

**2009-2010 PROGRESS TOWARDS IMPLEMENTATION OF:**

*Draft Document*

**A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE**

**Interagency Task Force on Antimicrobial Resistance**

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**Agency for Healthcare Research and Quality**

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**Department of Agriculture**

**Department of Defense**

**Department of Veterans Affairs**

**Environmental Protection Agency**

**Health Resources and Services Administration**

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

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### **A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE**

#### **Introduction**

Since 2002, the Interagency Task Force on Antimicrobial Resistance has released an annual report on the progress towards implementation of the 2001 Action Plan to Combat Antimicrobial Resistance. The final annual report provides updates on the participating agencies' activities for the 2001 Plan and is available on the CDC website (<http://www.cdc.gov/drugresistance/index.html>).

The Task Force has now revised the 2001 Action Plan and a draft of the revised Action Plan was recently released and published in the Federal Register for public comment. The revised draft is available at (<http://www.cdc.gov/drugresistance/index.html>). Although the revised Action Plan is not final, the participating agencies are releasing this annual progress report, to provide information on Federal activities during calendar years 2009 and 2010.

The revised Action Plan maintains the same four Focus Areas as the previous plan: Surveillance, Prevention and Control, Research and Product Development. Within these Focus Areas, there are a total of 11 goals: two for Surveillance, two for Prevention and Control, four for Research and three for Product Development. Further, each of the goals lists one or more Action Items that constitute the Federal government's commitment to targeted efforts to address the public health burden of antimicrobial resistance; there are a total of 53 such Action Items. Many of the Action Items also list implementation steps representing specific activities that one or more of the participating agencies will undertake to accomplish the Action Item. Most of these implementation steps are time-delimited; the planned completion date is given in parentheses as the year by which this step will be completed (indicating December 31 of that year). For example, (2011) means that the work is expected to be completed by the end of the 2011 calendar year. Other activities constitute continuing work of the agencies and are noted as "ongoing" with no set end date.

The format of this report is new, and differs from updates of the previous Action Plan by providing progress descriptions that are embedded into the Action Plan. The Task Force hopes that this format is useful for the reader in understanding the Federal agencies' activities as we move toward accomplishment of the Action Plans goals. The Task Force plans to continue to provide annual updates on these Action Items and implementation steps as was done in the past.

The goals, action items, and implementation steps represent current priorities based on today's science and threats to public health. 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. Thus, the Action Items and implementation steps will be updated at least every two years and more often if circumstances require.

## 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.<sup>a</sup> 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) Design, and implement (2010) 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).

**Progress:** Three pediatric sites and two adult sites have received funding for the study; all have obtained IRB-approval, and all are now enrolling patients. The study is challenging; for each patient, the aim is to collect multiple clinical specimens, and a variety of diagnostics tests need to be run in different laboratories. Site visits, conference calls, and investigators' meetings are being held to address the challenges. Enrollment in the study may be extended beyond the end of 2011, which would enhance our ability to measure etiologies, including resistant organisms.

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<sup>a</sup> 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.

- 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).

**Progress:** In July 2009, NARMS-CDC (i.e., the CDC NARMS investigative group) met with representatives from 5 state public health departments to understand the requirements for the developing a web interface which would enable state and local health departments to electronically submit data to the NARMS program at CDC. Following the meeting, representatives from NARMS-CDC worked with CDC's Information Technology team to begin construction of the new database. In March and May 2010, NARMS-CDC demonstrated the new database developments to state stakeholders to gather feedback for future development efforts.

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

**Progress:** During 2010, NARMS representatives participated in weekly interagency conference calls to understand database requirements for the construction of an integrated database at FDA that will house isolate-level NARMS data from humans, retail meats, and food animals. In August 2010, NARMS-CDC participated in preliminary user-acceptance testing for the integrated database and provided comments and feedback for the design and workflow functions of the database. In addition, NARMS-CDC contributed summary data for the NARMS interagency executive reports; these annual reports provide results of resistance testing among human, retail food, and food animal bacterial isolates. The executive reports, as well as two interactive graphs, can be accessed on the FDA NARMS webpage.

- 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:** CDC published the NARMS human isolate annual report for CY2008 in July 2010 on its NARMS website. In 2009 and 2010, NARMS-CDC published 9 peer-reviewed manuscripts describing clinically- and epidemiologically-relevant trends and mechanisms of resistance among *Shigella*, *E. coli*, and *Salmonella* serotype Typhi from humans and non-Typhi *Salmonella* from human, food, and food animal sources. Three additional manuscripts have been accepted for publication in peer-reviewed journals.

- 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:** In 2010, CDC provided technical assistance to the Texas Department of State Health Services Laboratory, the recently added state public health laboratory. The laboratory is undergoing external quality-assessment testing. If the testing demonstrates

proficiency in gonococcal antimicrobial susceptibility testing, the additional lab will begin testing GISP isolates during 2011.

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

**Progress:** During November and December of 2010, representatives from CDC and the participating external collaborators met to discuss the activity and planned implementation. A draft protocol has been circulated. Initiation of the activity is planned to begin during February, 2011.

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

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

- a) Expand NHSN to use electronically captured antimicrobial susceptibility data from participating facilities for reporting of resistance rates and trends; develop an expansion plan by 2010, pilot the plan in 2011, 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.

**Progress:** The Antimicrobial Resistance Option of the NHSN Antimicrobial Use and Resistance (AUR) Module was revised to allow submission of electronically captured data only; the protocol is undergoing final revisions, and informatics standardization of data submission via clinical document architecture (CDA) is planned for 2010/2011. Begin piloting of facility submission of aggregate antimicrobial resistance data via CDA in 2012, begin receiving data by 2013, 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 2007 and 2008 HAI data. The next report will cover 2009 and 2010 HAI data. Data review, cleaning, and programming for analysis will begin in late summer 2010 and writing by late 2010. Data entry completion from 2010 will continue through the first quarter of 2011. Final analysis and writing will be completed, and the second report will be submitted for publishing in the 3<sup>rd</sup> quarter of 2011.

- c) Evaluate the utility of electronic rules for identifying and reporting central line-associated bloodstream infections (2010), surgical site infections (2011), catheter-related urinary tract infections (2012), and ventilator-associated pneumonia (VAP) (2011), including

associated pathogens; and compare electronic algorithms with traditional manual surveillance by infection control professionals (2011 for CLABSIs).

**Progress:** Evaluation of algorithm-detected central line-associated bloodstream infection reporting measures is in progress at 19 facilities reporting to the National Healthcare Safety Network, and the preliminary assessment is anticipated in fourth quarter of CY 2010. Piloting of VAP measures has started in 9 facilities reporting to NHSN, correlation to clinical outcomes has been completed at 3 academic centers, and the report is in clearance. An expert panel charged with improving proposed definitions is planned for September 2010.

- d) Develop a system to collect representative sets of bacterial isolates to assess changes in resistance mechanisms or strain prevalence 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:** CDC conducts population-based surveillance, including isolate collection, for invasive MRSA and *C. difficile* infections through the EIP. There are no systems currently in place to collect nationally-representative isolates of other antimicrobial resistant organisms for antimicrobial susceptibility testing or strain characterization. Bacterial isolates with unusual resistance profiles, including multi-drug resistance, are frequently received at CDC's reference laboratory for expanded antimicrobial susceptibility testing. Emerging resistance mechanisms and unusual phenotypes are tested and reported according to CLSI guidelines. If CLSI-recommended testing methods fail to adequately detect unusual resistance, this data is shared with CLSI.

- 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 are ongoing in multiple EIP sites since 2005 and 2009, respectively. As part of this surveillance, MRSA and *C. difficile* isolates are collected and submitted to CDC for molecular characterization and antimicrobial susceptibility testing. A pilot project to assess the feasibility of conducting surveillance for infections due to multidrug-resistant gram-negative bacilli is being conducted in 2010 in 2 EIP sites; this assessment will inform the development of a multi-site surveillance effort with isolate collection, which is anticipated to begin in 2011.

- f) Design (2010), pilot (2010) and implement (2011) a periodic national prevalence survey for healthcare-associated infections, including those caused by antimicrobial-resistant pathogens.



**Progress:** The healthcare-associated infections and antimicrobial use point prevalence survey 2010 limited roll-out survey has been conducted; data collection was completed in December 2010 and preliminary results were presented at the April 2011 annual meeting of the Society for Healthcare Epidemiology of America (SHEA). Selection of hospitals to participate in the full-scale 2011 survey is complete and recruitment and training is underway. Surveys will be conducted in participating hospitals during summer 2011, and data collection is anticipated to be complete by December 31, 2011.

*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:** In March 2010, six FoodNet/NARMS retail sites began a 12-month pilot project to assess prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and *Clostridium difficile* in retail meats. Strains are being sent to FDA for antimicrobial susceptibility testing which is ongoing as strains are received.

- b) Evaluate the quantity of *Clostridium difficile* recovered from retail meats in FoodNet sites (2010).

