluated the effectiveness and parameters of UV and UV-ozone as a non-thermal intervention of red meat. Research is being conducted to identify how foodborne pathogens acquire, maintain and transmit genes for antimicrobial resistance and virulence within cattle from production to processing.

To understand a potential avenue by which *Salmonella* (MDR *Salmonella*) evades beef carcass decontamination steps, ARS has completed a variety of studies on bovine lymph nodes. Pathogens such as *Salmonella* have the ability to survive within bovine lymph nodes. When *Salmonella* are present in lymph nodes, they are protected from chemical and thermal antimicrobial interventions used in packing plants. We collaborated with industry groups and university scientists in isolating *Salmonella* from peripheral lymph nodes of healthy cattle presented for harvest. A necessary component of this study was validation of the microbiological analysis methods used to detect *Salmonella* harbored within lymph nodes. The results of these validation studies verified that the pathogens recovered originate from within lymph node tissues and are not the result of cross contamination of pathogens present on the surrounding adipose tissue. More research will be conducted.

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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).

Progress: This project will promote egg safety by improving processing and intervention strategies in three critical areas. The bactericidal effects of critical processing parameters (wash water, sanitizers, and sanitizer application methods) will be determined. Commercial egg wash detergents do an excellent job of cleaning eggs but are less lethal to bacteria when wash water pH is <10. Currently, the sanitizing chlorine solution sprayed onto eggs after washing does not reduce bacterial numbers. Research is needed to document the importance of pH and to identify an effective post-wash egg sanitizer. Second, improved sanitation procedures within processing facilities will be developed through research on the areas and equipment most contaminated in egg processing. A recent new law requires egg producers to test for *Salmonella enteritidis* (SE) in houses and flocks. Rapid, objective tests specific for SE will enable the egg industry in complying with this rule. Analyzing DNA from *Salmonella* collected at farms, processing facilities, and eggs allow for tracking of important contamination sources. Also, improved testing methods are required for a scientifically-based assessment of how different housing types affect egg microbiology.

On a single visit to an egg processing facility, environmental, water, and egg samples were collected. Environmental sampling including, rollers, trays, transport equipment {spindles, belts}, brushes, tanks drains, and egg waste buckets. Temperature and pH readings were recorded for wash water. Eggs from each of the housing systems were collected and sampled before and after washing. None of the environmental swab samples were positive for *Salmonella* or *Campylobacter*. Pooled egg slurry prepared from unwashed eggs laid by traditionally caged hens, was positive for *Salmonella*.

Campylobacter was recovered from pooled slurry prepared from washed eggs laid by hens housed in the enriched cages.

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).

Progress: 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).

Progress: The USDA Food Safety Discovery Zone was launched on May 6, 2010 . For several months during 2010 and 2011, the newly-revamped Food Safety Discovery Zone travelled throughout the United States visiting local community events to educate consumers about food safety. Since its launch, the Food Safety Discovery Zone has reached 982, 941 consumers with its food safety messages, collected over 17,891 pledges from consumers promising to change behaviors in handling and preparing foods, visited 17 states and Washington, DC and participated in 77 events. The Food Safe Families messages of Clean, Separate, Cook, and Chill are being heard, and consumers at every event appreciate the Food Safety Discovery Zone's ability to communicate valuable information in a new and engaging way to both children and adults. As designed, the USDA Food Safety Discovery Zone is increasing consumer food safety awareness and knowledge and positively impacting consumer safe food-handling behaviors.

In FY 2012, the USDA Food Safety Discovery Zone will be once again visit local venues within the DC Metropolitan area and will also travel to North Carolina, Georgia, Mississippi, Louisiana, and Texas.

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).

Progress: Staffed exhibits on food safety education at USDA and HHS complexes in Washington, DC for National Nutrition Month, March 2011. Conduct food safety education events for National Nutrition Month March 2012.

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.

Progress: See 2009-2010 Annual Progress Report.

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

Progress: See 2009-2010 Annual Progress Report.

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).

Progress: DHQP continues to communicate with WHO on a regular basis regarding national hand hygiene efforts. As of February 2012, over 2500 US facilities signed up for WHO's world-wide hand hygiene campaign. CDC is working together with WHO and partners from Columbia University to analyze data from US facilities who completed WHOs hand hygiene framework, which includes an extensive facility survey.

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).

Progress: CDC continues to partner with academic colleagues using innovative and inexpensive wireless technologies to monitor healthcare worker movement and approximate hand hygiene adherence. In 2011 this partnership resulted in the publication

of two manuscripts in an effort to further the science and implementation of hand hygiene adherence measurement. One manuscript used data from wireless sensors as a backdrop for simulated human observers of hand hygiene practices; by altering the simulated human observer schedule, authors were able to determine which observer schedules would all viewing of the maximum number of hand hygiene events and the most diversity in healthcare workers observed. Additionally, a qualitative analysis of healthcare worker perceptions of automated hand hygiene technologies found that transparency about the use of the data and accuracy of the technology was key to healthcare worker acceptance and buy-in. DHQP continues to collaborate with colleagues to assess the implications of healthcare worker movement on other infection control practices in non-acute settings (e.g., dialysis).

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).

Progress: The AUR module of NHSN is operating to accept electronic data from pharmacy systems which will dramatically reduce the data collection burden for antibiotic use. Four health departments received funds through ELC to develop a network of 5-15 hospitals each and implement reporting through AUR. As of March 2012, 1 facility has successfully piloted submission. Expectation is 30 facilties by end of 2012 complete validation and implement sustainable reporting, 100 facilities by end of 2013.

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

Progress: Pilot testing of the change package and driver diagram at 8 facilities began in October of 2011.

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.

Progress: Data collection on a project to perform in-depth analysis of course of antibiotic therapy on patients from a variety of hospitals around the country was recently completed by the Center for Disease Dynamics and Economic Policy. Detailed information on more than 1,000 courses of therapy was obtained and is being analyzed to look for factors that influence decisions on antibiotic use.