**[Note: This project will be combined with project 1.3 a]**

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

**Progress:** In 2010, the protocol for this study was developed and approved by CDC, state health department, and the local hospital IRB. Enrollment of cases and controls will start in December 2010. The goal of the study is to enroll a total of 40 households, both cases and control households. For each household, 20 environmental samples will be collected and tested for *C. difficile*. For the control households and for households of community-acquired *C.difficile* cases, water samples will also be obtained and tested for the presence of *C.difficile* spores.

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

**Progress:** USDA is conducting a collaborative study with Texas A & M to identify and compare *C. difficile* in humans, swine production, and retail meats. Sampling has been completed and further analysis is being done. Studies have been done on *C. difficile* isolation and typing methods. Emerging pathogens related to resistance and the NARMS project will be sampled depending on the decisions made by the NARMS agencies.

*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 (2010).

**Progress:** In 2010, the CDC's Emerging Infections Program began population-based surveillance for *Clostridium difficile* infection (CDI) in select counties across 8 states. For each CDI case identified, a standardized case report form, containing demographic and clinical data, was abstracted from patients' records. The first year of surveillance data will be analyzed in the spring of 2011 when all 2010 data entry will be completed.

Population-based surveillance for MRSA began in 2005 in 9 US metropolitan areas, and data from this surveillance has continued to be analyzed annually to identify any changes in the epidemiology of invasive MRSA.

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 soliciting applications to conduct preliminary comparative effectiveness research (CER) projects on Eradication Methods for MRSA. One grant has been funded as a result of this solicitation.

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

**Progress:** CDC is collaborating with Emory University Children's HealthCare of Atlanta, GA Emerging Infections Program and VA Medical Center to conduct a nasopharyngeal carriage survey in Atlanta. This study is currently ongoing and will assess overall colonization as well as that with non-susceptible *S. pneumoniae* following introduction of the new 13-valent pneumococcal conjugate vaccine (PCV13) among children <5 years. As of Nov 1, 2010, 387 children have been enrolled; final results are expected by the end of 2011.

The NIAID-supported Bacterial Respiratory Pathogen Research Unit (BRPRU) conducts pre-clinical and clinical studies for the diagnosis, prevention, and management of selected bacterial respiratory pathogens. BRPRU is evaluating the effects of immunization with different *Streptococcus pneumoniae* antigens on protection against both colonization and infection [Infect Immun. 2010 May;78(5):2231-9].

*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*, extensively drug-resistant tuberculosis [XDR TB], oseltamivir-resistant influenza viruses), and strive for more timely dissemination of surveillance data.

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

**Progress:** Three public health laboratories have been contracted and trained and are currently conducting antiviral testing using molecular assays. In addition to those 3 labs, 31 additional public health and clinical laboratories have received SOPs, reagents, reference viruses, and technical support on setting up one or more antiviral testing assays. The Influenza Division at CDC is presently evaluating 3 different neuraminidase (NA) inhibition assay kits that could potentially be used in the future for detecting resistance NA inhibitors. Testing and improving some web-based reporting systems that were developed in collaboration with the 3 contracting labs is currently undergoing. Once the system is fully implemented, it will be expanded to include other state and public health labs.

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

**Progress:** A PCR assay is nearly complete that will identify pneumococcus as well as whether the organism is susceptible or not to beta-lactam agents. In 2010, web-based trainings have been held with state health laboratory staffs on traditional and new diagnostics for *Neisseria meningitidis* and *pneumococcus*, the major pathogens causing bacterial meningitis.

- c) Routinely evaluate isolates submitted from ABCs sites 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 (2010 and annually).

**Progress:** Trends in the incidence of infections caused by antimicrobial resistant *Streptococcus pneumoniae* show that the introduction of the 7-valent pneumococcal conjugate vaccine in 2000 has continued to have substantial benefits in terms of preventing resistant infections. No vancomycin-resistant isolates have been identified. 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. To date, no unusual GAS isolates have been found; GBS with increasing MICs to beta lactams remain extremely rare. Infrastructure for isolate collection is in place to sustain ongoing evaluation in 2011 and future years. Testing of 2010 isolates is not yet complete.

- d) Assess the impact of including fluoroquinolone susceptibility data to the national TB reporting system for enhanced detection of XDR TB (2010).

**Progress:** CDC has expanded the list of fluoroquinolone drugs treatment and drug susceptibility that can be reported through the National TB Surveillance System (NTSS) to include levofloxacin and moxifloxacin in order to enhance the potential for detection/reporting of XDR TB. These additional fluoroquinolones were added to the NTSS starting in 2009 and are being phased in over a 2 year period. These drugs add to a panel of DST results collected through the NTSS since 1993 that included ofloxacin and ciprofloxacin. In 2011, CDC will assess the impact of these reporting changes on the rates of XDR TB infections.

- e) Complete a pilot exercise to expand routine nationwide surveillance for MDR-TB and determine whether this additional surveillance provides useful information that warrants broader implementation (2010).

**Progress:** CDC has completed a pilot exercise to determine the feasibility of adding additional routine nationwide surveillance for MDR TB. CDC has not yet determined whether this additional surveillance provides useful information that warrants broader implementation of this surveillance.

- 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 (2010).

**Progress:** On July 15-16, 2010 the NARMS program held a public scientific meeting in Atlanta, Georgia with domestic and international stakeholders from public health, industry, and consumer groups. NARMS gathered comments and feedback from participants to help guide future strategic planning.

In addition, an annual NARMS meeting will be held July 20, 2011 following the Annual AVMA meeting in St. Louis, MO. The emphasis of the meeting will be on the Animal

Arm Sampling Program. The meeting will feature presentations by invited speakers and updates of the NARMS program.

*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 develop consensus definitions for outbreaks of antimicrobial-resistant pathogens, formative interviews were conducted with select state health departments during Jan-April 2010 to understand current reporting infrastructures for healthcare-associated outbreaks and to identify potential barriers to reporting. Additional input was solicited from a wider audience of state and local health departments during a facilitated roundtable discussion at the 2010 Council of State Territorial Epidemiologists Annual Conference. Based on the information provided, a framework for reporting healthcare-associated outbreaks, including those caused by antimicrobial-resistant pathogens, is currently being developed. As an initial step towards developing a model for public health response to outbreaks of antimicrobial-resistant pathogens, interested state health departments will participate in surveying facilities within their jurisdiction for surveillance activities and infection control measures for carbapenem-resistant Enterobacteriaceae; the implementation and feedback from this activity will guide future efforts in refining outbreak reporting.

- b) Disseminate expert recommendations for effective state-based surveillance for multidrug-resistant organisms related to healthcare-associated infections (2010).

**Progress:** Information on state-based MDRO surveillance for HAIs was shared and discussed with state health departments at the CSTE session mentioned in item 1.6.a. CDC is also working with some states on ways to facilitate the electronic reporting of MDROs into NHSN. CDC is hosting regular calls with a group of 10-15 states who are interested in enhancing surveillance efforts for carbapenem-resistant Enterobacteriaceae.

- c) Implement standard protocols for antimicrobial susceptibility testing through CDC's ELC Program (2010 and ongoing).

**Progress:** Funds were awarded on August 27, 2010 to Nebraska through the ELC grant to initiate a pilot program for surveillance for  $\beta$ -Lactam Resistant Enterobacteriaceae isolates in an area where resistance is normally expected to be low. The goal is to collect a total of 800 isolates from 8 regional sites throughout Nebraska. An early unusual finding is that an initial spike of cases of *Enterobacter cloacae* producing a KPC

carbapenemase (an enzyme conferring resistance) has been detected, and a resistance plasmid was transferred to a *Serratia marcescens* isolate from the same patient. This program will serve as a model for antimicrobial resistance detection by other ELC recipients.

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

**Progress:** In 2009 a CDC/APHL survey was conducted to determine the ability of 51 U.S. public health laboratories (PHLs) to detect and /or confirm antimicrobial resistance. Most PHLs were able to provide testing to detect resistance to first-line and second-line TB drugs and to detect resistant *Staphylococcus aureus*. Less than 30% offered testing to detect multidrug-resistant gram-negative bacilli. This survey will serve as a baseline for targeting where future training programs are needed.

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

**Progress:** A team of subject matter experts have been identified to begin updating the Multi-Level Antimicrobial Susceptibility Testing Resources (MASTER). The project timeline is on track for a 2013 pilot.

*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 (2010-2011).

**Progress:** Forty-nine states and 2 territories received funding in 2009-2010 through the American Recovery and Reinvestment Act (ARRA). State health departments used this funding to create state-based HAI programs to bring relevant stakeholders together for the purposes of needs assessment and planning for HAI surveillance initiatives and prevention efforts. A number of state-healthcare facility collaboratives are underway that are using NHSN to conduct surveillance on MRSA, *C. difficile*, and other MDROs. The surveillance data are being utilized to guide and implement necessary prevention efforts.