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

Progress: A second round of formative research with parents and adult patients was completed in 2011. The results from the two rounds of formative research resulted in the development of educational materials to improve provider/patient communication around antibiotic-associated adverse drug events. A manuscript is in progress to describe the outcomes from this study.

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

Progress: The AHRQ funded "ERASE C diff" project continues. Baseline assessments at the various hospitals have been completed and this information is now being used to inform the implementation of interventions to improve antibiotic use.

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).

Progress: The CDC Epidemiology of Pneumonia in the Community study will complete enrollment in 2012. The data collected will be used to examine and evaluate antimicrobial use for community-acquired pneumonia in the context of the IDSA clinical practice guidelines which were released in 2007. Preliminary data are currently being analyzed.

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).

Progress: FDA has received comments indicating that some aspects of guidance 152 (particularly the antimicrobial drug ranking in Appendix A) are in need of updating. CVM is working in collaboration with CDER to develop a process for obtaining the appropriate input (both form scientific experts and the public) on updating Appendix A, as necessary.

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).

Progress: In June 2010, FDA released Draft Guidance 209, Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals, which informs the public of FDA's current thinking on the use of medically-important antimicrobial drugs in food-producing animals and outlines several broad principles for assuring judicious use. On April 11, 2012, FDA announced the publication of three documents intended to support its strategy for implementing the principles outlined in Guidance 209 for assuring the judicious use of medically important antimicrobial drugs in food-producing animals. The three documents include 1) a final guidance for industry (#209), *The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*, that recommends phasing out the agricultural production use of medically important drugs and phasing in veterinary oversight of therapeutic uses of these drugs; 2) a draft guidance (#213), which will assist drug companies in voluntarily removing production uses of antibiotics from their FDA-approved product labels; adding, where appropriate, scientifically-supported disease prevention, control, and treatment uses; and changing the marketing status to include veterinary oversight; and 3) a draft proposed Veterinary Feed Directive regulation, that outlines ways that veterinarians can authorize the use of certain animal drugs in feed, which is important to make the needed veterinary oversight feasible and efficient.
The public comment period for the two draft documents closed on July 12, 2012. FDA is currently analyzing the submitted comments.

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

Progress: FDA issued an order in July 2008 to prohibit the extralabel use of the cephalosporin class of antimicrobial drugs in food-producing animals due to antimicrobial resistance concerns. The order was withdrawn in November 2008 to allow the agency to fully consider comments submitted regarding the July order. In response to the public comments, FDA has developed a revised order that prohibits certain extralabel uses of cephalosporin drugs in cattle, swine, chickens, and turkeys. The revised order was published on January 6, 2012 and went into effect on April 5, 2012.

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.

Progress: In 2011, extensive resistance monitoring was conducted by researchers at Michigan State University for the presence of antibiotic resistance in nontarget bacteria that had previous exposure or no prior exposure to kasugamycin. The objective of the monitoring effort was to isolate commensal bacteria from apple trees and soil under apple trees treated with kasugamycin and assess resistance to five antibiotics that are critical: ampicillin, cefotaxime, gentamicin, tetracycline, and streptomycin. The data from the 2011 monitoring effort did not reveal any exceptional findings with the overall

conclusion that the current level of use has not impacted the antibiotic resistance profile in apple orchard bacteria.

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.

Progress: A colorimetric test for amodiaquine/artesunate has been developed and is currently being evaluated on actual samples. A manuscript is being prepared.

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).

Progress: Get Smart update: The University of Utah and CDC are working with experts in the field of pediatrics, infectious diseases, family practice and emergency medicine to update the Principles. The updated Principles have been drafted and will be submitted for publication to the journal Pediatrics late 2012/early 2013.

NIAID is supporting clinical trials to evaluate treatment algorithms, including Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance. These are described in section 7.2.

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).

Progress: This process has not been initiated but is still planned for 2014 timeline.

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.

Progress: NIH funds a wide variety of grants on the basic mechanisms of antimicrobial resistance through its investigator-initiated R01, R03, and R21 grant programs. Representative examples of ongoing basic research are given below. For a full list of antimicrobial resistance projects, see the NIH RePORTER (Research Portfolio Online Reporting Tool) website.

o Daptomycin resistance in Enterococus has been reported, but remains rare in clinical populations. In 2011, two groups of NIAID-supported researchers provided insight into the mechanism of *E. faecalis* resistance to daptomycin. The first group found that at least seven proteins in *E. faecalis* can undergo point mutations that confer resistance to daptomycin. This mechanism is distinct from the transmission of mobile elements described in *S. aureus*. [Palmer KL et al. Genetic basis for daptomycin resistance in enterococci. Antimicrob Agents Chemother. 2011 Jul;55(7):3345-56]. A second group of investigators described two mutations associated with daptomycin resistance that arose during the course of treatment of a patient with fatal VRE bacteremia [Arias, CA et al. Genetic basis for *in vivo* daptomycin resistance in enterococci. N Engl J Med. 2011 Sep 8;365(10):892-900]

o Rapid whole genome sequencing technologies are increasingly being used to understand how resistance mutations evolve over time. In 2011, two groups of NIH-supported investigators published studies mapping how resistance develops. The first group used a novel *in vitro* culture system to generate mutations in response to constant selective pressure of different antibiotics. While some antibiotics generated diverse mutations, others produced a reproducible sequence of mutations leading to resistance. [Toprak E et al. Evolutionary paths to antibiotic resistance under dynamically sustained drug selection. Nat Genet. 2011 Dec 18;44(1):101-5. doi:10.1038/ng.1034]. The second group sequenced drug-resistant strains of *M. tuberculosis* (Mtb), both lab-generated and isolated from patients, and identified mutations associated with rapid growth. Such mutations likely represent compensatory mutations necessary for drug-resistant strains to overcome the fitness costs of resistance. [Comas I et al. Whole-genome sequencing of rifampicin-resistant *Mycobacterium tuberculosiss* strains identifies compensatory mutations in RNA polymerase genes. Nat Genet. 2011 Dec 18;44(1):106-10. doi:10.1038/ng.1038]

• NIAID supports several Centers of Excellence for infectious disease research that are conducting studies on antimicrobial resistance.

o Work conducted at NIAID's Great Lakes Regional Center of Excellence for Biodefense and Emerging Infectious Diseases began to unravel the molecular basis of cephalosporin resistance in E. faecalis. *E. faecalis* is naturally resistant to cephalosporins and prior treatment with cephalosporins is an important risk factor for hospital-acquired *E. faecalis* infections. [Kristich CJ et al. Reciprocal regulation of cephalosporin resistance in Enterococcus faecalis. mBio. 2011 Nov 1;2(6):199-211]

o The NIAID Centers for Excellence for Influenza Research and Surveillance funds two projects focused on the understanding the fitness cost of and possible prevention strategies for the emergence of oseltamivir-resistant influenza strains.