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

**Progress:** FDA has initiated contact with several veterinary diagnostic laboratories to determine feasibility of pursuing a monitoring plan for select veterinary bacterial pathogens based on the NARMS platform.

*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 (2010 and ongoing).

**Progress:** From October 2009 to present, NARMS partnered with WHO's Global Foodborne Infections Network (GFN) to provide training courses to four countries. The training courses included training on antimicrobial resistance.

- b) Support and assist WHO on matters related to integrated surveillance of AR and containment of food-related AR through participation in the newly established WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR) (2010 and ongoing).
- NARMS scientists from FDA, CDC, and USDA continue to provide expert advice to the WHO-AGISAR steering committee through participation and information sharing (2010-2012).
  - 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 1<sup>st</sup> and 2<sup>nd</sup> 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](http://www.who.int/foodborne_disease/resistance/agisar/en/index.html)).

From October 2009 to present, NARMS partnered with WHO Global Foodborne Infections Network (GFN) to provide training courses to four countries. The courses included training on antimicrobial resistance.

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.

- 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 (2010 and ongoing).

**Progress:** Two IEIP program sites, Guatemala and Egypt, have initiated studies of antimicrobial use to understand patterns of use and identify where there are opportunities to reduce antibiotic use to decrease the spread of resistance.

- 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:** Laboratory staff from the Kenya IEIP have now been trained on antimicrobial susceptibility testing for pneumococcus and are completing assessing resistance among carriage strains in children and HIV-infected adults.

*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*, HSV), 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:** Infection of *T. vaginalis* isolates with *Mycoplasma hominis* is not responsible for increased resistance to 5-nitroimidazole drugs. A method to genotype *T. vaginalis* isolates using microsatellites has been developed in collaboration with investigators at the New York University School of Medicine. The plan is to apply this method to comparison of drug resistant and sensitive isolates. The STD Surveillance Network (SSuN) assessment of prevalence of resistance in *T. vaginalis* isolates in 6 cities (100 isolates per city) is nearing completion. There is significant variation between cities, with an overall resistance prevalence of 4.2% (range 1 to 6.9%).

- 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:** Efforts are underway to characterize molecular markers associated with ACT resistance. The *pfmdr1* genetic background, including copy number as potential markers for ACT partner drugs, is extensively studied. Additional potential markers are also being explored. Three research papers on the role of *pfmdr1* as a potential marker for ACT have been published recently (Vinayak S. et al., J Infect Dis. 2010 May 15;201(10):1551-60, Griffing S, et al., Antimicrob Agents Chemother. 2010 Apr;54(4):1572-9. Epub 2010 Feb 9. Alam MT et al., J. Infect Dis. In press).

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



**Progress:** An in vivo efficacy study is ongoing in Kenya and an IRB protocol to start an in vivo efficacy study has been submitted in another EIP site in Africa. Plans are ongoing to start an in vivo efficacy study in a West African country. In vitro drug sensitivity testing has begun in two African countries and is planned to begin in 2011 in another African country.

- 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:** Collection of specimens has started in Kenya and Tanzania in 2010, and it is in the planning stage for Ghana, which is anticipated to begin in 2011. In addition, efforts are being made to work with other international partners especially in South America and Asia to collect additional specimens from regions where ACT has been implemented. These efforts are anticipated to begin in 2011.

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

**Progress:** Onsite training was provided in three countries since 2009 for performing in vitro drug sensitivity assays. Training was provided to staff from at least 10 countries in using molecular markers for drug resistance since 2008, and training was planned for staff from at least 3 more countries in the next six months.

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

**Progress:** Surveillance systems to monitor for insecticide resistance to malaria vectors have been established in the 15 countries of the President's Malaria Initiative. High levels of resistance to insecticides have been found in a number of countries, particularly in Benin, Ethiopia and Zambia. In Ethiopia, documentation of the timeline of events that led to the decision by the Directorate of Health Promotion and Disease Prevention to change the class of insecticides used in indoor residual spraying has been completed. Two new insecticides classes will be used for indoor residual spraying in 2010, and the impact on resistance to insecticides will be monitored to establish an evidence base for the susceptibility to insecticides as well as for maintaining the susceptibility to insecticides for which high levels of resistance have not yet been found.

*Coordinator: CDC; Collaborator: DoD*

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

*Coordinator: FDA; Collaborator: EPA*

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

2.1 Identify sources of antimicrobial use information in the United States for humans, animals, agriculture, aquaculture, and other sectors to establish baseline data on antimicrobial use. Develop standards for collecting and reporting antimicrobial use data (comparable to “defined daily doses” in humans) 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:** CDC’s Get Smart program has gained limited access to proprietary antimicrobial prescription data in the community setting. Additional data will be shared once a mutually-acceptable contract has been signed.

- b) Perform a national antibiotic use point-prevalence survey (pilot survey to be completed by 2010 and full survey by 2012).

**Progress:** The 2010 limited roll-out healthcare-associated infections and antimicrobial use point prevalence survey has been conducted in 10 Emerging Infections Program sites. Data collection is being completed, and data validation activities are commencing. It is anticipated that 2010 survey activities will be completed by early 2011. Full-scale survey planning is underway, and it is anticipated that the full-scale effort will be completed by 2010.

- 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 Resistance Option of the NHSN Antimicrobial Use and Resistance (AUR) Module was revised to allow only submission of electronically captured data; the protocol is undergoing final revisions, and informatics standardization of data submission via clinical document architecture (CDA) is planned for 2010, will begin piloting facility submission of aggregate antimicrobial use data via CDA in 2011, begin receiving data by 2012, and provide ongoing periodic reports of the collected use data by 2013.

- d) Collect and publish animal antimicrobial drug distribution data through implementation of Section 105 of the Animal Drug User Fee Amendments of 2008 (2010).

**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 2009 summary report of sales and distribution data of antimicrobial drugs approved for food-producing animals on December 9, 2010.

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:

- 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:** A series of information sheets highlighting the prevalence, antimicrobial resistance, and have been produced as follows. These are available on the NAHMS website ([http://www.aphis.usda.gov/animal\\_health/naahms/](http://www.aphis.usda.gov/animal_health/naahms/)):

[Dairy 2007: \*Salmonella\*, \*Listeria\*, and \*Campylobacter\* on U.S. Dairy Operations, 1996-2007](#) (pdf 1.3mb 3/11)

[Salmonella and Campylobacter on U.S. Dairy Operations, 1996-2007](#) (pdf 47kb 7/09)

[Campylobacter on U.S. Beef Cow-calf Operations, 2007-08](#) (pdf 30kb 6/09)

[Enterococcus on U.S. Beef Cow-calf Operations, 2007-08](#) (pdf 30kb 6/09)

[Salmonella on U.S. Beef Cow-calf Operations, 2007-08](#) (pdf 29kb 6/09)

Questions and Answers: Judicious Use of Antimicrobials in Food Producing Animals, APHIS. Factsheet June 2010

[http://www.aphis.usda.gov/publications/animal\\_health/content/printable\\_version/faq\\_antimicrobial\\_drugs.pdf](http://www.aphis.usda.gov/publications/animal_health/content/printable_version/faq_antimicrobial_drugs.pdf)

[Clostridium difficile on U.S. Beef Cow-calf Operations](#) (pdf 56kb 5/11)

[Clostridium difficile on U.S. Dairy Operations](#) (pdf 57kb 5/11)

[Clostridium difficile on U.S. Swine Operations](#) (pdf 56kb 5/11)

[Salmonella on U.S. Swine Sites--Prevalence and Antimicrobial Susceptibility](#) (pdf 59kb 1/09)

[Escherichia coli on U.S. Swine Sites--Antimicrobial Drug Susceptibility](#) (pdf 30kb 1/09)

[Campylobacter on U.S. Swine Sites--Antimicrobial Susceptibility](#) (pdf 32kb 12/08)

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 healthcare and veterinary institutions (e.g., cephalosporin use and prevalence of vancomycin-resistant enterococci) 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:** CDC has completed an analysis evaluating the relationship between antimicrobial prescribing and *S. pneumoniae* antibiotic resistance in ABCs sites. A manuscript is being prepared for publication. Additional analyses assessing geographic differences in antimicrobial prescribing were presented at the Infectious Diseases Society of America meeting on October 22, 2010 (Abstract #339).

*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 streptococcal 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 2012 or 2013 is being planned 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 this year and are in clearance.

*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:** A new 13-valent pneumococcal conjugate vaccine was licensed for the young children in the U.S. in February 2010. A large, 12-site case control study has started that will assess the effectiveness of PCV13 on drug-resistant pneumococcus.

CDC conducts annual studies of the effectiveness of influenza vaccines in preventing medically-attended RT-PCR-confirmed influenza infections. Viral isolation in tissue culture is subsequently attempted for respiratory specimens that are positive for influenza by RT-PCR. Influenza isolates are tested at CDC for antiviral resistance. Each season, CDC can make an estimate of vaccine effectiveness for antiviral resistant versus susceptible viruses, if sufficient numbers of resistant viruses are detected.

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

**Progress:** CDC's Get Smart program provided educational materials to the Hospital Corporation of America (HCA) to implement an academic detailing program in primary care practices in New Hampshire and Missouri. Prescribing practices for certain conditions will be monitored by HCA and the outcomes will be shared with CDC.

*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:** Several multicenter prevention collaboratives focused on device and procedure-related infections (i.e., central line associated bloodstream infection [CLABSI], surgical site infection [SSI], catheter-associated urinary tract infection [CAUTI]) were created or expanded with funding from the American Recovery and Reinvestment Act (ARRA). As of June 2010, 15 state health departments are actively working with the Comprehensive Unit-based Safety Program (CUSP) to reduce and eliminate CLABSIs. In addition, three other ARRA-funded states are currently conducting non-CUSP CLABSI prevention collaboratives. Six states are conducting SSI prevention collaboratives, and five states are conducting CAUTI prevention collaboratives. States are currently at different points in the spectrum of prevention collaborative activities, including organizing staffing, creation of multidisciplinary advisory groups, recruitment of facilities (both acute and non-acute settings), and conducting kick-off events and collaborative learning sessions. CDC (PRB/DHQP) is facilitating these state prevention collaboratives through resources such as toolkits, scheduled webinars, infection-specific conference calls, and dedicated scientific and programmatic support.

- 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:** Adherence to recommended hand hygiene, isolation precaution, and environmental cleaning practices are processes known to prevent HAIs. With financial support and technical input from DHQP, academic partners developed an iPhone/iPod Touch application to assist observers in evaluating adherence to recommended hand hygiene and isolation precaution practices. This application is now available for free to anyone with the device. The application has been deployed in several CDC-led outbreak investigations, and has been used by members of various prevention collaboratives for consistent and efficient data collection by observers. DHQP will assist with a study to determine the most effective mode of feedback for data generated by these devices; that study will begin at three hospitals in Q1 of 2011 and will last 9 months. DHQP has also collaborated with academic partners to develop a standardized set of criteria for evaluating environmental cleaning processes.

- c) Describe (or assess) correlations between adherence to best catheter insertion practices and CLABSI rates (2011).

**Progress:** The first analysis of central line insertion practices (CLIP) data reported to NHSN took place in Q4 of 2009. The adherence rate from all reported data at that time was 91%. However CLIP data could be assessed for only a small number of CLABSIs at that time. A second analysis to test the association between CLIP and CLABSI trends will be run in Q4 of 2010, with subsequent report and write-up in Q1-Q2 of 2011.

- d) Revise and publish HICPAC guidance for prevention of catheter-associated bloodstream infections (2010).

**Progress:** The revised Guidance for the Prevention of Intravascular Catheter-Related Infections was approved by HICPAC and is currently undergoing clearance at CDC. Anticipated release of this document is late Fall 2010.

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

**Progress:** In July 2010, the proposal to update to the Guideline for the Prevention of Surgical Site Infection, 1999 was presented. This will include an update to the core section, an expansion to the *Staphylococcus aureus* screening and decolonization section, and a new specialty/procedure specific component section focused on the prevention of surgical-site infections in arthroplasties. For the November 2010 HICPAC meeting, the names of all potential co-author/high-level reviewer candidates as submitted by the American College of Surgeons (ACS), the American Academy of Orthopaedic Surgeons (AAOS), the Surgical Infection Society (SIS), and the Musculoskeletal Infection Society (MSIS) will be recorded. These surgical societies are all new participants in the HICPAC guideline development process. Additional candidates from nonsurgical disciplines will be included. Anticipate the guideline update to begin by the February 2011 HICPAC meeting.

*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:** Several state-based MDRO and *C. difficile* (CDI) prevention collaboratives have been created or expanded with funding from the American Recovery and Reinvestment Act (ARRA). As of June 2010, two states are conducting a general MDRO prevention collaborative; ten states are currently conducting a MRSA collaborative; two states are conducting a MDR-gram-negative collaborative; and one other state is conducting an *Acinetobacter* collaborative. In addition, two states are conducting prevention collaboratives focusing on hand hygiene as the primary infection-prevention strategy. Twelve states are conducting CDI collaboratives. States are currently at different points in the spectrum of prevention collaborative activities, including organizing staffing, creation of multidisciplinary advisory groups, recruitment of facilities (both acute and non-acute settings), and conducting kick-off events and collaborative learning sessions. Evaluations (both process and outcome) are also underway to assess the impact through the use of surveys and surveillance systems such as the National Healthcare Safety Network (NHSN).

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

**Progress:** The CMS-QIO MRSA prevention initiative from the 9<sup>th</sup> SOW is in its final follow-up months of required reporting and will be completed by Jan 2011. CMS and the QIO Steering Committee are responsible for analyzing the data and determining whether a successful level of reduction in MRSA rates was reached by the funded QIOs and their participating facilities. The CDC will be conducting analyses using these same data to determine the level of correlation between MRSA rates reported as healthcare-associated infections through the Infection Surveillance piece of the NHSN MDRO/CDI Module and MRSA rates reported as LabID Events (proxy measure for infections) through the LabID Event Reporting piece of the Module from within the same facility locations. Data review, cleaning, and programming for these analyses has begun. Results and findings will be reported at a major scientific conference and/or through a peer-reviewed published manuscript, as appropriate.

- 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 (2010).

**Progress:** The initial evaluation of the impact of the Department of Veterans Affairs National MRSA Prevention initiative has been completed and has been submitted for peer review publication. Preliminary results were presented in an abstract form at the Decennial Conference on Healthcare Associated Infections. The “MRSA bundle” was implemented in all 153 acute care VA medical centers nationwide in an effort to decrease MRSA HAIs. The bundle consisted of 1) nasal surveillance for MRSA on all admissions, in-hospital transfers, and discharges, 2) contact precautions for patients carrying MRSA, 3) an emphasis on hand-hygiene, and 4) a culture change where infection control became everyone’s responsibility. From October 2007 through June 2009 when the bundle was fully implemented, there were 1,213,646 admissions and transfers (230,470 to intensive care units (ICUs) and 983,176 to non-ICUs) and 5,296,757 bed-days of care (846,570 ICU and 4,450,187 non-ICU). MRSA HAI rates declined 24% in the non-ICU setting ( $P = 0.04$ ) and 77% in the ICU setting ( $P < 0.001$ ), following full implementation of the bundle. Additional analyses are underway, including the change in *S. aureus* antibiogram following implementation of the program and an examination of factors that explain variability of impact among individual facilities. CDC staff are now technical advisors to the VA working group implementing CDI measurement and prevention strategies on a national scale.

- 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:** A statewide collaborative targeting the prevention of multidrug-resistant organisms (MDROs) and involving nearly all the acute and long-term care facilities in Vermont will commence with a kick-off meeting on September 16, 2010. This effort will



target clusters of acute and long-term care facilities from the same areas and attempt to implement regional strategies for MDRO prevention. In addition, the effort will utilize electronic data collection to measure outcomes. The goal of this effort will be to both decrease transmission of MDROs already present in Vermont and to prevent the emergence of new MDROs.

*Coordinator: CDC; Collaborators: AHRQ, VA, CMS*

- 3.4 Evaluate the effectiveness of infection-control practices, products, and devices in healthcare facilities, including long-term healthcare and outpatient settings.
- a) Expand CDC's Prevention Epicenter Program to include additional academic centers, integrated health systems, and healthcare departments to support early translation of technical advances and epidemiologic knowledge into evidence-based recommendations (2011).

**Progress:** The CDC Prevention Epicenters Program has evolved to become part of a larger HAI Prevention Research Program. The SHEPheRD Program has begun to take shape with the development and funding of three new initiatives. These initiatives include a diverse group of partners and prevention research activities. Currently, the initiatives under the SHEPheRD Program are designed to maximize the ability to fill current prevention knowledge gaps and identify novel prevention strategies. To date, the Prevention Epicenters Program has been re-structured and expanded to utilize a translation prevention research framework. Funded sites will address target areas of the HAI Action plan through Investigator and CDC-initiated efforts. Currently, the FOA has been published and will go to peer-review in the fall of 2011. The new FOA has received significant interest from state and academic partners, and will be implemented in spring of 2012. The Health Department Cooperative Agreement has been developed and, through EIP sites, will address whether the use of regular chlorhexidine bathing of (or "by") nursing home residents results in a reduction in prevalence of MDRO colonization in that population. As a supplement through EIP, this new FOA has also received interest from state partners and will be implemented early next year. The HAI Prevention Task Order System is still in the development stages and will include diverse recipients and research activities. However, currently, a single contract which will serve as a pilot for managing multiple mechanisms under the SHEPheRD Program structure is being funded. Resources for the Future has been contracted to define the epidemiology of antimicrobial use in in-patient acute care hospitals. This research will provide a deeper understanding of what types of clinical syndromes tend to prompt antimicrobial therapy, and what information then prompts changes in that therapy that will be critical to on-going CDC efforts to improve in-patient 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:** State health departments in Illinois, Vermont and Maryland recruited fifteen acute care hospitals and nursing homes for the study. The protocol is pending human subjects' exemption review by CDC. Intergovernmental Personnel Act agreements are in place with academic institutions to provide funding for collection of appropriate environmental samples. Training of the samplers will occur in October 2010 at CDC. The study will begin in fall 2010 pending human subjects' exemption approval and facility availability. Environmental sampling and analyses would conclude in summer 2011.