• Ongoing NIAID intramural research aims to identify candidate genes that contribute to drug resistance and study their function, develop gene databases, and screen for new antimicrobial drugs.

o High-throughput chemical and gene analysis methods were used to identify promising new leads for antimalarial drugs that could be used in combination to suppress the development of drug resistance [Yuan J et al. Chemical genomic profiling for antimalarial therapies, response signatures, and molecular targets. Science. 2011 Aug 5;333:724-9]

o Researchers provided microbiological evidence for the contribution of the M. tuberculosis gene, gidB, in streptomycin resistance and examined the clinical implications of mutations in this gene [Wong SY et al. Mutations in gidB confer low-level streptomycin resistance in *Mycobacterium tuberculosiss* . Antimicrob Agents Chemother. 2011; 55(6): 2515–2522]

• NIAID made ten awards to establish "International Centers of Excellence for Malaria Research" (RFA-AI-09-017). The seven-year awards will establish International Centers of Excellence for Malaria Research (ICEMRs) in all malaria endemic regions of the globe, including parts of Africa, Asia, the Pacific Islands and Latin America, in an effort to accelerate the control of malaria and help eliminate it worldwide. The Centers will also conduct multi-disciplinary research on malaria in all endemic regions of the globe, including research on rates and mechanisms of resistance to antimalarials.

Coordinator: NIH

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

Progress: NIAID funds numerous studies on horizontal gene transfer and host-pathogen interactions through its investigator-initiated grants program. For a full list of antimicrobial resistance projects, see the NIH RePORTER website.

o Examples of funded projects include:

- Plasmids as vectors of antibiotic resistance: The evolution of plasmid host-range
- Host-associated regulation of *Pseudomonas aeruginosa* colonization and virulence
- Mechanism of host cell apoptosis inhibition by *Mycobacterium tuberculosis*
- Studies of fundamental molecular mechanisms of host-pathogen interactions and resistance gene transfer are ongoing in the NIAID intramural research program. NIAID researchers and colleagues provided a possible explanation for the worldwide success of a penicillin-resistant *S. aureus* strain of the 1950s and 1960s (phage type 80/81) and the restriction of related modern MRSA strains (CC30) to hospitals. In addition to penicillin resistance, two genes contained in nearly all *S. aureus* strains, agr and hla, were essential for world dominance of phage-type 80/81 *S. aureus*. In contrast, key single nucleotide polymorphisms (SNPs) in these genes in contemporary CC30 clones reduce their virulence and restrict them largely to immunocompromised persons or those with other risk factors, such as hospitalized patients. [DeLeo FR et al. Molecular differentiation of historic phage-type 80/81 and contemporary epidemic *Staphylococcus aureus*. Proc Natl Acad Sci U S A. 2011 Nov 1;108(44):18091-6**]**

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.

Progress: Biofilms play a key role in antimicrobial resistance in a number of different disease states and organ systems. For this reason, many different NIH institutes and centers fund grants on the basic biology of biofilms, as well as the development of novel prevention and treatment strategies to combat biofilms. For a complete list of biofilm-related grants, visit the NIH RePORTER website. Representative projects include:

o Metabolic heterogeneity and antibiotic susceptibility in biofilms (NIAID)

o Prevention of biofilm related infections using a novel, broad spectrum antimicrobial (NIAMS)

o Biofilm infections in postsurgical, trauma, and critically-ill patients (NIGMS)

• Research on the physiology of staphylococcal biofilms and biofilm-associated infection is ongoing in the NIAID intramural program. NIAID researchers are currently focusing on the mechanisms of biofilm maturation and detachment, which may cause the dissemination of a biofilm-associated infection and lead to severe sepsis and second site infection. Using a mouse model of subcutaneous catheter-related infection, the researchers identified S. epidermidis peptides that promote biofilm maturation and dissemination of biofilm-associated infection. Antibodies to these peptides prevented bacteria from spreading to all organs except the lymph nodes, where numbers were significantly reduced. [Wang R et al. Staphylococcus epidermidis surfactant peptides promote biofilm maturation and dissemination of biofilm-associated infection in mice. J Clin Invest. 2011 Jan 4;121(1):238-48]. In another study, NIAID researchers and

colleagues describe how *S. aureus* biofilms develop their characteristic structure, providing a deeper understanding of biofilm development processes and an important basis for strategies to interfere with biofilm formation [Periasamy S et al. How *Staphylococcus aureus* biofilms develop their characteristic structure. Proc Natl Acad Sci U S A. 2012 Jan 24;109(4):1281-6]

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.

Progress: NIAID has made a significant investment in genomic-related activities that provide genomic sequencing, structural genomics, systems biology, bioinformatics and proteomic resources and reagents to the scientific community. For example, NIAID has sequenced more than 2900 bacterial strains including more than 250 *S. aureus* strains, all of which have been deposited in GenBank. In addition, 20 Actinomycetes were sequenced and mined for antibiotic gene cluster for potential new antibiotics. Protein expression clones and DNA microarrays are available for a large number of bacteria and 3D structures of many bacterial proteins have been completed or are in process of being done. NIAID supports Bioinformatics Resource Centers that collect, integrate, and provide open access to research data of microbial organisms in a user friendly format for the scientific community, including bioinformatics analysis capability and tools.

• NIAID continues its support of EuPathDB, a bioinformatics resource center for eukaryotic pathogens. Additional contract resources support VectorBase, a bioinformatics resource center for invertebrate vectors of infectious disease.

• BEI Resources acquires, authenticates, and produces reagents that scientists need to carry out basic research and develop improved diagnostic tests, vaccines, and therapies. By centralizing these functions within BEI Resources, access to and use of these materials in the scientific community is monitored and quality control of the reagents is assured. In addition to supplying the infectious disease community with materials, BEI Resources also encourages and supports the deposit of materials from researchers and institutions. Numerous bacterial strains, antigens, and nucleic acid related to resistant pathogens of concern are available through BEI. In 2011, resources from the Malaria Research and Reference Reagent Resource Center (MR4) were moved to BEI.

• In 2011, NIAID supported a genome sequencing study of an unusual serotype Shiga-toxin-producing *Escherichia coli* (O104:H4) strain responsible for a large diarrheal outbreak that began in Germany in May 2011. The genome of the German outbreak strain can be distinguished from other O104:H4 strains because it contains a prophage encoding Shiga toxin 2 and a distinct set of additional virulence and antibiotic-resistance factors. The authors' findings suggest that horizontal genetic exchange allowed for the emergence

of the highly virulent Shiga-toxin-producing enteroaggregative *E. coli* O104:H4 strain that caused this outbreak. [Rasko DA et al. Origins of the *E. coli* strain causing an outbreak of hemolytic-uremic syndrome in Germany. N. Engl. J. Med. 2011 Aug 25;365(8):709-17]

• In 2011, NIAID supported a genome sequencing study of clinical isolates of *Vibrio cholerae* responsible for a cholera epidemic in Haiti – the first such Haitian outbreak in a century. The results showed that the Haitian clinical isolates shared features with South Asian strains, namely hypervirulence, drug resistance, and an enhanced capacity for environmental persistence that is new to cholera in the Western hemisphere. [Chin CS et al. The origin of the Haitian cholera outbreak strain. N. Engl. J. Med. 2011 Jan 6;364(1):33-42. Epub 2010 Dec 9]

• Researchers in NIAID's intramural program have obtained thousands of single nucleotide polymorphisms (SNPs) from 185 malaria parasites, tested the parasite responses to seven antimalarial drugs, used genotype/phenotype data in genome wide association analysis, and identified candidate genes associated with parasite responses to mefloquine, dihydroartemisinin, and other drugs. Their 8000-SNP typing array has been made available to the malaria research community**.**

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.

Progress: NIAID supports young scientists and clinical investigators through pre-and post-doctoral National Research Service Awards (NRSA) and various types of career development awards, including: Mentored Research Scientist Award (K01), Independent Scientist Award (K02), Mentored Clinical Scientist Development Award (K08), Mentored Patient Oriented Research Career Development Award (K23), Mid-career Investigator Award in Patient Oriented Research (K24), Mentored Quantitative Research Development Award (K25), and NIH Pathway to Independence Award (K99).

o Representative career development projects include:

- Characterization of the secretion pathways for surface proteins in *S. aureus* (NRSA)
- Structural topology of a small multidrug resistant efflux pump (K22)
- MRSA in Children: Epidemiology, pathogenesis, and prevention (K23)

• NIH funds scientific conferences through its R13 grant program. In 2011, NIAID provided support for several antimicrobial resistance-related conferences via this mechanism. These conferences offered a limited number of travel awards to enable students to attend and present their work.

o 2011 Antimicrobial Peptides Gordon Research Conference

o 2011 Staphyloccocal Diseases Gordon Research Conference

• In 2009, the NIAID intramural program began a collaboration with the Henan Provincial Health Bureau to begin studies on highly drug-resistant TB in Zheng Zhou, the capital city of Henan province in central China. NIAID has provided training in the conduct of clinical trials to scientists and physicians from Zheng Zhou and has worked with the province to prepare for the studies. Patient enrollment in the first clinical trial undertaken under this agreement began in March 2010. (ClinicalTrials.gov Identifier: NCT01071603)

• In Southeast Asia and Africa, where artemisinin combination therapies are first-line treatments against malaria, NIAID investigators are working with local scientists to define the response to artemisinin. This project will build local research capacity and inform future approaches to artemisinin resistance and malaria treatment in these areas.

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.

Progress: NIAID funds numerous investigator-initiated R01 and small business grants focused on the development of therapeutics for resistant pathogens of concern. Examples of projects focused on the preclinical therapeutics development for resistant infections include:

o Antibacterial agents that restrict the emergence of resistance

o Novel antibacterials targeting Gram-negative nonfermenters

o A synergy-based therapy against *C. difficile*

• NIAID stimulates preclinical development of therapeutics for infectious diseases via a number of mechanisms.

o The Molecular Libraries Roadmap offers public sector biomedical researchers access to the large-scale screening capacity necessary to identify small molecules that can be optimized as chemical probes to study the functions of genes, cells, and biochemical pathways. These projects may also facilitate the development of new drugs by providing early stage chemical compounds that will enable researchers in the public and private sectors to validate new drug targets, which could then move into the drug-development pipeline. Through this program, several novel small molecule inhibitors of bacterial pathways, including quorum sensing, DNA replication and beta lactamases, have been discovered.

o NIAID supports preclinical development of new antibacterial agents through directed contracts to companies involved in novel drug design and synthesis. These contracts are

solicited by an annual Broad Agency Announcement, "Development of Therapeutics for BioDefense." (BAA-NIAID-DMID-NIHAI2010097)

- Trius Therapeutics has developed a number of lead compounds that have dual-targeting capabilities against Gram-negative bacteria. By targeting the ATP binding subunits of DNA gyrase and Topoisomerase IV, these agents provide broad spectrum activity with an expected low rate of emergence of bacterial resistance. These novel compounds have completed early screening for *in vitro* activity and have shown efficacy in animal infection models. In 2011, one candidate was selected to move into IND-enabling studies necessary to advance to clinical trials in humans.