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

**Progress:** DHQP's Office of Prevention Research and Evaluation (OPRE) has established an evaluation team and a plan for an iterative evaluation to thoroughly describe state-based CDC-funded prevention collaboratives in terms of activities, year-one outcomes, and year-two outcomes. The four domains evaluated will be infrastructure, surveillance, prevention, and communication. An initial report, describing inputs, activities and year-one outcomes will be completed by December 2010. The evaluation team is targeting completion of the full evaluation by 2013.

- d) Quantify the national impact of HAI prevention efforts by publishing annual national summary statistics (standardized infection ratio) of HAI data reported to CDC's NHSN (2010 and ongoing).

**Progress:** National summary statistics reflecting the HAI experience in the U.S. were published in June 2010 for central line-associated bloodstream infections. National summary statistics including CLABSI and surgical site infections are prepared for publication in December 2010. Planning for annual publication of these summary statistics (i.e., standardized infection ratios) is underway for a spring publication, and the results are anticipated to include state-specific summary statistics as NHSN reporting increases to accurately reflect the experience of the state.

*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, and formulate guidelines on "best practices."

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

**Progress:** Data from the NAHMS Dairy 2007 study were analyzed for risk factors for the recovery of *Salmonella* and MDR *Salmonella* on farms. The work has been published and is available at: [Zoonoses and Public Health](#) 57 (7-8), pp. e217-e225.

ARS researchers are conducting research on potential risk factors and management practices that affect *Salmonella* (and *E. coli*) shedding in dairy cattle. There will be focused attention on the prevalence and potential causes of MDR *Salmonella* Newport in

dairy cattle. This research is being conducted at College Station, Texas, and is in progress.

- 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. Grant awards will be announced in June 2010. These 4-year grants will begin in 2010 and must be completed no later than 2015.

**Progress:** A National Integrated Food Safety Initiative (NIFSI) grant for \$2 million was awarded to researchers at Washington State University focusing on "Minimizing antibiotic resistance transmission using the dairy farm as a model system." An NIFSI grant for \$2 million was also awarded to researchers at Kansas State University focusing on "Practical interventions to effectively manage antibiotic resistance in beef and dairy cattle systems using a fully integrated approach." Both are 4-year grants that will commence in 2010. Annual progress will be reported in USDA's Current Research Information System (CRIS).

- c) Identify factors important for assuring that antimicrobial drugs are used judiciously in veterinary, agriculture and aquaculture environments (2010).

**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. FDA is currently evaluating 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:** ARS researchers at Athens are conducting research on various sanitizers and natural ingredients that may be used in the processing of poultry carcasses. Research is focused on the effect on reduction of foodborne pathogens, such as *Salmonella*, as well as the effect on antimicrobial resistance. This research is being expanded to identify new potential processing technologies as well as chlorine. Ongoing.

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

**Progress:** ARS researchers at Clay Center continue their research on the identifying and developing novel intervention strategies focused on cattle hides and decreasing hide contamination. These include testing effective reagents and the design and use of a hide wash cabinet. These strategies are in addition to preharvest food safety strategies. Research is continuing.

- 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:** ARS researchers at Athens are conducting research on the effects of various sanitizers on the microbial quality of eggs and within the shell egg processing facility. For example, sodium hypochlorite and calcium hypochlorite reduced the level of Enterobacteriaceae in the vacuum loader cups. More research is being conducted in the commercial setting and on potential sanitizers.

*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.

**Progress:** The 2010 Food Safety Education Conference Planning Committee orchestrated the largest food safety education conference ever presented by USDA. Attendance reached over 770 with more than 80 on the waitlist. The theme of this four-day conference was “Advancements in Food Safety Education: Trends, Tools, and Technologies.” The conference audience was increased through use of social media tools, reaching nearly 650,000 exposures through Twitter messages. Additionally, six videos posted on YouTube were viewed over 1,200 times, and three entries on the USDA blog were seen by almost 400 Twitter users and other blog readers. In addition, the conference also had a blog entry on the White House site. Conference participants demonstrated a commitment to serve as information multipliers, sharing conference foodborne illness prevention resources, expanding the reach to an estimated 327,000 persons. Therefore, the impact of the conference extends well beyond the large audience immediately on hand in Atlanta.

- 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.

**Progress:** The USDA Food Safety Discovery Zone was launched on May 6, 2010 during Public Service Recognition Week on the National Mall in Washington, D.C. During the 2010 tour season (March – October), the Discovery Zone has traveled the country visiting 19 states and over 45 events. The program has offered consumers the in-depth, interactive, and hands on demonstrations as promised. The Be Food Safe messages 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.

- c) Host USDA Nutrition Month to include Food Safety Day on March 10, 2010 to increase consumer awareness about food safety.

**Progress:** National Nutrition Month was observed in March 2010. This year's theme was "Local, Sustainable, Safe, and Healthful Eating." FSIS staffed an exhibit at the kick-off event, which was held on March 3, 2010. Over 150 participants visited the exhibit to take a food safety quiz, select educational materials, and get answers to their specific food safety questions. Additional exhibits were displayed at the USDA South Building cafeteria and the Whitten Café for Food Safety Day, March 10.

*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:** Curriculum has been posted on the Michigan State University website (<http://amrls.cvm.msu.edu>)

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

**Progress:** In FY2010, the Get Smart on the Farm program funded 3 state health departments to promote appropriate use of antimicrobial agents in veterinary medicine and animal agriculture. The programs fostered collaborations between state public health departments and veterinary communities and implemented community-based programs for the appropriate use of antimicrobial agents in animals. The programs included educational materials for veterinarians and animal producers. In addition, NARMS-CDC staff continued to work with Michigan State University to create a series of online teaching modules that explain the basic principles and impacts of antimicrobial resistance and promote the prudent use of appropriate antimicrobial use in veterinary settings. These will be available at no cost on the Antimicrobial Resistance Learning Site hosted by Michigan State University and the site is expected to launch in early FY2011.

*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 (2010).

**Progress:** DHQP has written a pledge showing willingness to be a global partner in WHO's hand-hygiene promotion campaign. As part of the WHO's Hand Hygiene Awareness Day (May 5<sup>th</sup>, 2010), CDC launched a new hand-hygiene website promoting CDC-generated tools and guidelines and WHO's implementation tools for the improvement of hand hygiene in healthcare settings. As part of the global campaign, DHQP led a Clinician Outreach and Communication Activity (COCA) call to promote hand-hygiene activities and discuss pertinent issues with over 1000 providers around the nation. DHQP plans to convene a national hand-hygiene workgroup in Q4 of 2010 to make strategic decisions about hand-hygiene measurement and guidance and to promote national participation in the WHO's hand-hygiene campaign.

- 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:** Through an interagency agreement formed in 2009, DHQP has supported research towards the development and utilization of automated wireless devices (located in dispensers and with healthcare personnel) to measure hand-hygiene adherence. After several experimental pilots in Q1 and Q2 of 2010, the technology was piloted in a healthcare setting in July and August of 2010. Additional pilots at two other hospitals are planned for Q4 of 2010. CDC conducted focus groups with administrators, unit managers, and frontline healthcare personnel in March 2010 to assess the acceptability of this type of technology. Data generated from these focus groups have been quantitatively and qualitatively analyzed and recorded in manuscripts. Authors aim to publish these manuscripts by the end of 2010. A full report on the experimental healthcare pilots of the technology will be completed by the end of Q3 (2010).

*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 (design 2010, pilot 2011, and implement 2012) and resistance rates (develop 2010 and pilot 2011).

**Progress:** The AUR module of NHSN has now been revised to accept electronic data from pharmacy systems which will dramatically reduce the data collection burden for antibiotic use. The technical specifications of the revised module were approved on October 2010 by the HL7 organization and are now available for use by vendors of commercial pharmacy systems. CDC is now in discussions with several vendors about pilot projects to implement the AUR module.

- b) Develop a “change package” for improving antimicrobial use in in-patient healthcare settings by 2010.

**Progress:** A change package has been developed in partnership with the Institute for Healthcare Improvement (IHI).

- 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:** CDC is now working with IHI and the Public Health Foundation on an effort to pilot test the “change package” for improving antimicrobial use in order to refine it.

- d) Examine knowledge, attitudes, and behaviors of healthcare providers regarding adverse events and antimicrobial use (focus testing to be completed in 2010).

**Progress:** Formative research examining healthcare provider attitudes and behaviors toward prescribing in the outpatient setting has been completed and is under review. Additional formative research is currently being conducted with patients and parents. Educational materials will be developed once the patient and parent components are complete.

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

**Progress:** CDC is providing subject-matter expertise and participating in an AHRQ funded project in New York that is examining specific antibiotic risk factors associated with *C. difficile* and assessing the impact of improving antibiotic use on *C. difficile*. CDC is also providing technical expertise and collaborating with state led projects in GA and MA that are seeking to reduce *C. difficile* infections by improving 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:** Organize a meeting of experts from CMS, CDC, and AHRQ to explore potential study designs (2012)

*Coordinator: CDC; Collaborators: AHRQ, FDA, VA*

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

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

**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 has initiated contact with CDER to identify scientific experts who will be involved in the revision process (e.g. medical/veterinary advisory meeting).

- 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 (2010).

**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. FDA is currently evaluating 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. FDA has completed its analysis of the comments and intends to issue a revised order regarding the extralabel use of cephalosporin drugs by the 4<sup>th</sup> 1<sup>st</sup> quarter CY 2011.

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



**Progress:** Targeted field monitoring for emerging resistance was conducted as a condition of a special agricultural clearance from EPA for the apple producers in Michigan. The clearance permits the use of a new bacterial control agent, kasugamycin, against high disease pressure involving the pathogen that is responsible for the plant disease fire blight (*Erwinia amylovora*). Based on soil, flower, and leaf samples, about 600 gram-negative bacteria from apple orchards were identified. Of these, 102 enteric organisms, which are more closely related to the fire blight pathogen, were seen. Five of the flower and leaf isolates and 8 of the soil enteric isolates were capable of growing on medium amended with 250 or 500 ug/lm kasugamycin. Monitoring efforts and characterization are ongoing.

*Coordinators: CDC, FDA; Collaborators: EPA, USDA*

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

**Progress:** An evaluation of a colorimetric assay has been completed that simultaneously measures the amount of both artemether and lumefantrine in Artemisinin combination therapy (ACT) drugs. We are now working on a similar method for artesunate/amodiaquine drugs ACTs.

*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 detailing sheet with diagnosis and treatment algorithms (2012).

**Progress:** CDC is collaborating with experts in the field, including representation from the American Academy of Pediatrics to update the Principles. The work group is in the process of reviewing published data and compiling recommendations.

- 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 the work ongoing in the basic research portfolio are given.

For a full list of antimicrobial resistance projects, see the [NIH RePORT website](#).

Funding of two R01s (multidrug-resistant *Acinetobacter baumannii* and challenges in beta-Lactamase mediated resistance) led to the dissection of resistance mechanisms used by *Acinetobacter baumannii* and *Klebsiella pneumoniae*. These findings lay the foundation for the design of inhibitors to circumvent resistance in these gram-negative bacteria. [[Antimicrob Agents Chemother. 2010 Feb;54\(2\):890-7](#); [Antimicrob Agents Chemother. 2009 Sep;53\(9\):3628-34](#)]

Work supported by an NIH director's pioneer award (A Network Biology Approach to Antibiotic Action and Bacterial Defense Mechanisms) showed that sublethal concentrations of an antibiotic can induce mutations, which can confer multidrug resistance in pathogenic bacteria. This was found to occur via the production of free radicals, which induced enhanced mutation rates and gave rise to cross-resistance for heterogeneous antibiotics. These findings have important implications for the treatment of bacterial infections, including the importance of administering adequate doses of antimicrobial agents. Furthermore, the components of the bacterial reactive oxygen species response may be promising targets for the development of novel antibacterial agents. [[Mol Cell. 2010 Feb 12;37\(3\):311-20](#)]

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

- Work conducted at NIAID's New England Regional Center of Excellence for Biodefense and Emerging Infectious Diseases examined *S. aureus* wall teichoic acid (WTA) as an unexploited therapeutic target. A lead candidate targeting WTA has been identified and optimized. [[Bioorg Med Chem Lett. 2010 Mar 1; 20\(5\):1767-70](#)]
- The NIAID Centers for Excellence for Influenza Research and Surveillance funds two projects focused on understanding the fitness cost of and possible prevention

strategies for the emergence of oseltamivir-resistant influenza strains. [PLoS Pathog. 2010 Jul; 6(7): e1001022; J Virol. 2010 Aug; 84(21): 11219-26]

Ongoing NIAID intramural research on antimalarial drug resistance aims to identify candidate genes that contribute to drug resistance and study their function, develop gene databases, and screen for new antimalarial drugs. Researchers screened seven parasite lines for differences in responses to 1,279 bioactive chemicals. This work identified new leads for antimalarial drugs and demonstrated the utility of a high throughput chemical genomic strategy for studying parasitic resistance mechanisms. (Nat Chem Biol. 2009 Oct;5(10):765-71.)

*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 RePORT website.

Examples of funded projects include:

Conjugal transfer of bacteriodes antibiotic resistances  
New approaches to study *Pseudomonas*-host interactions  
Staphylococcal adaptations to platelet microbicidal protein

Studies funded by the Harvard-wide program on Antibiotic Resistance examined the mechanisms of horizontal gene-transfer in *Enterococcus faecalis*. Data from these studies showed that the mobilization of antibiotic resistance and virulence genes requires the presence of a pheromone-responsive plasmid and several other genetic elements. [Proc Natl Acad Sci U S A. 2010 Jul 6;107(27):12269-74]

Studies of fundamental molecular mechanisms of host-pathogen interactions and resistance gene-transfer are ongoing in the NIAID intramural research program. In 2009, NIAID scientists and collaborators discovered a potent staphylococcal toxin responsible for disease severity and found that its gene was located within the *Staphylococcus* methicillin resistance-encoding mobile genetic element (MGE). MGEs usually carry genes for either virulence or antibiotic resistance, but not both. The study showed that acquisition of methicillin resistance may be combined with gaining possession of potent toxins by a single event of genetic exchange, which likely represents an important feature accelerating the evolution of MRSA virulence. [PLoS Pathog. 2009 Jul;5(7):e1000533.]

ARS scientists are developing various methodologies and technologies that will help understand and investigate antimicrobial resistance transmission and persistence. ARS scientists at College Station continue to use models (darkling beetles) to study plasmid transfer among foodborne pathogens. ARS scientists at Athens GA have developed a micro-array for the detection of multiple resistant pathogens simultaneously, and

continue to develop sequencing and “omic” approaches to better understand resistance transfer. A database of sequenced strains is being developed. Ongoing.

Pilot projects involving metagenome analyses of fecal communities are being conducted at FDA using high-throughput sequencing efforts (see 5.4). While the primary motivation involves a better understanding of issues related to nutrition and toxicity, the studies should also yield information on the “resistome” associated with commensal communities. In addition, more basic studies with resistance development and transfer are currently being conducted on microbial species being marketed as dietary supplements with probiotic properties.

*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:** Studies are on-going as to the role of biofilms in processing plants and in food animal production environments on antimicrobial resistance in foodborne pathogens. 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 [RePORTER website](#). Representative projects include:

- Regulation of biofilm formation in clinical isolates of *Staphylococcus aureus* (NIAID)
- Evolution of antibiotic resistance in bacterial biofilms (NCRR)
- Controlling bacterial biofilms in cystic fibrosis airways (NHLBI)

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 and showed that interfering with biofilm maturation mechanisms may inhibit dissemination of biofilm-associated infection.

*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, functional genomics, bioinformatics, and proteomic resources and reagents to the scientific community. For example, NIAID has sequence more than 800 bacterial strains including more than 100 *S. aureus* strains, all of which have been deposited in GenBank. In addition, Actinomycetes are being sequenced and mined for antibiotic gene clusters 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 the process. NIAID supports Bioinformatics Resource Centers that serve to 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. More information on these services can be found [here](#).

ARS scientists at Athens GA have collaborated in a public database of SNPs for *Salmonella enteritidis* in poultry. This is part of the NCBI database (National Center for Biotechnology Information).

ARS researchers maintain the US VetNet which contains pulsefield strains of NARMS isolates. These strains can be used by CDC's PulseNet to compare human and animal strains.

FDA has recently invested in next-generation high-throughput sequencers for comparative genomics of bacterial foodborne outbreak isolates in regulated products and their clinically-associated counterparts (in cooperation with CDC). Over the past year, *Salmonella montevideo* and the current *S. enteritidis* in eggs are being analyzed in this manner. This adds to the interrogation efforts that already include custom DNA microarray designs that contain antibiotic resistance gene panels for whole genome genotyping of such outbreak strains.

*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 the following: 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).

Representative career development projects include the following:

- Eukaryotic perception of prokaryotic quorum signals (NRSA)
- Rapid molecular testing for neonatal antibiotic-resistant pathogens (K23)

- Pathogen survival in transport-limited environments (K25)

In 2009 and 2010, NIH dedicated funds from the American Reinvestment and Recovery Act (ARRA) to provide opportunities for grantee institutions to support summer research experiences for students (high school and college) and teachers across the country. NIAID supported over 200 of these supplements, some of which were focused on antimicrobial resistance, the development of novel diagnostics, and vaccines and therapeutics for resistant pathogens of concern.