- Achaogen, Inc., is developing novel broad-spectrum aminoglycosides. Thus far, a number of lead compounds have been identified and screened for preclinical toxicity and efficacy. In 2011, a lead compound was selected to advance into IND-enabling preclinical development. The lead candidate is active against Gram-negative pathogens that are resistant to existing aminoglycosides as well as pathogens carrying the NDM-1 enzyme, which confers resistance to virtually all licensed antibiotics.

- CUBRC Inc., in collaboration with Tetraphase, Inc., was awarded a contract in 2011 to advance development of TP-271, a novel tetracycline-based derivative, to treat Gram-negative and Gram-positive bacterial pathogens. TP-271 exhibits high potency against many bacteria that are resistant to other tetracyclines, and therefore represents a substantial improvement over existing drugs. IND-enabling preclinical, drug process development and manufacturing, and human Phase I trials will be undertaken.

- Enanta Pharmaceuticals was awarded a contract in 2011 to advance EDP-788, a novel macrolide molecule for the treatment of Gram-negative and Gram-positive pathogens, including bacteria that are resistant to other macrolides. IND enabling preclinical safety studies, animal efficacy testing in selected pathogens, and Phase I clinical trials will be conducted under this contract.

o NIAID's Partnerships Program supports collaborative efforts and multidisciplinary approaches to advance candidate products or platform technologies through the product development pathway, and has supported numerous grants addressing resistance since its inception in 2000.

- In FY 2010, NIAID funded 19 awards under the "Partnerships for the Development of Therapeutics and Diagnostics for Drug-Resistant Bacteria and Eukaryotic Parasites" research initiative (RFA-AI-09-026), focused on advancing the development of diagnostics and therapeutics for drug-resistant pathogens. Work under these awards continued in 2011.

- In FY 2010, NIAID issued the "Partnerships for the Development of New Therapeutic Classes for Select Viral and Bacterial Pathogens" (RFA-AI-10-010) research initiative. This initiative targets novel therapeutics for three pathogens for which resistances is of concern: *Neisseria gonorrhoeae,* hepatitis B virus, and *Clostridium difficile.* Seven awards were made in FY 2011: 3 for *Clostridium difficile,* 1 for *Neisseria gonorrhoeae,* and 3 for hepatitis B virus.

- In FY 2011, NIAID issued the "Targeting Resistance in Select Gram-Negative Pathogens"(RFA-AI-11-009) phased innovation award research initiative. This initiative

targets early translational research towards the development of novel therapeutic approaches to treat resistant Gram-negative bacteria. NIAID anticipates making 12 awards in 2012, half of which will advance to the second phase of funding in two years based on the attainment of milestones, programmatic priorities and available funds.

o In FY 2007, NIH issued the "Pharmacological Approaches to Combating Antimicrobial Resistance" (RFA-AI-07-025) research initiative, to solicit applications aimed at determining the proper dosing of currently prescribed antimicrobial agents used in the treatment of clinically relevant infectious disease for which drug resistance poses a significant problem. Funded projects (ongoing) focus on drugs commonly used to treat tuberculosis, influenza, and malaria, as well as hospital-acquired infections caused by Gram-negative bacteria. Twenty-five publications cite funding under this initiative.

• NIAID provides a broad array of pre-clinical and clinical research resources and services to researchers in academia and industry designed to facilitate the movement of products from bench to bedside. By providing these critical services to the research community, NIAID can help to bridge gaps in the product development pipeline and lower the financial risks incurred by industry to develop novel antimicrobials.

o Two NIAID preclinical services contracts were awarded in FY 2011 that will provide resources to support the broad preclinical development of small molecule and biopharmaceutical therapeutics. Services available to researchers include: product synthesis, manufacturing and formulation development, pharmacodynamic and pharmacokinetic studies, a full range of toxicity testing, and development strategic planning. Multiple new and improved drugs and formulations are being supported under these service contracts to fulfill the regulatory requirements for entering human clinical trials. Examples include studies to support development of an efflux pump inhibitor, a novel broad-spectrum antibacterial for topical use and a novel monobactam with activity against resistant Gram-negative bacteria.

o NIAID's *In vitro* Assessments of Antimicrobial Activity contracts provide *in vitro* testing services, including Minimal Inhibitory Concentration (MIC) determination, for candidate therapeutics against a wide array of infectious organisms, including MRSA, VRE, *Mycobacterium tuberculosiss* , and resistant strains of *Klebsiella* and *Acinetobacter* species. This program is a free service to the research and antimicrobial discovery and development communities, whereby investigators can submit compounds/therapies for screening.

o NIAID's Animal Models of Infectious Diseases contracts provide *in vivo* animal model efficacy testing services for promising therapeutic candidates submitted by researchers. Animal models are available for a wide range of pathogens, including *S. aureus, E. coli*, and *N. gonorrhoeae*.

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.

Progress: NIAID supports numerous investigator-initiated studies on vaccines for the prevention of resistant pathogens of concern. Examples of ongoing studies include:

o *Staphylococcus aureus* vaccine development

o Development and manufacture of adjuvants for vaccines targeting MDR tuberculosis

o Mucosal vaccines against gonorrhea

• The Partnerships for Development of Vaccines for Selected Pathogens initiative (RFA-AI-09-016) focused on advancing development of vaccines against select pathogens that have a significant impact on public health, including respiratory syncytial virus (RSV), *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Clostridium difficile*. The six funded awards are ongoing.

• For over ten years, the NIAID-supported Tuberculosis Research Materials and Vaccine Testing Contract has provided the research community with materials and reagents to facilitate basic, translational and applied research focused at the control and eradication of *Mycobacterium tuberculosiss* . The contract also includes the development of animal models and testing of candidate vaccines against tuberculosis.

• NIH also supports the development of novel products for infection control, including antimicrobial materials for healthcare facility surfaces and indwelling devices. Examples of current grants include:

o Micro-patterned surfaces for reducing the risk of catheter-associated UTI

o Biomaterials that prevent biofilm colonization and device-based infections

o Design and analysis of random copolymers with antimicrobial activity

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.

Progress: NIAID, in collaboration with NICHD, CDC, FDA, and the Office of the Global AIDS Coordinator (PEPFAR) organized a workshop on TB and HIV diagnostics in adult and pediatric populations in June 2011. The purpose of this workshop was for the U.S. government to engage with public and private partners to identify research gaps in the TB diagnostics research field and develop strategies to accelerate and capitalize on current research efforts. Topics included clinical research and development activities in TB diagnostics for adults and particularly pediatrics and strategies for implementing molecular point-of-care diagnostics for HIV and TB.
• Under the auspices of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), NIAID staff along with their counterparts in the European Commission's Directorate General for Research and Innovation organized a workshop on the Challenges and Solutions for the Development of New Diagnostic Tests to Combat

Antimicrobial Resistance. The workshop took place in September 2011 and brought together academicians, diagnostic developers and regulators from both sides of the Atlantic. The workshop aimed to identify existing barriers and possible solutions in the following areas:

o Factors limiting the development and use of contemporary diagnostic tools

o Identification of key partners that need to join the effort to advance diagnostics into clinical practice

o The role of improved diagnostic tests in enhancing clinical development of novel antimicrobials

Presentations are posted at the TATFAR website.

• NIAID funds numerous investigator-initiated grants focused on the development of diagnostics for resistant pathogens of concern.

o Examples of ongoing projects include:

- A rapid point-of-care diagnostic for *Neisseria gonorrhoeae* STDs
- Point of care flu drug resistance test
- Rapid molecular testing for neonatal antibiotic-resistant pathogens

o Work conducted under an NIAID investigator-initiated grant contributed to the development of the Xpert MTB/RIF TB test, which provides specific, sensitive and rapid detection of Tb and MDR-TB. The time to result of 2 hours for this test is a significant improvement over existing TB diagnostics, which takes 3-12 weeks. The World Health Organization endorsed this test in December, 2010. NIAID is supporting studies to understand how best to use this new test in different populations.

• Targeted Diagnostics Initiatives

o The "Partnerships to Improve Diagnosis and Treatment of Selected Drug-Resistant Healthcare-Associated Infections (U01)" (RFA-AI-06-036) research initiative supports the development of therapeutics or rapid diagnostics for specific bacterial strains and drug resistant phenotypes for the following healthcare-associated pathogens: *Clostridium difficile*, *Pseudomonas*, *Acinetobacter*, *Enterobacter*, *Klebsiella*, *Serratia*, *Proteus*, and *Stenotrophomonas maltophilia*. Twenty publications cite funding from the four funded projects.

o The "Partnerships for Point of Care (POC) Diagnostic Technologies for Nontraditional Health Care Settings" (RFA-AI-08-003) research initiative focused on advancing the development of POC diagnostics for pathogens causing sexually transmitted infections (STIs), urinary tract infections (UTIs), and respiratory infections, many of which demonstrate a high degree of resistance. Research under the five awarded grants is ongoing.

o The "Partnerships for Development of Therapeutics and Diagnostics for Drug-Resistant Bacteria and Eukaryotic Parasites" research initiative (RFA-AI-09-026) is described under section 6.1.

• The Tuberculosis Clinical Diagnostics Research Consortium (CDRC) was awarded in 2009 and is currently evaluating four early stage diagnostic tests for clinical feasibility and is contributing to cost-effectiveness modeling studies for the Xpert MTB/RIF TB test.

Coordinator: NIH

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

Progress: BARDA awarded an additional contract for the development of novel antibiotics. The contract supports the development of a completely novel class of antibiotics and could represent the first novel class of antibiotics to treat hospital acquired gram negative infections in 40 years. The contract supports drug manufacturing, Phase II HAP/VAP studies, Phase III cIAI, as well as animal efficacy studies against the biothreat pathogens anthrax, plague, and tularemia. BARDA continues management of the development of a next generation aminoglycoside. In 2011, improvements in process chemistry have allowed for more efficient manufacturing processes to be implemented. Clinical pharmacology studies have also been initiated and are completing their in-life phase.

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.

Progress: Several NIAID-funded HIV/AIDS clinical research sites in sub-Sahara Africa are partnering with Aeras and Crucell to evaluate the safety and efficacy of Aeras-402/Crucell Ad35 TB vaccine in HIV-uninfected infants.

• NIAID supports clinical trials infrastructure focused on evaluating new vaccines and therapeutics through the Vaccine and Treatment Evaluation Units (VTEUs) and the Phase I Clinical Trial Units for Therapeutics. Investigators may access these services at no cost. Examples of activities in these clinical trials units include:

o Completed:

• Two Phase I clinical trials of the antimycobacterial agent, SQ109, have been completed in Phase I clinical trial units [NCT00866190, NCT01358162]. SQ109 has a molecularly distinct mechanism of action, and has FDA fast track designation due to activity against an ethambutol-resistant TB strain and promise in fulfilling an unmet need for the treatment of MDR-TB.

• A recently completed VTEU supported trial, revealed that strains of community-acquired MRSA colonizing healthy children differed significantly from strains associated with staphylococcal infections. [Thomsen I et al. Molecular distinctions exist between community-associated methicillin-resistant *Staphylococcus aureus* colonization and disease-associated isolates in children. Pediatr Infect Dis J. 2011 May;30(5):418-21]

o Ongoing:

- A Phase I clinical trial to determine the safety and immune response generated by an experimental endotoxin vaccine for Gram-negative bloodstream infections [NCT01164514]
- A Phase I clinical trial to test a novel means of endotracheal tube decontamination to reduce biofilm formation, healthcare-associated infections and emergence of resistance
- A Phase I study to determine the safety of nasal decolonization of *S. aureus* using novel, topical agent
- Nasal decolonization of methicillin-resistant *S. aureus* (MRSA) using topical antibiotic in neonatal intensive care units
- A Phase II study to determine the safety and effectiveness of novel monoclonal antibody to treat *Staphylococcus aureus* infection
- Two Phase I clinical trials to determine safety, pharmacokinetics, and optimal dose of a novel narrow spectrum agent with activity against *Clostridium difficile*
- A Phase I trial of the TB vaccine candidate Aeras 422
- A trial to assess different vaccination schedules of 13-valent conjugate *S. pneumoniae* (Spn) vaccine (Prevnar-13®) in adults 65 years and older
- Several studies of drug-resistant TB and clinical trials of novel TB treatments are planned or underway through the collaborative efforts of NIAID intramural investigators, the Korean Ministry of Health and Welfare's National Masan Tuberculosis Hospital, Yonsei University's College of Medicine of the Republic of Korea, and private sector partners. Characterization of MDR and XDR TB isolates and their contribution to human disease is being studied under clinical protocol NCT00341601, which has enrolled more than 750 volunteers. Clinical studies of metronidazole and linezolid to treat DR TB are underway, and a protocol is in development to study meropenem and clavulanic acid for XDR TB 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.