NIH funds scientific conferences through its R13 grant program. In 2009 and 2010, 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. Examples of conferences include the following:

- Antibiotics and Resistance: Challenges and Solutions, Keystone Symposium, 2010
- New Antimicrobial Drug Discovery and Development, Gordon Research Conference 2010
- Tuberculosis Drug Development, Gordon Research Conference 2009

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 capitol city of the 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)

*Coordinators: CDC, NIH; Collaborator: FDA, VA*

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 development of therapeutics for resistant infections include the following:

- Creation of a human recombinant polyclonal antibody therapy against *C. difficile*
- Novel antibacterials targeting gram-negative nonfermenters
- In vivo testing of *S. aureus* alpha-hemolysin inhibitors

NIAID stimulates preclinical development of therapeutics for infectious diseases via a number of mechanisms, including the following:

- 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.
- 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.” Some examples of the work that NIAID supports, includes the following:
  - Trius Therapeutics has developed a number of lead compounds that have dual-targeting capabilities against gram-negative bacteria. By inhibiting two distinct enzymes, 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 are advancing through preclinical efficacy testing.
  - Achaogen, Inc. is developing novel broad-spectrum aminoglycosides. Thus far, a number of lead compounds have been successfully identified and screened for preclinical toxicity. They are advancing to preclinical efficacy testing.

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. Some examples of the work that NIAID supports, includes the following:

- In FY10, NIAID supported 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.
- In FY10, NIAID issued the “Partnership for Development of New Therapeutic Classes for Select Viral and Bacterial Pathogens” (RFA-AI10-010) research initiative. This initiative targets novel therapeutics for three pathogens for which resistances is of concern: *Neisseria gonorrhoeae*, hepatitis B Virus, and *Clostridium difficile*. Awards will be issued in FY11.

In FY07, 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 diseases 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.

- 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.
- The Preclinical Services for the Development of Therapeutics provides preclinical development services to researchers, including the following: product synthesis, sensitivity screening, efficacy, pharmacodynamic and pharmacokinetic studies, and a full range of toxicity testing. The contract further supports investigation of new formulations of existing drugs to expand their use; examples are the creation of an oral formulation of vancomycin and tablet formulation for delafloxacin.
- In vitro Assessments of Antimicrobial Activity provides in vitro testing services, including Minimal Inhibitory Concentration (MIC) determination, for candidate therapeutics against a wide array of infectious organisms, including MRSA, VRSA, VRE, and resistant strains of *Klebsiella spp.* and *Acinetobacter spp.* This program is a free service to the research and antimicrobial discovery and development communities, whereby investigators can submit compounds/therapies for screening.
- NIAID has a series of contracts to supply animal model testing services for promising vaccines and therapeutic candidates submitted by researchers. Animal models are available for a wide range of pathogens.

*Coordinator: NIH; Collaborators: CDC, FDA, VA*

- 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, in collaboration with FDA and CDC, hosted a workshop on the development of Staphylococcal vaccines in 2010. An effective *Staphylococcus* vaccine could be given to those at risk for acquiring MRSA, thereby reducing the spread of this resistant pathogen in healthcare settings. The purpose of the workshop was to bring together academic scientists, small biotech and pharmaceutical company representatives, and government officials to advance the field.

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



*Production of polysaccharide-protein conjugates as vaccines*

*Mucosal vaccines against gonorrhea*

*Synthetics PNAG and multi-component vaccines against emerging pathogens*

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

*Nitric-Oxide-Releasing wound dressing for preventing chronic wound infections*

*Biomaterials that prevent biofilm colonization and device-based infections*

*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 tuberculosis. Combined with these reagent provision activities has been the development of animal models and the testing of candidate vaccines against tuberculosis.*

In 2010, NIAID scientists and researchers from the University of Chicago identified a possible mechanism to reduce the severity of skin and soft-tissue damage caused by USA300, the leading cause of community-associated *Staphylococcus aureus* infections in the United States. By neutralizing alpha hemolysin, a key toxin associated with the bacteria, they found they could greatly reduce the damaging effects of the infection on skin and soft tissue in mice. This study highlights the potential for antitoxin treatment to become an effective alternative to traditional antibiotics. [[J Infec Dis 2010;202:1050–1058](#)]

ARS researchers are conducting research in identifying and evaluating the use of bacteriophages in poultry, swine, and cattle for the reduction of foodborne pathogens. ARS researchers continue research on vaccines in poultry and swine for the reduction of *Salmonella*.

ARS researchers are also collaborating with academia on larger population studies to demonstrate the use and effectiveness of *E.coli* vaccines for the reduction of *E.coli* 0157:H7.

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

- 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 CDC and FDA, organized a workshop on TB diagnostics in June 2010. The purpose of this workshop was for the US government to work with public and private partners to identify intellectual and procedural gaps in the

development of TB diagnostics and to explore models and strategies that may expedite the development of new TB diagnostics and biomarkers.

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

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 of 2 hours for this test is a significant improvement over existing TB diagnostics, which takes 3-12 weeks. The World Health Organization is considering recommending the use of the new test by its member countries [N Engl J Med 2010; 363:1005-1015].

- Examples of ongoing projects include the following:
  - Detection of antibiotic resistance genes in bacterial agents of hospital-acquired infections
  - Rapid high-throughput *Mycobacterium tuberculosis* genotyping
  - Detection of bacteria using nanoparticle-polymer sensors

Targeted Diagnostics Initiatives include the following:

- In 2004, NIAID issued “Sepsis and CAP: Partnerships for Diagnostics Development” (RFA-AI-04-043), which focused on the development of diagnostics for early detection of the common causes of sepsis and community-acquired pneumonia (CAP). Funding of the resulting awards continued through 2009 and helped advance two candidate technologies to clinical testing.
- 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 to treat and to identify specific bacterial strains and drug resistant phenotypes for the following healthcare-associated pathogens: *C. difficile*, *Pseudomonas*, *Acinetobacter*, *Enterobacter*, *Klebsiella*, *Serratia*, *Proteus*, and *Stenotrophomonas maltophilia*. The four funded projects are ongoing.
- The “Partnerships for Point of Care (POC) Diagnostic Technologies for Nontraditional Health Care Settings” (RFA-AI-08-003) research initiative focuses 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.
- 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. The CDRC will conduct the evaluation of new TB diagnostics to provide data early in the developmental pipeline on the performance of investigational diagnostics and their potential impact on TB management algorithms in endemic countries. Evaluations will be performed at four clinical sites in Uganda, South Africa, Brazil and Korea. The CDRC will contribute to the science of diagnostics and will inform and advise scientists and manufacturers on further development and refinement of diagnostics that promise to accelerate and improve the accuracy of TB diagnosis and the rapid detection of drug resistance.

*Coordinator: NIH; Collaborator: VA*

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

**Progress:** In 2010 ASPR/BARDA began support to industry for the advanced development of broad-spectrum antimicrobial drugs that have dual efficacies against both biothreat pathogens (e.g., anthrax, plague, tularemia) and community-acquired bacterial pathogens. The first contract supported the advanced development of a next generation aminoglycoside designed to be effective against many antimicrobial-resistant bacterial pathogens. Manufacturing activities, Phase Ib clinical studies in special populations, and a Phase II study for HAP/VAP are supported under the contract. In addition to development of this drug for the treatment of hospital acquired infections, the contract also supports development of this drug for biodefense indications against plague and tularemia. ASPR/BARDA plans to award additional contracts to industry in FY11 that support advanced development of entirely new classes of antimicrobial drugs effective against both biodefense and public health bacterial pathogens and known antimicrobial-resistant bacterial strains. .

*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:** In 2010, NIAID issued a new policy on investigator-initiated clinical trials. NIAID will continue to support clinical trial planning (R34) grants for planning, design, and document preparation for clinical trials. In addition, implementation of investigator-initiated clinical trials can be funded through either milestone-driven research project grants (R01) or cooperative agreements (U01), depending on the assessment of risk as delineated in the NIAID-specific criteria. For all three mechanisms, pre-approval is required for submission.

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 the following:

- Phase II evaluation of novel antiviral agent, DAS-181, in the treatment of influenza is being conducted in the VTEUs. Because the therapy utilizes a host-targeted mechanism, the novel antiviral acts on many strains of influenza virus, including strains that are resistant to oseltamivir.
- A Phase 1B, randomized, placebo-controlled, double-blinded, dose-escalation study to evaluate safety, tolerability, and pharmacokinetics of single-daily doses of the antimycobacterial agent SQ109 in normal, healthy male and female volunteers was recently completed in the Phase I clinical trials unit. A second Phase 1B trial for this agent is under development.
- A number of protocols to test therapeutics for resistant pathogens of concern are being developed for the Phase I clinical trials units, including the following:
  - A study to assess safety tolerability and pharmacokinetics of a novel oxazolidinone
  - A study to determine the safety and pharmacokinetics of a novel narrow spectrum agent with activity against *C. difficile*
  - A study to examine the safety, tolerability, and pharmacokinetics of two formulations of a novel fluoroquinolone

*Coordinator: NIH; Collaborator: VA*

- 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](#)).