Progress: NIAID is supporting clinical trials to inform the rational use of existing antimicrobial drugs to help limit the development of antimicrobial resistance. Since 2007, NIAID has made 8 awards for targeted clinical trials designed to help answer key questions about proper antimicrobial dose, treatment duration and whether antimicrobial treatment is necessary in all cases. All of these trials are ongoing or in development. More information about each trial can be found at the following links: skin and soft tissue infections caused by CA-MRSA (2007); catheter-related bacteremia and urinary tract infections (2009); Gram-negative bacteremia, acute otitis media and community-acquired pneumonia (2010).

• NIAID is supporting a clinical study to optimize the use of colistin, an antibiotic approved in the late 1950s that is increasingly being used today to treat MDR Gram-negative infections. Based on data from 105 critically-ill patients, the preliminary results provide the first science-based colistin dosing recommendations for patients with varying degrees of kidney function. [Garonzik SM et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically-ill patients from a multi-center study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother. 2011 Jul; 55(7):3284-94]

• Combination therapies are another approach to preventing the emergence of resistance. NIAID is studying new ways to treat cephalosporin-resistant *N. gonorrhea* infections by using existing antibiotic therapies in combination (i.e., gentamicin and azithromycin vs. gemifloxacin and azithromycin [NCT00926796]). NIAID-supported clinical trials evaluating the effectiveness of different drug combinations in treating influenza, HIV and malaria are also ongoing.

• In collaboration with the Global Alliance for TB Drug Development, the NIAID-funded AIDS Clinical Trials Group (ACTG) is participating in a study comparing two Moxifloxacin containing treatment shortening regimens with the standard regimen in pulmonary TB (study A5304/REMOX). In addition, ACTG is evaluating short course Rifapentine and INH to prevent tuberculosis in people with latent TB (TBTC S26, A5279 [NCT01404312]) and the role of empiric TB treatment to reduce early morbidity and mortality of TB in HIV infected individuals living in areas with high rates of TB infection (A5274 [NCT01380080]).

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.

Progress: The Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA), developed and supported by NIAID, is a multidisciplinary international network of basic scientists, clinical microbiologists, and clinical investigators that focus on *S. aureus* and other staphylococcal species that exhibit antimicrobial resistance. The Network coordinates with established surveillance networks for nosocomial infections, including CDC's National Healthcare Safety Network (NHSN), for the purpose of collecting information and obtaining samples of isolates from relevant cases identified through these surveillance systems. NARSA provides a central repository of staphylococcal isolates to researchers.

• NIAID funds numerous grants examining the molecular epidemiology of resistant pathogens. Examples include:

o Neighborhood level determinants of pneumococcal disease transmission

o Epidemiology of *Acinetobacter baumannii*: An emerging nosocomial pathogen

o Extra-nasal colonization and epidemiology of community-associated MRSA

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.

Progress: In 2008, NIH implemented a new computerized reporting process called Research, Condition, and Disease Categorization (RCDC), which all NIH institutes must now use to categorize and report funding in 215 research, condition, and disease categories, including antimicrobial resistance. The NIH RePORTER (Research Portfolio Online Reporting Tool) is a web query tool within the RCDC system that allows the public to drill deeper into each RCDC category. In addition to NIH, RePORTER also includes information from AHRQ, CDC, HRSA, SAMHSA, FDA and the VA. This web-based tool provides links to abstracts and other project-level data such as histories and start/end dates. It also features links to publications and patents associated with the research. Funding levels and project lists for antimicrobial resistance can be found on the NIH RePORT categorical spending website.

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).

Progress: See 3.5a for dairy cattle research. ARS scientists are evaluating the effects of antimicrobials on swine intestinal microbiomes, and on the expression and transmission of virulence, fitness, and antimicrobial resistance genes in culture and the host. Develop a functional metagenomic approach to identify gene products that inhibit foodborne pathogen growth, interfere with virulence gene expressions, or reduce antimicrobial resistance. Specifically, they are assessing the role of commensal intestinal bacteria in evolution, persistence, or transmission of resistance genes. Publication, PNAS, 2012. Determine particular ecological niches/reservoirs for pathogenic/antimicrobial-resistant bacteria, identifying nutritional/biological/environmental factors affecting ability to

colonize/survive/persist within gut of food-producing animals & their production environment (e.g. distillers grains, organic acids, other diets, competitive exclusion). Develop understanding of microbial adaption to intrinsic/extrinsic stressors on acquisition/exchange/expression of incompatibility plasmids & antimicrobial resistance elements in foodborne pathogens in production/processing environments**.**

Coordinator: CDC; Collaborator: FDA, USDA

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

Progress: The *Action Plan to Combat Antimicrobial Resistance* and the annual progress reports are being converted, starting in 2013, to web documents available on the Internet. This transition should greatly facilitate the Task Force's ability to link information on research activities from various agencies and increase its accessibility.

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).

Progress: Manuscript in final stages of preparation. Plan is to submit the manuscript to a peer-reviewed journal in 2012 for consideration for publication.

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).

Progress: Reviewing comments submitted to the docket in response to draft guidance, including comments from FNIH Biomarkers Consortium. Plan to issue final guidance in 2013.

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).

Progress: Reviewing comments submitted to the docket in response to draft guidance, November 4, 2011 Advisory Committee meeting to discuss endpoints and trial designs for HABP/VABP to make trials more feasible. As part of these efforts there are discussions of the potential role of nonmortality clinical efficacy endpoints for hospital acquired and ventilator associated bacterial pneumonia. The results of these scientific discussions may impact upon recommended clinical trial designs for studying antibacterial drugs for HABP/VABP.

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).

Progress: Reviewing comments submitted to docket in response to draft guidance, including comments from FNIH Biomarkers Consortium. November 3, 2011 Advisory Committee meeting to discuss new efficacy outcome measure of symptom improvement and trial designs for CABP to make trials more feasible. Plan to issue updated draft guidance 2012.

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).

Progress: None.

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

Progress: Two guidance documents for MRSA (nucleic acid based, and culture based) were finalized June 2012; publication is pending.

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

Progress: Draft Guidance published. Currently reviewing comments submitted to the docket in response to the draft guidance; final document pending.

Draft Guidance for Industry and Food and Drug Administration Staff – Establishing the Performance Characteristics of *In vitro* Diagnostic Devices for the Detection of *Clostridium difficile.*

(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidaneDocuments/ucm234868.htm)

Publication of the Class II special control guidance document, Toxin Gene Amplification Assays for the Detection of *Clostridium difficile* is pending (2012).

Publication of the Class II special control guidance document, Multiplex Nucleic Acid Assay for Identification Of Microorganisms and Resistance Markers from Positive Blood Cultures in pending (2012).

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).

Progress: FDA established a CDER Antibacterial Drug Development Task Force with a goal to address issues in antibacterial drug development for human use. In addition, the Engelberg Center for Health Care Reform at Brookings established the Brookings Council on Antibacterial Drug Development that will identify issues and new approaches to promote antibacterial drug development. Work in providing regulatory advice for product development is 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.

Progress: See 2009-2010 Annual Progress Report.

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).

Progress: The study is ongoing.

Coordinator: HHS/ASPE; Collaborator: FDA

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).

Progress: Ongoing participation in TATFAR including periodic teleconferences. Exchange of guidance documents on clinical trial designs for studying new antibacterial drugs. European Medicines Agency and FDA representatives are engaging in relevant public meetings and workshops to inform and share in discussions on recommended clinical trial designs for studying antibacterial drugs.

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).

Progress: FDA staff attend the twice-yeaerly meeting of CLSI Antimicrobial Susceptibility Testing Subcommittee.

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).

Progress: FDA website established that provides the date of FDA's most recent review of a sponsor's *in vitro* susceptibility interpretative criteria contained in product labeling: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm275763.htm

Coordinators: CDC, FDA; Collaborator: USDA

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

11.1 Encourage development, testing, and evaluation of new rapid diagnostic methods for human and veterinary use to help guide antimicrobial therapy. Specifically, promote the development of tests for infections cause by fastidious (e.g. TB) 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.

Progress: In September 2011, NIAID collaborated with the European Commission's Directorate General for Research and Innovation to organize the TATFAR workshop on the Challenges and Solutions for the Development of New Diagnostic Tests to Combat Antimicrobial Resistance. This is described in section 6.3.

The Office of *In vitro* Diagnostic Device Evaluation and Safety (OIVD) continues to work with industry in developing clinical and pre-clinical studies to demonstrate performance of *in vitro* diagnostic devices for detection of microorganisms and related resistance biomarkers.

FDA published the Draft Guidance for Industry and FDA Staff Medical Devices: The Pre-Submission Program and Meetings with FDA Staff. (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm)
FDA allowed marketing of the first nucleic acid test that can identify 12 different bacterial types known to cause bloodstream infections as well as three resistance genes. This was done through the DeNovo process.

FDA published the Draft Guidance for Industry and Food and Drug Administration Staff - Class II Special Controls Guidance Document: Nucleic Acid-Based *In vitro* Diagnostic Devices for the Detection of *Mycobacterium tuberculosiss* Complex in Respiratory Specimens (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm296205.htm).

Additionally, the Final Guidance for Industry and FDA Staff - Establishing the Performance Characteristics of *In vitro* Diagnostic Devices for the Detection or Detection and Differentiation of Influenza Viruses was published in 2011 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079171.htm).

FDA held the public meeting in 2011 - Advancing Regulatory Science for Highly Multiplexed Microbiology/MCM Devices. A white paper was published and comments were received and implemented (http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm267410.htm). Publication of the draft guidance document, Highly Multiplexed Microbiological /Medical Countermeasure Devices is pending (2012).

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

Progress: In the NIAID intramural program, several collaborations involving new diagnostic tools are underway, including work on the next generation GenXpert test for RIF; an XDR test for detection of fluoroquinolone and Kanamycin resistance in Mtb; biomarkers of treatment success; and to assess the presence of fragments of Mtb in easily accessible human samples, such as urine and exhaled breath condensate, for development of point of care tests. 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).

In June 2011, FDA held an inter-agency meeting to discuss molecular diagnostics for the detection of *Mycobacterium tuberculosiss* complex and the detection of genetic mutations which confer antibiotic resistance in *M. tuberculosis* complex.

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

Progress: None.

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

Progress: 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).

Progress: NIAID has a long-standing intramural research program focused on development and clinical testing of prototype malaria vaccines in collaboration with many partners from malaria-endemic countries and the public and private sectors. Specific vaccines under development and a product development timeline (updated May 2010) can be found here.

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

Progress: See action item 6.2.

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).

Progress: Vaccines for viral respiratory infections are a major focus of the NIAID intramural research program. Lead candidates for RSV and human parainfluenza virus 3 (HPIV3) vaccines are in Phase I and II clinical trials supported in part by collaboration with industry.

Coordinator: FDA; Collaborators: CDC, NIH, VA

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

Progress: None.

Coordinator: HHS/ASPR

Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
APHL	Association of Public Health Laboratories
AR	Antimicrobial resistance
OASH	Office of the Assistant Secretary for Health
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