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).

Combination therapies are another approach to preventing the emergence of resistance. NIAID is supporting several combination clinical trials studying the effectiveness of different drug combinations in treating gonorrhea, influenza, HIV, and malaria.

*Coordinator: NIH; Collaborator: VA*

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 healthcare-associated infections, including CDC's 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 the following:

- National surveillance of emerging MDR in pediatric Enterobacteriaceae infections
- Epidemiology of *Acinetobacter baumannii*: An emerging nosocomial pathogen
- 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. RePORTER 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 RePORT 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 3.6. Current research program starts early 2011 to investigate risk factors for AR development in dairy cattle.

*Coordinator: CDC; Collaborator: FDA, USDA*

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

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

## Focus Area IV: Product Development

### Overarching goals

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

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

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

- a) Perform pilot phase of study to evaluate trends over time for new drug applications for systemic antibacterial drugs (2010). Complete assessment of trends over time for new drug applications for systemic antibacterial drugs (2011) and publish findings (2012).

**Progress:** A manuscript is in preparation that evaluates trends in antibacterial drug development and will be submitted for publication by mid-2011. Data collection and analysis evaluating applications for marketing a new antibacterial drug is ongoing; goal is to prepare a manuscript will be completed for submission by late 2011.

*Coordinator: FDA*

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

- a) Publish draft guidance on recommended approaches to clinical trial designs for evaluating antibacterial drugs for acute bacterial skin and skin structure infections (2010). Publish final guidance (2012).

**Progress:** A Draft Guidance on developing antibacterial drugs for acute bacterial skin and skin structure infections (ABSSSI) was published in August 2010. In addition to the published Draft Guidance on ABSSSI, agency staff have also participated in ongoing work led by the Foundation for the National Institutes of Health, the Biomarkers Consortium, to further evaluate endpoints for clinical trials of drugs for ABSSSI.

- b) Publish draft guidance on recommended approaches to clinical trial designs for evaluating antibacterial drugs for hospital acquired and ventilator associated bacterial pneumonia (2010). Publish final guidance (2012).

**Progress:** Issues in the design of clinical trials for hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) were discussed at an August 2010 FDA workshop. A Draft Guidance document on developing drugs for HABP and VABP was published in November 2010 for public comment. ,

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

**Progress:** Agency staff are participating in ongoing work led by the Foundation for the National Institutes of Health, the Biomarkers Consortium, to further evaluate endpoints for clinical trials of drugs for community-acquired bacterial pneumonia (CABP). This scientific work on endpoints will inform the revised draft guidance document for CABP.

*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:** The Guidance for Premarket Notification [510(k)] Submissions for Medical Devices that Include Antimicrobial Agents will be published in 2011.

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

**Progress:** On January 5, 2011, the Draft Guidance for Industry and Food and Drug Administration Staff - Establishing the Performance Characteristics of Nucleic Acid-Based *In vitro* Diagnostic Devices for the Detection and Differentiation of Methicillin-Resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (SA) was published. The guidance for establishing performance of *in vitro* diagnostics for VRE is in progress.

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

**Progress:** On November 29, 2010 the 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* was published.

*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:** 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:** A Part 15 public hearing was held on April 28, 2008, on issues in AR and the Orphan Drug Act. The transcript for the meeting is available at:

<http://www.regulations.gov/search/Regs/contentStreamer?objectId=090000648054f596&disposition=attachment&contentType=pdf>

*Coordinator: FDA*

9.6 Sponsor a study to evaluate incentives to promote the development of antibacterial drugs and rapid diagnostic tests (including antimicrobial susceptibility tests), including the impact of such strategies upon appropriate use of such products.

**Progress:** Work to initiate the study has been progressing well.

*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:** CDC, FDA, NIH staff are participating in the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) that will focus on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which can be better addressed by intensified cooperation between the EU and the US.

*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-yearly meetings of CLSI.

*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).

**Progress:** A guidance document titled, Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices published in June 2009. The guidance describes procedures for updating susceptibility testing information in product labeling for drugs and devices. On October 26, 2009, the FDA convened a meeting of the Anti-Infective Drugs Advisory Committee to discuss approaches to updating susceptibility testing information in drug product labeling.

- 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 (2010-2011).

**Progress:** USDA, FDA and CDC scientists serve as members and advisors for CLSI which develops approved standards for susceptibility testing and controls. Meetings are held 1-2 times per year.

*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.

- 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:** FDA co-sponsored a workshop along with CDC and the National Institute of Allergy and Infectious Diseases (NIAID) within NIH that addressed the 2009 Federal

Tuberculosis Task Force recommendations regarding the development of new rapid methods for laboratory confirmation of tuberculosis and the identification of drug-resistant tuberculosis.

NIAID intramural researchers and South Korean collaborators analyzed more than 500 clinical isolates to support development of the Hain test for XDR TB, which is being submitted to the Scientific and Technical Advisory Group (STAG) for the World Health Organization for implementation in national TB programs. The STAG will meet in fall 2010 to consider this data along with results from several other groups and finalize a recommendation from WHO.

- 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:** FDA continues to work with industry in providing guidance for clinical trial design and evaluating new technologies that would provide rapid methods to confirm diagnoses of possible bacterial respiratory infections and to identify pathogens associated with these infections.

- 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.

**Progress:** FDA continues to work with industry in providing guidance for clinical trial design and evaluating new technologies that would provide rapid methods for identification and characterization of *C. difficile*, MRSA, and other multidrug-resistant organisms.

USDA-APHIS NAHMS collaborated with USDA-ARS BEAR to identify optimal culture methods for *C. difficile* from feces of various types of animals on farms. A manuscript comparing the success of different culture methods has been accepted for publication in a peer-reviewed journal.

*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. Specifically,

- 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:** The FDA published a Guidance document titled, General Principles for the Development of Vaccines to Protect against Global Infectious Diseases in September

2008; the document provides recommendations and general information on the development of vaccines to protect against global infectious diseases.

NIAID has a long-standing intramural research program focused on the development and clinical testing of prototype malaria vaccines in collaboration with many partners from malaria-endemic countries and the public and private sectors.

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

**Progress:** To facilitate *S. aureus* vaccine development, FDA has initiated a research program focused on 1) the development of animal models of disease; 2) the development of correlates of protection; and 3) the development of novel genetic methods to facilitate the study of the organism and the production of vaccine antigens. This program involves investigators with expertise in gram-positive bacterial genetics, animal modeling of infectious disease, protein chemistry, and assay design and development.

The overall research plan for the Staphylococcal Vaccine Research Group is as follows:

- Develop animal models for different *S. aureus* disease forms.
- Identify potential *S. aureus* vaccine candidates.
- Clone, express, and purify recombinant forms of these proteins.
- Test the antigens as vaccines in multiple animal models that represent both acute and chronic infections.
- Identify protective immune mechanisms.

Also, FDA participated as members of the organizing committee for an NIAID Staphylococcal Vaccine Workshop that was held on May 10, 2010.

FDA has taken the following specific actions to facilitate tuberculosis vaccine development:

- Developed an assay to measure the potency and assess the safety of new tuberculosis vaccines.
- Characterized the safety and effectiveness of novel live attenuated tuberculosis vaccines.
- Evaluated certain T-cells as potential correlates of protective immunity against tuberculosis.

FDA has also worked with the World Health Organization and the Aeras Global Tuberculosis Foundation on tuberculosis vaccine issues.

To facilitate malaria vaccine development, FDA has:

- Developed a highly sensitive technique for measuring the number of malaria parasites in blood during vaccine studies.

- Developed a tuberculosis-malaria co-infection model for evaluating the safety and effectiveness of co-administration of tuberculosis and malaria vaccines.
- Identified excellent targets for genetic attenuation of blood-stage attenuated whole parasite vaccine.

To facilitate new pneumococcal vaccines, FDA has led the development and testing of a new standard reference serum essential for serologic evaluation of vaccine immunogenicity.

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

**Progress:** Vaccines for viral respiratory infections are a major focus of the NIAID intramural research program. Vaccines for respiratory syncytial virus (RSV), human parainfluenza virus serotypes 1, 2, and 3 (HPIV1-3), and human metapneumovirus are in development for intranasal administration to infants as a universal pediatric vaccine. Lead candidates for RSV and 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*.

*Coordinator: HHS/ASPR*

## Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
APHL	Association of Public Health Laboratories
AR	Antimicrobial resistance
ARS	Agricultural Research Service (USDA)
ASPE	<i>Office of the Assistant Secretary for Planning and Evaluation</i>
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 <i>Staphylococcus aureus</i>
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